ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

Online-Only Supplement Part 2.

2. Research Protocols

Research Protocol, Question 1	
Question	Should chest CT be routinely performed on chronic cough patient with normal chest X-ray and physical examination?
Objective	To examine the diagnostic utility of chest CT in chronic cough patients with normal chest X-rays and physical examination
Criteria	Randomised trials or observational studies on the diagnostic utility of chest CT in in chronic cough patients with normal chest X-rays and physical examination
Population	Chronic cough patients with normal chest X-ray and physical examination
Investigation	Chest CT scan
Comparison	None
Outcomes	• Change in treatment decision (important) • Sensitivity and specificity (important) • Direct adverse events (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND chest CT Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised trial or observational study Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 2

Question	Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?
Objective	To examine the utility of FeNO and blood eosinophils to predict treatment response to corticosteroids and anti-leukotrienes in chronic cough patients
Criteria	Randomised trials or observational studies on the utility of FeNO and blood eosinophils to predict treatment response to corticosteroids and anti-leukotrienes in chronic cough patients
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Investigation	FeNO or blood eosinophils
Comparison	None
Outcomes	• Association with treatment response (important) • Change in treatment decision (important) • Sensitivity and specificity (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND FeNO/blood eosinophils AND corticosteroids/anti-leukotrienes Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised trial or observational study Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 3	
Question	Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?
Objective	To compare anti-asthmatic drugs (inhaled or systemic corticosteroids, inhaled bronchodilators, or anti-leukotrienes) to placebo for improving cough outcomes in chronic cough patients

Criteria	Randomised placebo-controlled trials comparing anti-asthmatic drugs (inhaled or systemic corticosteroids, inhaled bronchodilators, or anti-leukotrienes) with placebo in adults or children with chronic cough as the main complaint (regardless of underlying conditions)
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Intervention	Inhaled or systemic corticosteroids, inhaled bronchodilators, or anti-leukotrienes
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important) • Treatment specific adverse events (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND anti-asthmatic drugs (inhaled or systemic corticosteroids, inhaled bronchodilators, or anti-leukotrienes) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 4

Question	Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?
Objective	To compare anti-acid drugs (PPIs and H2 antagonists) to placebo for improving cough outcomes in chronic cough patients
Criteria	Randomised placebo-controlled trials comparing anti-acid drugs (PPIs and H2 antagonists) with placebo in adults or children with chronic cough as the main complaint (regardless of underlying conditions)
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Intervention	PPIs or H2 antagonists
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important) • Treatment specific adverse events (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND anti-acid drugs (PPIs and H2 antagonists) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 5	
Question	Should drugs with pro-motility activity (reflux inhibitors, prokinetics, or macrolides with pro-motility activity) be used to treat patients with chronic cough?
Objective	To compare drugs with pro-motility activity (reflux inhibitors, prokinetics, or macrolides with pro-motility activity) to placebo for improving cough outcomes in chronic cough patients
Criteria	Randomised placebo-controlled trials comparing drugs with pro-motility activity (reflux inhibitors, prokinetics, or macrolides with pro-motility activity) with placebo in adults or children with chronic cough as the main complaint (regardless of underlying conditions)
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Intervention	Reflux inhibitors, prokinetics, or macrolides with pro-motility activity
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important) • Treatment specific adverse events (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND drugs with pro-motility activity (reflux inhibitors, prokinetics, or macrolides with pro-motility activity) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL)

	Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 6	
Question	Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?
Objective	To compare cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) to placebo for improving cough outcomes in adults with chronic cough
Criteria	Randomised placebo-controlled trials comparing cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) with placebo in adults with chronic cough as the main complaint (regardless of underlying conditions)
Population	Adult with chronic cough as the main complaint regardless of their underlying conditions
Intervention	Pregabalin, gabapentin, tricyclics, or opiates
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Treatment specific adverse events (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important)

Search strategy	Chronic cough populations (regardless of underlying conditions) AND cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 7	
Question	Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?
Objective	To compare non-pharmacological therapy (cough control therapy) to placebo for improving cough outcomes in chronic cough patients
Criteria	Randomised placebo-controlled trials comparing non-pharmacological therapy (cough control therapy) with placebo in adults or children with chronic cough as the main complaint (regardless of underlying conditions)
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Intervention	Cough control therapy
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important)

	• Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND non-pharmacological therapy (cough control therapy) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 8	
Question	Should a trial of antibiotics be used in children with chronic wet cough with normal chest x ray, normal spirometry and no warning signs?
Objective	To compare a trial of antibiotics to placebo for improving cough outcomes in children with chronic cough
Criteria	Randomised placebo-controlled trials comparing a trial of antibiotics with placebo in children with chronic wet cough with normal chest X-rays, normal spirometry and no warning signs
Population	Children with chronic wet cough with normal chest X-rays, normal spirometry and no warning signs
Intervention	Antibiotics (amoxicillin, clavulanate, erythromycin or clarithromycin)
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical)

	• Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Treatment specific adverse events (important) • Tussive response to cough challenge (important)
Search strategy	Chronic wet cough or bronchitis populations AND a trial of antibiotics (amoxicillin, clavulanate, erythromycin or clarithromycin) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

3. Electronic search strategies

Question 1: Should chest CT be routinely performed on chronic cough patient with normal chest X-ray and physical examination?

Last search: June 2018

Pubmed MEDLINE

#1. ("Cough"[Mesh] OR cough[TIAB] OR coughing[TIAB] OR coughs[TIAB] OR "Bronchitis"[Mesh:NoExp] OR "Bronchitis, Chronic"[Mesh] OR bronchitis[TIAB] OR bronchitic[TIAB])

#2. (chronic[TIAB] OR persistent[TIAB] OR longstanding[TIAB] OR long-standing[TIAB] OR longterm[TIAB] OR long-term[TIAB] OR uncontrolled[TIAB] OR “poorly controlled” [TIAB] OR lingering[TIAB] OR nagging[TIAB] OR resistant[TIAB] OR refractory[TIAB] OR unexplained[TIAB] OR idiopathic[TIAB] OR frequent[TIAB])

#3. #1 AND #2

#4. "Tomography, X-Ray Computed"[Mesh] OR ct[TIAB] OR "computed tomography"[TIAB] OR "computed tomogram"[TIAB] OR "computerized tomography"[TIAB] OR “computerised tomography”[TIAB] OR “computed X-ray tomography”[TIAB] OR "computer assisted tomography"[TIAB] OR "computerized axial tomography"[TIAB] OR “computerised axial tomography”[TIAB]

#5. #3 AND #4

#6. #5 NOT (animals[Mesh Term] NOT (humans[Mesh Term] AND animals[Mesh Term]))

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. chronic:ab,ti OR persistent:ab,ti OR longstanding:ab,ti OR 'long standing':ab,ti OR longterm:ab,ti OR 'long term':ab,ti OR uncontrolled:ab,ti OR 'poorly controlled':ab,ti OR lingering:ab,ti OR nagging:ab,ti OR resistant:ab,ti OR refractory:ab,ti OR unexplained:ab,ti OR idiopathic:ab,ti OR frequent:ab,ti = 3417568

#3. #1 AND #2

#4. 'computer assisted tomography'/exp OR ct:ab,ti OR "computed tomography":ab,ti OR "computed tomogram":ab,ti OR "computerized tomography":ab,ti OR “computerised tomography”:ab,ti OR “computed X-ray tomography”:ab,ti OR "computer assisted tomography":ab,ti OR "computerized axial tomography":ab,ti OR “computerised axial tomography”:ab,ti

#5. #3 AND #4

#6. #5 NOT ('animal experiment'/de OR 'animal model'/de OR 'in vitro study'/de OR 'nonhuman'/de)

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. chronic or persistent or longstanding or long-standing or longterm or long-term or uncontrolled or "poorly controlled" or lingering or nagging or resistant or refractory or unexplained or idiopathic or frequent:ti,ab,kw (Word variations have been searched)

#8. #6 AND #7

#9. MeSH descriptor: [Tomography, X-Ray Computed] explode all trees

#10. ct or "computed tomography" or "computed tomogram" or "computerized tomography" or "computerised tomography" or "computed X-ray tomography" or "computer assisted tomography" or "computerized axial tomography" or "computerised axial tomography":ti,ab,kw (Word variations have been searched)

#11. #9 OR #10

#12. #8 AND #11

#13. #12 in Trials

Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Adrenal Cortex Hormones"[Mesh:NoExp] OR "Glucocorticoids"[Mesh] OR "Hydroxycorticosteroids"[Mesh:NoExp] OR "Steroids"[Mesh:NoExp] OR "Beclomethasone"[Mesh] OR "Betamethasone"[Mesh] OR "Budesonide"[Mesh] OR "Fluticasone"[Mesh] OR "Mometasone Furoate"[Mesh] OR "Triamcinolone"[Mesh] OR "ciclesonide" [Supplementary Concept] OR "flunisolide" [Supplementary Concept] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Dexamethasone"[Mesh] OR "Cortisone"[Mesh] OR "Hydrocortisone"[Mesh] OR "Leukotriene Antagonists"[Mesh] OR "montelukast" [Supplementary Concept] OR "pranlukast" [Supplementary Concept] OR "zafirlukast" [Supplementary Concept]

#3. (glucocorticoid[TIAB] OR glucocorticoids[TIAB] OR corticosteroid[TIAB] OR corticosteroids[TIAB] OR steroid[TIAB] OR steroids[TIAB]) OR beclomethasone[TIAB] OR betamethasone[TIAB] OR budesonide[TIAB] OR fluticasone[TIAB] OR mometasone[TIAB] OR triamcinolone[TIAB] OR ciclesonide[TIAB] OR

flunisolide[TIAB] OR prednisolone[TIAB] OR prednisone[TIAB] OR methylprednisolone[TIAB] OR dexamethasone[TIAB] OR cortisone[TIAB] OR hydrocortisone[TIAB] OR montelukast[TIAB] OR pranlukast[TIAB] OR zafirlukast[TIAB] OR leukotriene[TIAB] OR leukotrienes[TIAB] OR leukotrien[TIAB] OR leucotriene[TIAB] OR leucotrienes[TIAB] OR leucotrien[TIAB] OR anti-leukotriene[TIAB] OR anti-leukotrienes[TIAB] OR anti-leukotrien[TIAB] OR anti-leucotriene[TIAB] OR anti-leucotrienes[TIAB] OR anti-leucotrien[TIAB]

#4. "Nitric Oxide"[Mesh] OR "Eosinophils"[Mesh] OR "Biomarkers"[Mesh] OR "Sensitivity and Specificity"[Mesh]

#5. "nitric oxide"[TIAB] OR eno[TIAB] OR feno[TIAB] OR eosinophil[TIAB] OR eosinophils[TIAB] OR eosinophilic[TIAB] OR biomarker[TIAB] OR biomarkers[TIAB] OR predict[TIAB] OR predictive[TIAB] OR predictable[TIAB] OR predictability[TIAB] OR predicted[TIAB] OR predicts[TIAB] OR predictor[TIAB] OR predictors[TIAB] OR sensitivity[TIAB] OR sensitive[TIAB] OR sensitivities[TIAB] specificity[TIAB] OR specific[TIAB] OR specificities[TIAB] OR accuracy[TIAB] OR accurate[TIAB] OR accuracies[TIAB] OR “diagnostic value”[TIAB] OR “diagnostic test value”[TIAB] OR “diagnostic utility”[TIAB] OR “diagnostic test utility”[TIAB]

#6. #2 OR #3

#7. #4 OR #5

#8. #1 AND #6 AND #7

#9. #8 NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms])

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'corticosteroid'/de OR 'glucocorticoid'/de OR 'hydroxycorticosteroid'/exp OR 'steroid'/de OR 'beclometasone'/exp OR 'betamethasone'/exp OR 'budesonide'/exp OR 'fluticasone'/exp OR 'mometasone furoate'/exp OR 'triamcinolone'/exp OR 'ciclesonide'/exp OR 'flunisolide'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR 'methylprednisolone'/exp OR 'dexamethasone'/exp OR 'cortisone'/exp OR 'hydrocortisone'/exp OR 'leukotriene receptor blocking agent'/de OR 'montelukast'/exp OR 'pranlukast'/exp OR 'zafirlukast'/exp

#3. corticosteroid:ab,ti OR corticosteroids:ab,ti OR glucocorticoid:ab,ti OR glucocorticoids:ab,ti OR steroid:ab,ti OR steroids:ab,ti OR beclomethasone:ab,ti OR betamethasone:ab,ti OR budesonide:ab,ti OR fluticasone:ab,ti OR mometasone:ab,ti OR triamcinolone:ab,ti OR ciclesonide:ab,ti OR flunisolide:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti OR methylprednisolone:ab,ti OR dexamethasone:ab,ti OR cortisone:ab,ti OR hydrocortisone:ab,ti

OR montelukast:ab,ti OR pranlukast:ab,ti OR zafirlukast:ab,ti OR leukotriene:ab,ti OR leukotrienes:ab,ti OR leukotrien:ab,ti OR leucotriene:ab,ti OR leucotrienes:ab,ti OR leucotrien:ab,ti OR 'anti leukotriene':ab,ti OR 'anti leukotrienes':ab,ti OR 'anti leukotrien':ab,ti OR 'anti leucotriene':ab,ti OR 'anti leucotrienes':ab,ti OR 'anti leucotrien':ab,ti

#4. 'nitric oxide'/exp OR 'eosinophil'/exp OR 'biological marker'/exp OR 'pharmacological biomarker'/exp OR 'sensitivity and specificity'/exp OR 'predictive value'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'diagnostic value'/exp

#5. 'nitric oxide':ab,ti OR eno:ab,ti OR feno:ab,ti OR eosinophil:ab,ti OR eosinophils:ab,ti OR eosinophilic:ab,ti OR biomarker:ab,ti OR biomarkers:ab,ti OR predict:ab,ti OR predictive:ab,ti OR predictable:ab,ti OR predictability:ab,ti OR predicted:ab,ti OR predicts:ab,ti OR predictor:ab,ti OR predictors:ab,ti OR sensitivity:ab,ti OR sensitive:ab,ti OR sensitivities:ab,ti OR specificity:ab,ti OR specific:ab,ti OR specificities:ab,ti OR accuracy:ab,ti OR accurate:ab,ti OR accuracies:ab,ti OR 'diagnostic value':ab,ti OR 'diagnostic test value':ab,ti OR 'diagnostic utility':ab,ti OR 'diagnostic test utility':ab,ti

#6. #2 OR #3

#7. #4 OR #5

#8. #1 AND #6 AND #7

#9. #8 NOT ('conference review'/it OR 'review'/it)

Cochrane Library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Adrenal Cortex Hormones] this term only

#8. MeSH descriptor: [Glucocorticoids] explode all trees

#9. MeSH descriptor: [Hydroxycorticosteroids] this term only

#10. MeSH descriptor: [Beclomethasone] explode all trees

#11. MeSH descriptor: [Beclomethasone] explode all trees

#12. MeSH descriptor: [Betamethasone] explode all trees

#13. MeSH descriptor: [Budesonide] explode all trees

#14. MeSH descriptor: [Fluticasone] explode all trees

#15. MeSH descriptor: [Mometasone Furoate] explode all trees

#16. MeSH descriptor: [Triamcinolone] explode all trees

#17. MeSH descriptor: [Prednisolone] explode all trees

#18. MeSH descriptor: [Prednisone] explode all trees

#19. MeSH descriptor: [Dexamethasone] explode all trees

#20. MeSH descriptor: [Cortisone] explode all trees

#21. MeSH descriptor: [Hydrocortisone] explode all trees

#22. MeSH descriptor: [Leukotriene Antagonists] explode all trees

#23. glucocorticoid or glucocorticoids or corticosteroid or corticosteroids or steroid or steroids or beclomethasone or betamethasone or budesonide or fluticasone or mometasone or triamcinolone or ciclesonide or flunisolide or prednisolone or prednisone or methylprednisolone or dexamethasone or cortisone or hydrocortisone or montelukast or pranlukast or zafirlukast or leukotriene or leukotrienes or leukotrien or leucotriene or leucotrienes or leucotrien or anti-leukotriene or anti-leukotrienes or anti-leukotrien or anti-leucotriene or anti-leucotrienes or anti-leucotrien:ti,ab,kw (Word variations have been searched)

#24. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23

#25. MeSH descriptor: [Nitric Oxide] explode all trees

#26. MeSH descriptor: [Eosinophils] explode all trees

#27. MeSH descriptor: [Biomarkers] explode all trees

#28. MeSH descriptor: [Sensitivity and Specificity] explode all trees

#29. "nitric oxide" or eno or feno or eosinophil or eosinophils or eosinophilic or biomarker or biomarkers or predict or predictive or predictable or predictability or predicted or predicts or predictor or predictors or sensitivity or sensitive or sensitivities specificity or specific or specificities or accuracy or accurate or accuracies or "diagnostic value" or "diagnostic test value" or "diagnostic utility" or "diagnostic test utility":ti,ab,kw (Word variations have been searched)

#29. #25 or #26 or #27 or #28 or #29

#30. #6 and #24 and #29

#31. #30 in Trials

Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Beclomethasone"[Mesh] OR "Betamethasone"[Mesh] OR "Budesonide"[Mesh] OR "Fluticasone"[Mesh] OR "Mometasone Furoate"[Mesh] OR "Triamcinolone"[Mesh] OR "ciclesonide" [Supplementary Concept] OR "flunisolide" [Supplementary Concept] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Dexamethasone"[Mesh] OR "Cortisone"[Mesh] OR "Hydrocortisone"[Mesh] OR "Leukotriene Antagonists"[Mesh] OR "montelukast" [Supplementary Concept] OR "pranlukast" [Supplementary Concept] OR "zafirlukast" [Supplementary Concept]

#3. "Adrenergic beta-2 Receptor Agonists"[Mesh] OR "Formoterol Fumarate"[Mesh] OR "vilanterol"[Supplementary Concept] OR "Salmeterol Xinafoate"[Mesh] OR "indacaterol"[Supplementary Concept] OR "olodaterol"[Supplementary Concept] OR "Albuterol"[Mesh] OR "tulobuterol"[Supplementary Concept] OR "Terbutaline"[Mesh] OR “Cholinergic Antagonists"[Mesh:NoExp] OR "Muscarinic Antagonists"[Mesh] OR "Ipratropium"[Mesh] OR "Glycopyrrolate"[Mesh] OR "Tiotropium Bromide"[Mesh] OR "aclidinium bromide"[Supplementary Concept] OR "GSK573719"[Supplementary Concept]

#4. beclomethasone[TIAB] OR betamethasone[TIAB] OR budesonide[TIAB] OR fluticasone[TIAB] OR mometasone[TIAB] OR triamcinolone[TIAB] OR ciclesonide[TIAB] OR flunisolide[TIAB] OR prednisolone[TIAB] OR prednisone[TIAB] OR methylprednisolone[TIAB] OR dexamethasone[TIAB] OR cortisone[TIAB] OR hydrocortisone[TIAB] OR montelukast[TIAB] OR pranlukast[TIAB] OR zafirlukast[TIAB]

#5. formoterol[TIAB] OR vilanterol[TIAB] OR salmeterol[TIAB] OR indacaterol[TIAB] OR olodaterol[TIAB] OR albuterol[TIAB] OR salbutamol[TIAB] OR levalbuterol[TIAB] OR tulobuterol[TIAB] OR terbutaline[TIAB] OR ipratropium[TIAB] OR glycopyrrolate[TIAB] OR tiotropium[TIAB] OR aclidinium[TIAB] OR umeclidinium[TIAB]

#6. #2-5/OR

#7. #1 AND #6

#8. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#9. #7 AND #8

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'beclometasone'/exp OR 'betamethasone'/exp OR 'budesonide'/exp OR 'fluticasone'/exp OR 'mometasone furoate'/exp OR 'triamcinolone'/exp OR 'ciclesonide'/exp OR 'flunisolide'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR 'methylprednisolone'/exp OR 'dexamethasone'/exp OR 'cortisone'/exp OR 'hydrocortisone'/exp OR 'leukotriene receptor blocking agent'/de OR 'montelukast'/exp OR 'pranlukast'/exp OR 'zafirlukast'/exp

#3. 'beta 2 adrenergic receptor stimulating agent'/exp OR 'formoterol'/exp OR 'vilanterol'/exp OR 'salmeterol'/exp OR 'indacaterol'/exp OR 'olodaterol'/exp OR 'salbutamol'/exp OR 'tulobuterol'/exp OR 'terbutaline'/exp OR

'cholinergic receptor blocking agent'/de OR 'muscarinic receptor blocking agent'/de OR 'ipratropium bromide'/exp OR 'glycopyrronium'/exp OR 'tiotropium bromide'/exp OR 'aclidinium bromide'/exp OR 'umeclidinium'/exp

#4. beclomethasone:ab,ti OR betamethasone:ab,ti OR budesonide:ab,ti OR fluticasone:ab,ti OR mometasone:ab,ti OR triamcinolone:ab,ti OR ciclesonide:ab,ti OR flunisolide:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti OR methylprednisolone:ab,ti OR dexamethasone:ab,ti OR cortisone:ab,ti OR hydrocortisone:ab,ti OR montelukast:ab,ti OR pranlukast:ab,ti OR zafirlukast:ab,ti

#5. formoterol:ab,ti OR vilanterol:ab,ti OR salmeterol:ab,ti OR indacaterol:ab,ti OR olodaterol:ab,ti OR albuterol:ab,ti OR salbutamol:ab,ti OR levalbuterol:ab,ti OR tulobuterol:ab,ti OR terbutaline:ab,ti OR ipratropium:ab,ti OR glycopyrrolate:ab,ti OR tiotropium:ab,ti OR aclidinium:ab,ti OR umeclidinium:ab,ti

#6. #2 OR #3 OR #4 OR #5

#7. #1 AND #6

#8. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#9. #7 AND #8

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Beclomethasone] explode all trees

#8. MeSH descriptor: [Betamethasone] explode all trees

#9. MeSH descriptor: [Budesonide] explode all trees

#10. MeSH descriptor: [Fluticasone] explode all trees

#11. MeSH descriptor: [Mometasone Furoate] explode all trees

#12. MeSH descriptor: [Triamcinolone] explode all trees

#13. MeSH descriptor: [Prednisolone] explode all trees

#14. MeSH descriptor: [Prednisone] explode all trees

#15. MeSH descriptor: [Dexamethasone] explode all trees

#16. MeSH descriptor: [Cortisone] explode all trees

#17. MeSH descriptor: [Hydrocortisone] explode all trees

#18. MeSH descriptor: [Leukotriene Antagonists] explode all trees

#19. beclomethasone or betamethasone or budesonide or fluticasone or mometasone or triamcinolone or ciclesonide or flunisolide or prednisolone or prednisone or methylprednisolone or dexamethasone or cortisone or hydrocortisone or montelukast or pranlukast or zafirlukast:ti,ab,kw (Word variations have been searched)

#20. MeSH descriptor: [Adrenergic beta-2 Receptor Agonists] explode all trees

#21. MeSH descriptor: [Formoterol Fumarate] explode all trees

#22. MeSH descriptor: [Salmeterol Xinafoate] explode all trees

#23. MeSH descriptor: [Albuterol] explode all trees

#24. MeSH descriptor: [Terbutaline] explode all trees

#25. MeSH descriptor: [Cholinergic Antagonists] this term only

#26. MeSH descriptor: [Muscarinic Antagonists] explode all trees

#27. MeSH descriptor: [Ipratropium] explode all trees

#28. MeSH descriptor: [Glycopyrrolate] explode all trees

#29. MeSH descriptor: [Tiotropium Bromide] explode all trees

#30. formoterol or vilanterol or salmeterol or indacaterol or olodaterol or albuterol or salbutamol or levalbuterol or tulobuterol or terbutaline or ipratropium or glycopyrrolate or tiotropium or aclidinium or umeclidinium:ti,ab,kw (Word variations have been searched)

#31. #7-30/OR

#32. #6 AND #31

#33. #32 in Trials

Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. "Cough"[Mesh]

#2. cough[TIAB] OR coughing[TIAB] OR coughs[TIAB]

#3. ("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh]

#4. bronchitis[TIAB] OR bronchitic[TIAB]

#5. #1 OR #2 OR #3 OR #4

#6. "Proton Pump Inhibitors"[Mesh] OR "Proton Pump Inhibitors" [Pharmacological Action]

#7. "proton pump inhibitor"[TIAB] OR "proton pump inhibitors"[TIAB] OR ppi[TIAB] OR omeprazole[TIAB] OR esomeprazole[TIAB] OR lansoprazole[TIAB] OR dexlansoprazole[TIAB] OR pantoprazole[TIAB] OR rabeprazole[TIAB] OR timoprazole[TIAB]

#8. #6 OR #7

#9. "Histamine H2 Antagonists"[Mesh] OR "Histamine H2 Antagonists"[Pharmacological Action]

#10. “H2 receptor blockaders”[TIAB] OR “H2 receptor blockader”[TIAB] OR “H2 receptor blockade”[TIAB] OR “H2 receptor blockers”[TIAB] OR “H2 receptor blocking”[TIAB] OR “H2 receptor blockers”[TIAB] OR “H2 receptor blocker”[TIAB] OR “H2 receptor antagonists”[TIAB] OR “H2 receptor antagonist”[TIAB] OR “H2 blockaders”[TIAB] OR “H2 blockader”[TIAB] OR "h2 blockade"[TIAB] OR “H2 blocking”[TIAB] OR “H2 blockers”[TIAB] OR “H2 blocker”[TIAB] OR “H2 antagonists”[TIAB] OR “H2 antagonist”[TIAB] OR (H2[TIAB] AND antihistamin*[TIAB]) OR (H2[TIAB] AND anti-histamin*[TIAB]) OR h2ra[TIAB] OR cimetidine[TIAB] OR famotidine[TIAB] OR lafutidine[TIAB] OR nizatidine[TIAB] OR ranitidine[TIAB] OR roxatidine[TIAB]

#11. #9 OR #10

#12. #8 OR #11

#13. #5 AND #12

#14. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#15. #13 AND #14

Embase

#1. 'coughing'/exp

#2. cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti

#3. 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp

#4. bronchitis:ab,ti OR bronchitic:ab,ti

#5. #1 OR #2 OR #3 OR #4

#6. 'proton pump inhibitor'/exp

#7. 'proton pump inhibitor':ab,ti OR 'proton pump inhibitors':ab,ti OR ppi:ab,ti OR omeprazole:ab,ti OR esomeprazole:ab,ti OR lansoprazole:ab,ti OR dexlansoprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR timoprazole:ab,ti

#8. 'histamine h2 receptor antagonist'/exp

#9. 'h2 receptor blockaders':ab,ti OR 'h2 receptor blockader':ab,ti OR 'h2 receptor blockade':ab,ti OR 'h2 receptor blocking':ab,ti OR 'h2 receptor blockers':ab,ti OR 'h2 receptor blocker':ab,ti OR 'h2 receptor antagonists':ab,ti OR 'h2 receptor antagonist':ab,ti OR 'h2 blockaders':ab,ti OR 'h2 blockader':ab,ti OR 'h2 blockade':ab,ti OR 'h2 blocking':ab,ti OR 'h2 blockers':ab,ti OR 'h2 blocker':ab,ti OR 'h2 antagonists':ab,ti OR 'h2 antagonist':ab,ti OR (h2:ab,ti AND antihistamin*:ab,ti) OR (h2:ab,ti AND 'anti histamin*':ab,ti) OR h2ra:ab,ti OR cimetidine:ab,ti OR famotidine:ab,ti OR lafutidine:ab,ti OR nizatidine:ab,ti OR ranitidine:ab,ti OR roxatidine:ab,ti

#10. #6 OR #7

#11. #8 OR #9

#12. #10 OR #11

#13. #5 AND #12

#14. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#15. #13 AND #14

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Proton Pump Inhibitors] explode all trees

#8. 'proton pump inhibitor' or 'proton pump inhibitors' or ppi or omeprazole or esomeprazole or lansoprazole or dexlansoprazole or pantoprazole or rabeprazole or timoprazole:ti,ab,kw (Word variations have been searched)

#9. MeSH descriptor: [Histamine H2 Antagonists] explode all trees

#10. "H2 receptor blockaders" or "H2 receptor blockader" or "H2 receptor blockade" or "H2 receptor blockers" or "H2 receptor blocking" or "H2 receptor blockers" or "H2 receptor blocker" or "H2 receptor antagonists" or "H2 receptor antagonist" or "H2 blockaders" or "H2 blockader" or "h2 blockade" or "H2 blocking" or "H2 blockers" or "H2 blocker" or "H2 antagonists" or "H2 antagonist" or (H2 and antihistamin*) or (H2 and anti-histamin*) or h2ra or cimetidine or famotidine or lafutidine or nizatidine or ranitidine or roxatidine:ti,ab,kw (Word variations have been searched)

#11. #7 OR #8

#12. #9 OR #10

#13. #11 OR #12

#14. #13 in Trials

Question 5: Should drugs with pro-motility activity (reflux inhibitors, prokinetics and macrolides with pro-motility activity) be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Metoclopramide"[Mesh] OR Metoclopramide[TIAB] OR Metaclopramide[TIAB] OR Metoclopromide[TIAB] OR Maxolon[TIAB] OR Primperan[TIAB] OR Reglan[TIAB] OR Cerucal[TIAB]

#3. "Domperidone"[Mesh] OR Domperidone[TIAB] OR Domperidon[TIAB] OR Motilium[TIAB]

#4. "Baclofen"[Mesh] OR Baclofen[TIAB] OR Baclophen[TIAB]

#5. "Macrolides"[Mesh:NoExp] OR Macrolides[TIAB] OR Macrolide[TIAB] OR "Erythromycin"[Mesh] OR Erythromycin[TIAB] OR Monomycin[TIAB] OR Mitemcinal[TIAB] OR Azithromycin[TIAB] OR Azythromycin[TIAB] OR Zithromax[TIAB] OR Sumamed[TIAB] OR Clarithromycin[TIAB] OR Biaxin[TIAB] OR Ketolides[TIAB] OR Roxithromycin[TIAB] OR Rulide[TIAB] OR Rulid[TIAB] OR "Troleandomycin"[Mesh] OR Troleandomycin[TIAB] OR Triacetyloleandomycin[TIAB] OR Telithromycin[TIAB] OR Ketek[TIAB]

#6. #2 OR #3 OR #4 OR #5

#7. #1 AND #6

#8. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#9. #7 AND #8

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'metoclopramide'/exp OR metoclopramide:ab,ti OR metaclopramide:ab,ti OR metoclopromide:ab,ti OR maxolon:ab,ti OR primperan:ab,ti OR reglan:ab,ti OR cerucal:ab,ti

#3. 'domperidone'/exp OR domperidone:ab,ti OR domperidon:ab,ti OR motilium:ab,ti

#4. 'macrolide'/de OR 'erythromycin'/exp OR 'mitemcinal'/exp OR 'erythromycin derivative'/exp OR 'azithromycin'/exp OR 'clarithromycin'/exp OR 'telithromycin'/exp OR 'roxithromycin'/exp OR 'troleandomycin'/exp OR macrolides:ab,ti OR macrolide:ab,ti OR erythromycin:ab,ti OR monomycin:ab,ti OR mitemcinal:ab,ti OR azithromycin:ab,ti OR azythromycin:ab,ti OR zithromax:ab,ti OR sumamed:ab,ti OR clarithromycin:ab,ti OR biaxin:ab,ti OR ketolides:ab,ti OR roxithromycin:ab,ti OR rulide:ab,ti OR rulid:ab,ti OR troleandomycin:ab,ti OR triacetyloleandomycin:ab,ti OR telithromycin:ab,ti OR ketek:ab,ti

#5. #2 OR #3 OR #4

#6. #1 AND #5

#7. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#8. #6 AND #7

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Metoclopramide] explode all trees

#8. Metoclopramide or Metaclopramide or Metoclopromide or Maxolon or Primperan or Reglan or Cerucal:ti,ab,kw (Word variations have been searched)

#9. MeSH descriptor: [Domperidone] explode all trees

#10. Domperidone or Domperidon or Motilium:ti,ab,kw (Word variations have been searched)

#11. MeSH descriptor: [Baclofen] explode all trees

#12. Baclofen or Baclophen:ti,ab,kw (Word variations have been searched)

#13. MeSH descriptor: [Macrolides] this term only

#14. MeSH descriptor: [Erythromycin] explode all trees

#15. MeSH descriptor: [Troleandomycin] explode all trees

#16. Macrolides or Macrolide or Erythromycin or Monomycin or Mitemcinal or Azithromycin or Azythromycin or Zithromax or Sumamed or Clarithromycin or Biaxin or Ketolides or Roxithromycin or Rulide or Rulid or Troleandomycin or Triacetyloleandomycin or Telithromycin or Ketek:ti,ab,kw (Word variations have been searched)

#17. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18. #6 and #17

#19. #18 in Trials

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Pregabalin"[Mesh] OR Pregabalin[TIAB] OR Lyrica[TIAB]

#3. "gabapentin" [Supplementary Concept] OR Gabapentin[TIAB] OR Neurontin[TIAB]

#4. "Antidepressive Agents, Tricyclic"[Mesh] OR (tricyclic[TIAB] AND (antidepressant[TIAB] OR antidepressants[TIAB] OR antidepressive[TIAB])) OR "Amitriptyline"[Mesh] OR Amitriptyline[TIAB] OR Amitriptylin[TIAB] OR Amitriptiline[TIAB] OR Amitriptilin[TIAB] OR Elavil[TIAB] OR "Clomipramine"[Mesh] OR Clomipramine[TIAB] OR Chlomipramine[TIAB] OR Chlorimipramine[TIAB] OR Anafranil[TIAB] OR Cyclobenzaprine[TIAB] OR Flexeril[TIAB] OR "Desipramine"[Mesh] OR Desipramine[TIAB] OR Desmethylimipramine[TIAB] OR Demethylimipramine[TIAB] OR Norpramin[TIAB] OR Pertofrane[TIAB] OR Desmethyldoxepin[TIAB] OR Dibenzepin[TIAB] OR Noveril[TIAB] OR "Dothiepin"[Mesh] OR Dothiepin[TIAB] OR Dosulepin[TIAB] OR Prothiaden[TIAB] OR "Doxepin"[Mesh] OR Doxepin[TIAB] OR Sinequan[TIAB] OR "Imipramine"[Mesh] OR Imipramine[TIAB] OR Melipramine[TIAB] OR Tofranil[TIAB] OR "Iprindole"[Mesh] OR Iprindole[TIAB] OR "Lofepramine"[Mesh] OR Lofepramine[TIAB] OR Melitracene[TIAB] OR Metapramine[TIAB] OR Mirtazapine[TIAB] OR Remeron[TIAB] OR "Nortriptyline"[Mesh] OR Nortriptyline[TIAB] OR Nortriptylin[TIAB] OR Nortriptiline[TIAB] OR Nortriptilin[TIAB] OR Aventyl[TIAB] OR Sensival[TIAB] OR Noxiptilin[TIAB] OR "Opipramol"[Mesh] OR Opipramol[TIAB] OR insidon[TIAB] OR "Protriptyline"[Mesh] OR Protriptyline[TIAB] OR Tianeptine[TIAB] OR "Trimipramine"[Mesh] OR Trimipramine[TIAB] OR Surmontil[TIAB]

#5. "Analgesics, Opioid"[Mesh] OR "Opium"[Mesh] OR "Opiate Alkaloids"[Mesh:NoExp] OR opioid[TIAB] OR opioids[TIAB] OR opium[TIAB] OR opiate[TIAB] OR opiates[TIAB] OR "Morphine"[Mesh] OR Morphine[TIAB] OR morphia[TIAB] OR "Codeine"[Mesh] OR codeine[TIAB] OR "pholcodine" [Supplementary Concept] OR pholcodine[TIAB]

#6. #2 OR #3 OR #4 OR #5

#7. #1 AND #6

#8. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#9. #7 AND #8

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'pregabalin'/exp OR pregabalin:ab,ti OR lyrica:ab,ti

#3. 'gabapentin'/exp OR gabapentin:ab,ti OR neurontin:ab,ti

#4. 'tricyclic antidepressant agent'/exp OR (tricyclic:ab,ti AND (antidepressant:ab,ti OR antidepressants:ab,ti OR antidepressive:ab,ti)) OR amitriptyline:ab,ti OR amitriptylin:ab,ti OR amitriptiline:ab,ti OR amitriptilin:ab,ti OR elavil:ab,ti OR clomipramine:ab,ti OR chlomipramine:ab,ti OR chlorimipramine:ab,ti OR anafranil:ab,ti OR cyclobenzaprine:ab,ti OR flexeril:ab,ti OR desipramine:ab,ti OR desmethylimipramine:ab,ti OR demethylimipramine:ab,ti OR norpramin:ab,ti OR pertofrane:ab,ti OR desmethyldoxepin:ab,ti OR dibenzepin:ab,ti

OR noveril:ab,ti OR dothiepin:ab,ti OR dosulepin:ab,ti OR prothiaden:ab,ti OR doxepin:ab,ti OR sinequan:ab,ti OR imipramine:ab,ti OR melipramine:ab,ti OR tofranil:ab,ti OR iprindole:ab,ti OR lofepramine:ab,ti OR melitracene:ab,ti OR metapramine:ab,ti OR mirtazapine:ab,ti OR remeron:ab,ti OR nortriptyline:ab,ti OR nortriptylin:ab,ti OR nortriptiline:ab,ti OR nortriptilin:ab,ti OR aventyl:ab,ti OR sensival:ab,ti OR noxiptilin:ab,ti OR opipramol:ab,ti OR insidon:ab,ti OR protriptyline:ab,ti OR tianeptine:ab,ti OR trimipramine:ab,ti OR surmontil:ab,ti

#5. 'opiate'/exp OR 'opiate agonist'/de OR 'codeine'/exp OR 'morphine'/exp OR 'pholcodine'/exp OR opioid:ab,ti OR opioids:ab,ti OR opium:ab,ti OR opiate:ab,ti OR opiates:ab,ti OR morphine:ab,ti OR morphia:ab,ti OR codeine:ab,ti OR pholcodine:ab,ti

#6. #2 or #3 or #4 or #5

#7. #1 AND #6

#8. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#9. #7 AND #8

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Pregabalin] explode all trees

#8. MeSH descriptor: [Antidepressive Agents, Tricyclic] explode all trees

#9. MeSH descriptor: [Amitriptyline] explode all trees

#10. MeSH descriptor: [Clomipramine] explode all trees

#11. MeSH descriptor: [Desipramine] explode all trees

#12. MeSH descriptor: [Dothiepin] explode all trees

#13. MeSH descriptor: [Doxepin] explode all trees

#14. MeSH descriptor: [Imipramine] explode all trees

#15. MeSH descriptor: [Iprindole] explode all trees

#16. MeSH descriptor: [Lofepramine] explode all trees

#17. MeSH descriptor: [Nortriptyline] explode all trees

#18. MeSH descriptor: [Opipramol] explode all trees

#19. MeSH descriptor: [Protriptyline] explode all trees

#20. MeSH descriptor: [Trimipramine] explode all trees

#21. MeSH descriptor: [Analgesics, Opioid] explode all trees

#22. MeSH descriptor: [Opium] explode all trees

#23. MeSH descriptor: [Opiate Alkaloids] this term only

#24. MeSH descriptor: [Morphine] explode all trees

#25. MeSH descriptor: [Codeine] explode all trees

#26. pregabalin or lyrica:ti,ab,kw (Word variations have been searched)

#27. gabapentin or neurontin:ti,ab,kw (Word variations have been searched)

#28. (tricyclic and (antidepressant or antidepressants or antidepressive)) or Amitriptyline or Amitriptylin or Amitriptiline or Amitriptilin or Elavil or Clomipramine or Chlomipramine or Chlorimipramine or Anafranil or Cyclobenzaprine or Flexeril or Desipramine or Desmethylimipramine or Demethylimipramine or Norpramin or Pertofrane or Desmethyldoxepin or Dibenzepin or Noveril or Dothiepin or Dosulepin or Prothiaden or Doxepin or Sinequan or Imipramine or Melipramine or Tofranil or Iprindole or Lofepramine or Melitracene or Metapramine or Mirtazapine or Remeron or Nortriptyline or Nortriptylin or Nortriptiline or Nortriptilin or Aventyl or Sensival or Noxiptilin or Opipramol or insidon or Protriptyline or Tianeptine or Trimipramine or Surmontil:ti,ab,kw (Word variations have been searched)

#29. opioid or opioids or opium or opiate or opiates or Morphine or morphia or codeine or pholcodine:ti,ab,kw (Word variations have been searched)

#30. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

#32. #6 and #30

#33. #32 in Trials

Question 7: Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Rehabilitation of Speech and Language Disorders"[Mesh] OR "Speech-Language Pathology"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR (“speech pathology”[TIAB] OR “speech therapy”[TIAB] OR “speech therapist”[TIAB] OR “speech pathologist”[TIAB] OR “speech rehabilitation”[TIAB] OR “speech disorder”[TIAB] OR “language pathology”[TIAB] OR “language therapy”[TIAB] OR “language therapist”[TIAB] OR “language pathologist”[TIAB] OR “language rehabilitation”[TIAB] OR physiotherapy[TIAB] OR physiotherapist[TIAB] OR “physical therapy”[TIAB] OR “physical therapist”[TIAB] OR neurophysiotherapy[TIAB] OR neurophysiotherapist[TIAB])

#3. #1 AND #2

#4. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#5. #3 AND #4

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'speech and language rehabilitation'/exp OR 'speech language pathologist'/exp OR 'speech disorder'/exp OR 'physiotherapy'/exp OR ‘speech pathology’:ab,ti OR ‘speech therapy’:ab,ti OR ‘speech therapist’:ab,ti OR ‘speech pathologist’:ab,ti OR ‘speech rehabilitation’:ab,ti OR ‘speech disorder’:ab,ti OR ‘language pathology’:ab,ti OR ‘language therapy’:ab,ti OR ‘language therapist’:ab,ti OR ‘language pathologist’:ab,ti OR ‘language rehabilitation’:ab,ti OR physiotherapy:ab,ti OR physiotherapist:ab,ti OR ‘physical therapy’:ab,ti OR ‘physical therapist’:ab,ti OR neurophysiotherapy:ab,ti OR neurophysiotherapist:ab,ti

#3. #1 AND #2

#4. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#5. #3 AND #4

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Rehabilitation of Speech and Language Disorders] explode all trees

#8. MeSH descriptor: [Speech-Language Pathology] explode all trees

#9. MeSH descriptor: [Physical Therapy Modalities] explode all trees

#10. "speech pathology" or "speech therapy" or "speech therapist" or "speech pathologist" or "speech rehabilitation" or "speech disorder" or "language pathology" or "language therapy" or "language therapist" or "language pathologist" or "language rehabilitation" or physiotherapy or physiotherapist or "physical therapy" or "physical therapist" or neurophysiotherapy or neurophysiotherapist:ti,ab,kw (Word variations have been searched)

#11. #7 OR #8 OR #9 OR #10

#12. #6 AND #11

#13. #12 in Trials

Question 8: Should a trial of antibiotics be used in children with chronic wet cough with normal chest x ray, normal spirometry and no warning signs?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Amoxicillin"[Mesh] OR "Clavulanic Acids"[Mesh] OR "Erythromycin"[Mesh:NoExp] OR "Clarithromycin"[Mesh]

#3. amoxicillin[TIAb] OR amoxycillin[TIAB] OR clavulanate[TIAB] OR “clavulanic acids”[TIAB] OR “clavulanic acid”[TIAB] OR augmentin[TIAB] OR co-amoxiclav[TIAB] OR coamoxiclav[TIAB] OR erythromycin[TIAB] OR clarithromycin[TIAB]

#4. #2 OR #3

#5. #1 AND #4

#6. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#7. #5 AND #6

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'amoxicillin'/exp OR 'clavulanic acid'/exp OR 'amoxicillin plus clavulanic acid'/exp OR 'erythromycin'/exp OR 'clarithromycin'/exp

#3. amoxicillin:ab,ti OR amoxycillin:ab,ti OR clavulanate:ab,ti OR 'clavulanic acids':ab,ti OR 'clavulanic acid':ab,ti OR augmentin:ab,ti OR 'co amoxiclav':ab,ti OR coamoxiclav:ab,ti OR erythromycin:ab,ti OR clarithromycin:ab,ti

#4. #2 OR #3

#5. #1 AND #4

#6. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#7. #5 AND #6

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Amoxicillin] explode all trees

#8. MeSH descriptor: [Clavulanic Acids] explode all trees

#15. MeSH descriptor: [Erythromycin] this term only

#16. MeSH descriptor: [Clarithromycin] explode all trees

#22. amoxicillin or amoxycillin or clavulanate or "clavulanic acids" or "clavulanic acid" or augmentin or co-amoxiclav or coamoxiclav or erythromycin or clarithromycin:ti,ab,kw (Word variations have been searched)

#23. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

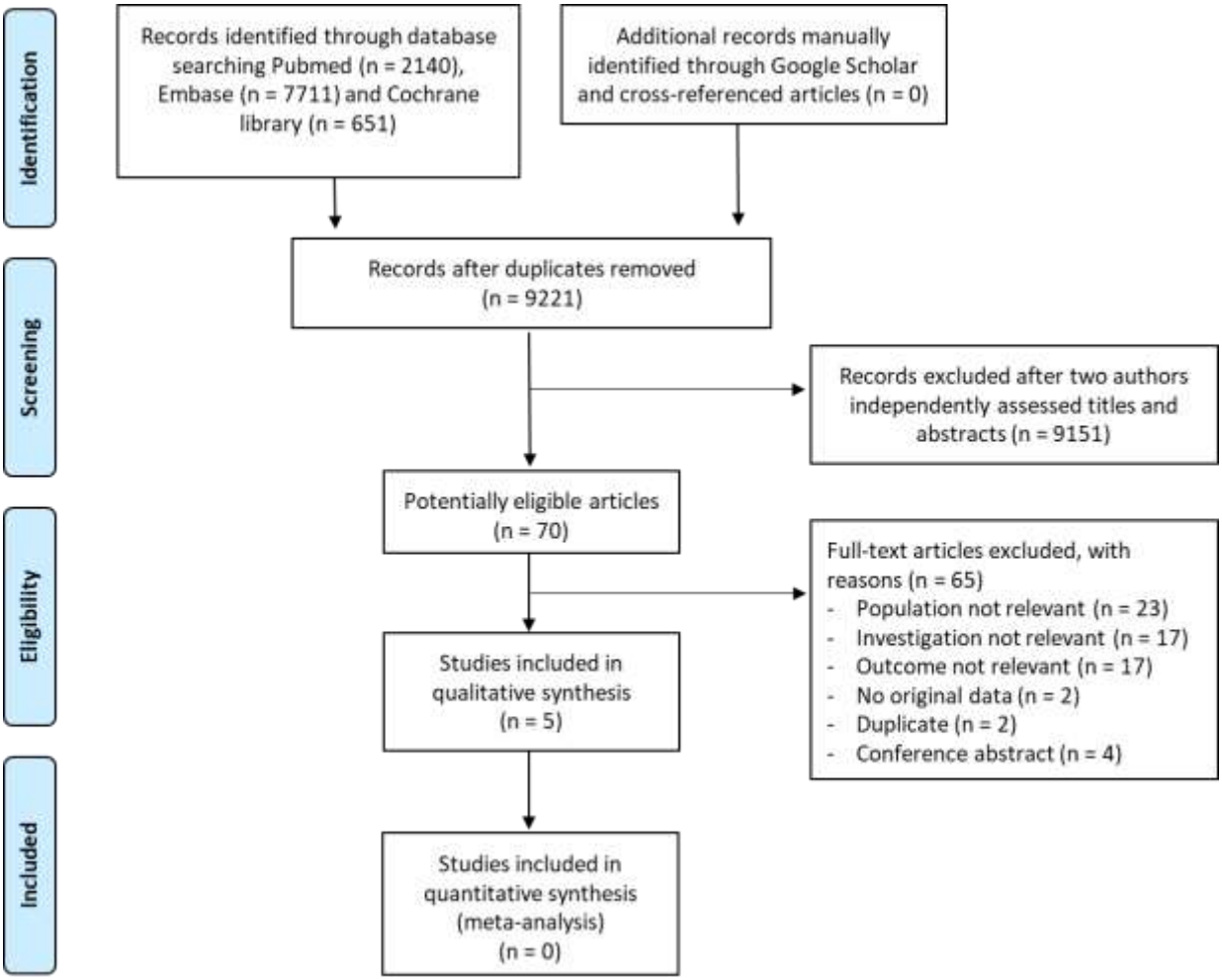
#24. #6 AND #23

#25. #24 in Trials

4. PRIMSA flow diagrams

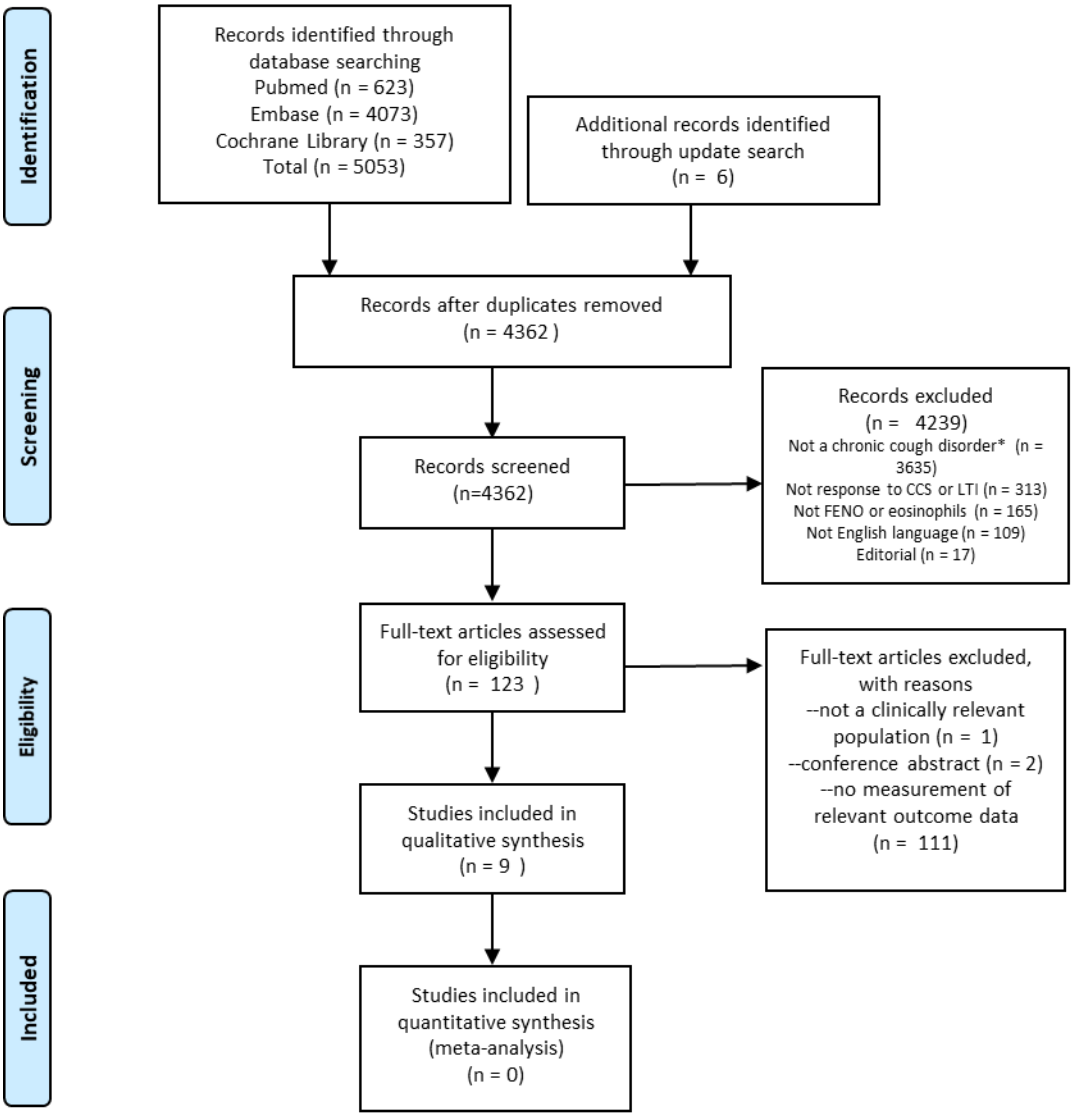
Question 1: Should chest CT be routinely performed on chronic cough patient with normal chest X-ray and physical examination?

Last search: June 2018



Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

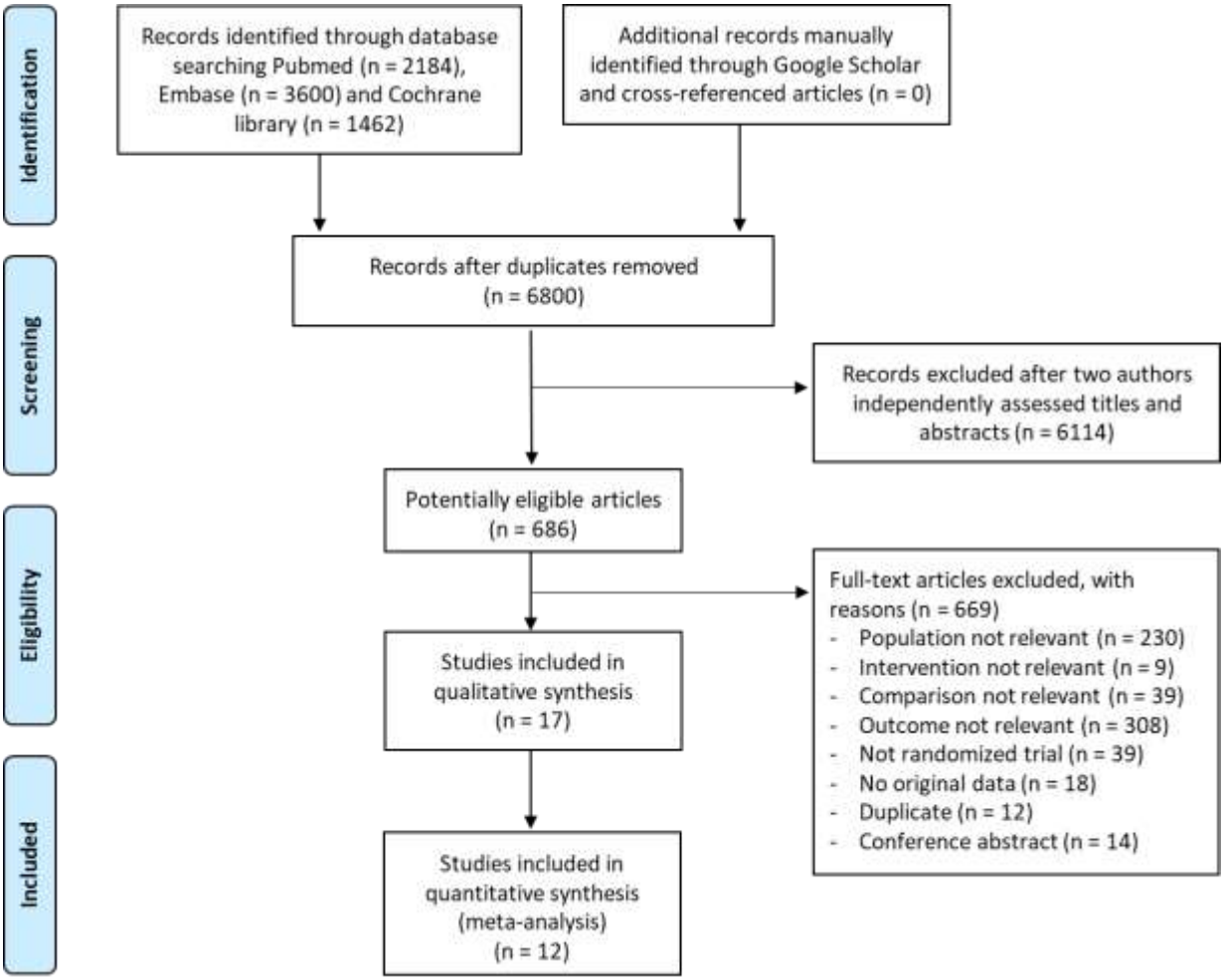
Last search: June 2018



* Included conditions: chronic cough, cough variant asthma, eosinophilic bronchitis, chronic bronchitis, atopic cough, psychogenic cough, cough hypersensitivity syndrome. Asthma and COPD were included if: cough was mentioned as a key feature AND diagnostic criteria/terminology were non-specific AND interventions/outcomes were relevant.

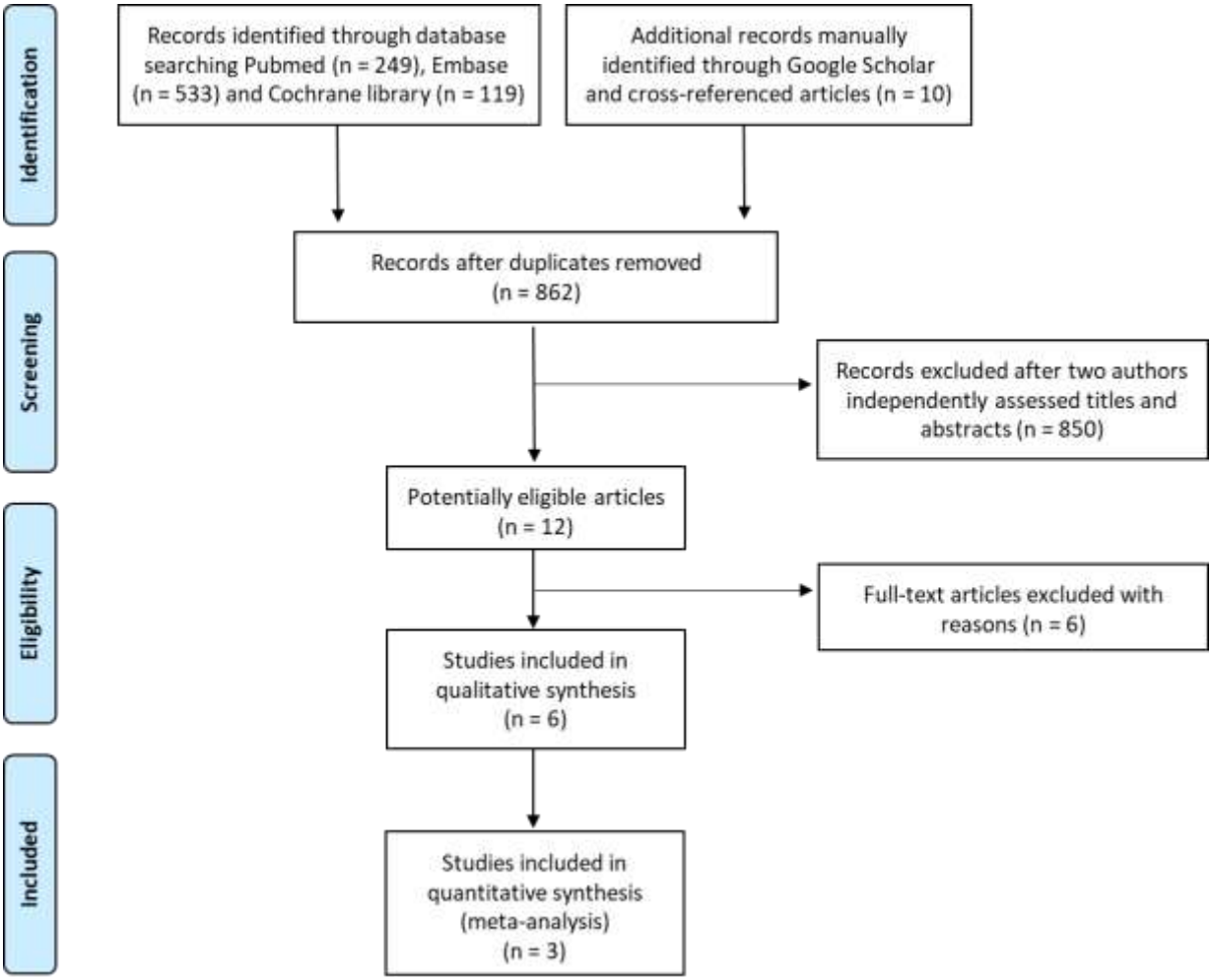
Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

Last search: June 2018



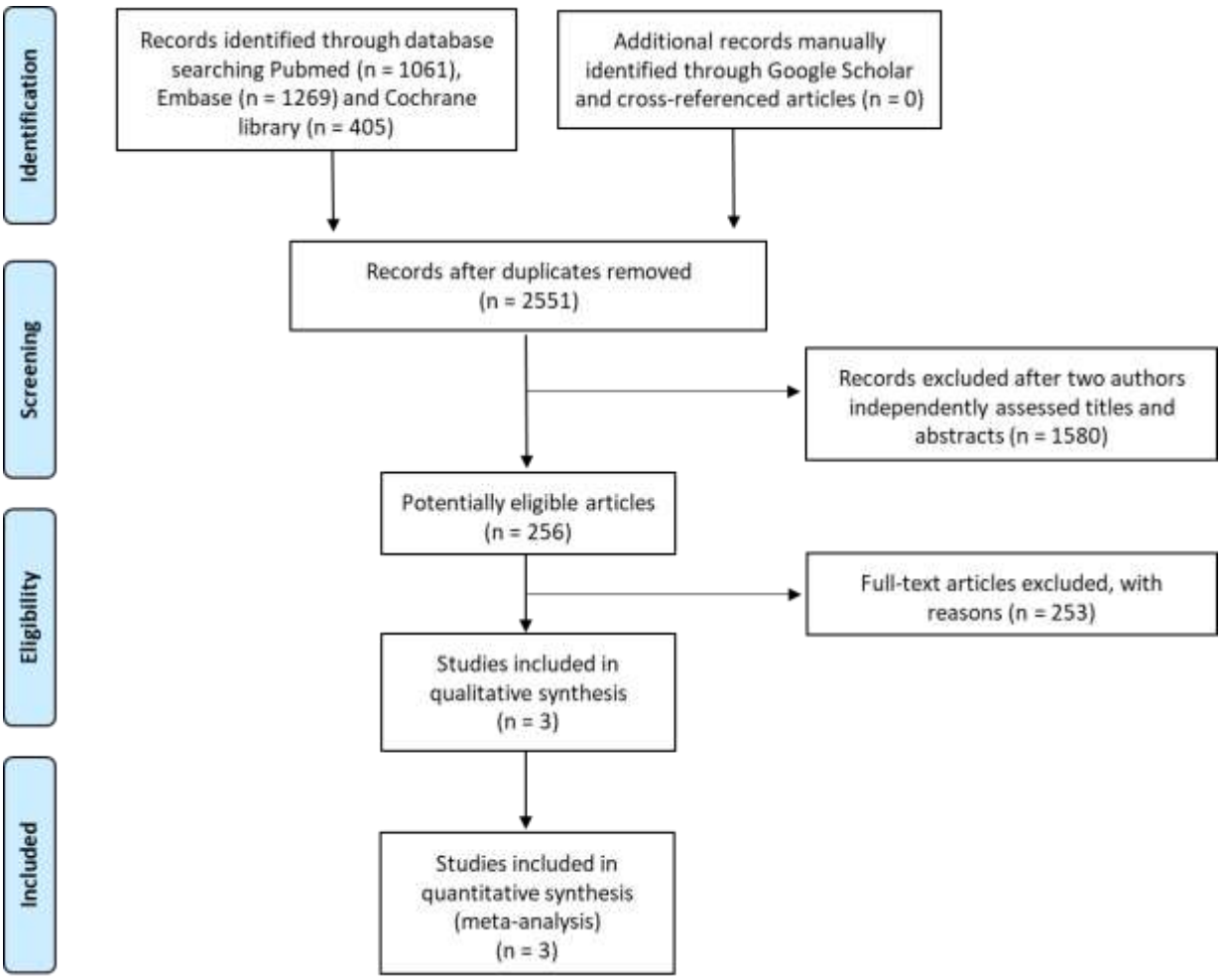
Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

Last search: June 2018



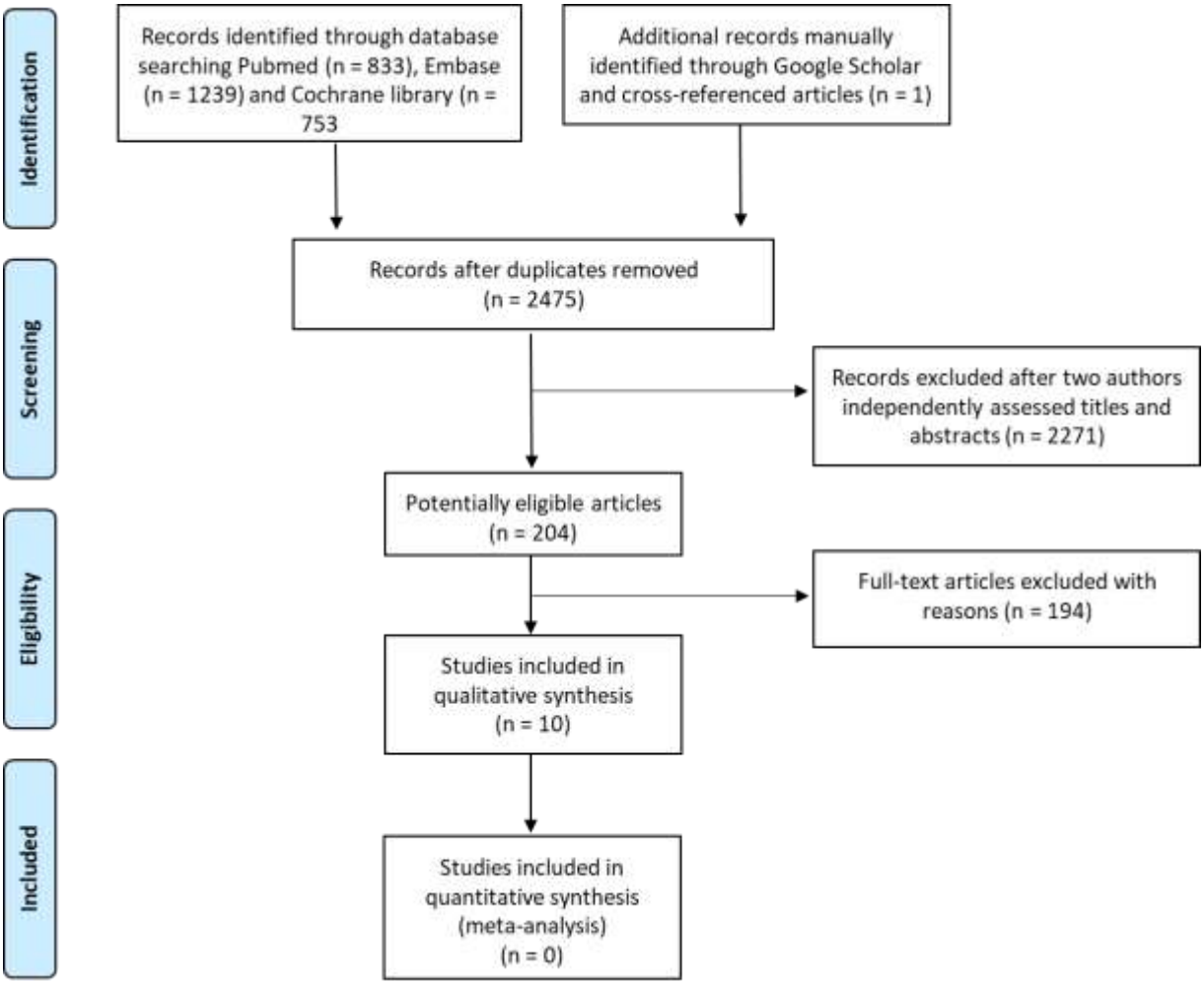
Question 5: Should drugs with pro-motility activity (reflux inhibitors, prokinetics and macrolides with pro-motility activity) be used to treat patients with chronic cough?

Last search: June 2018



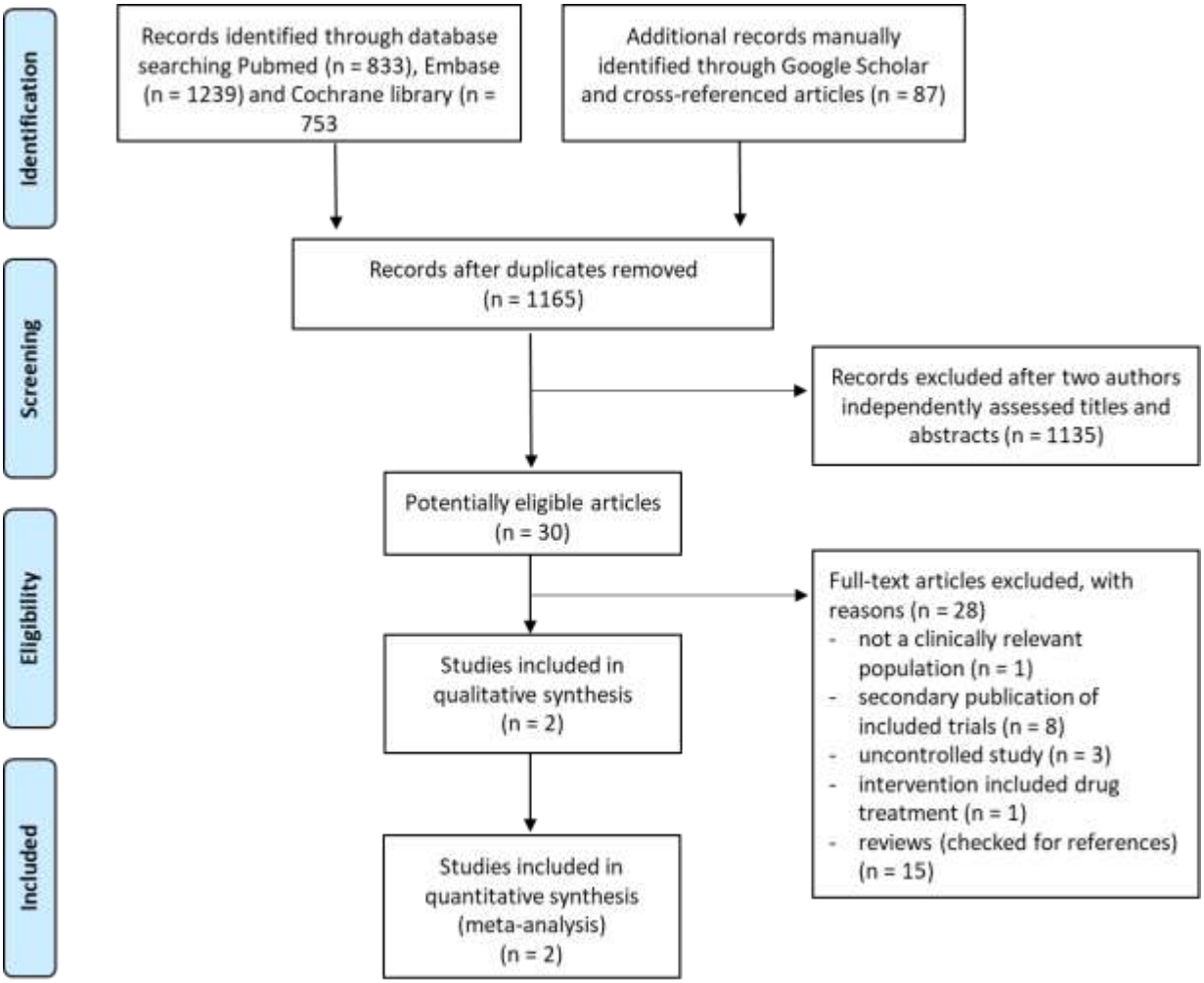
Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Last search: June 2018



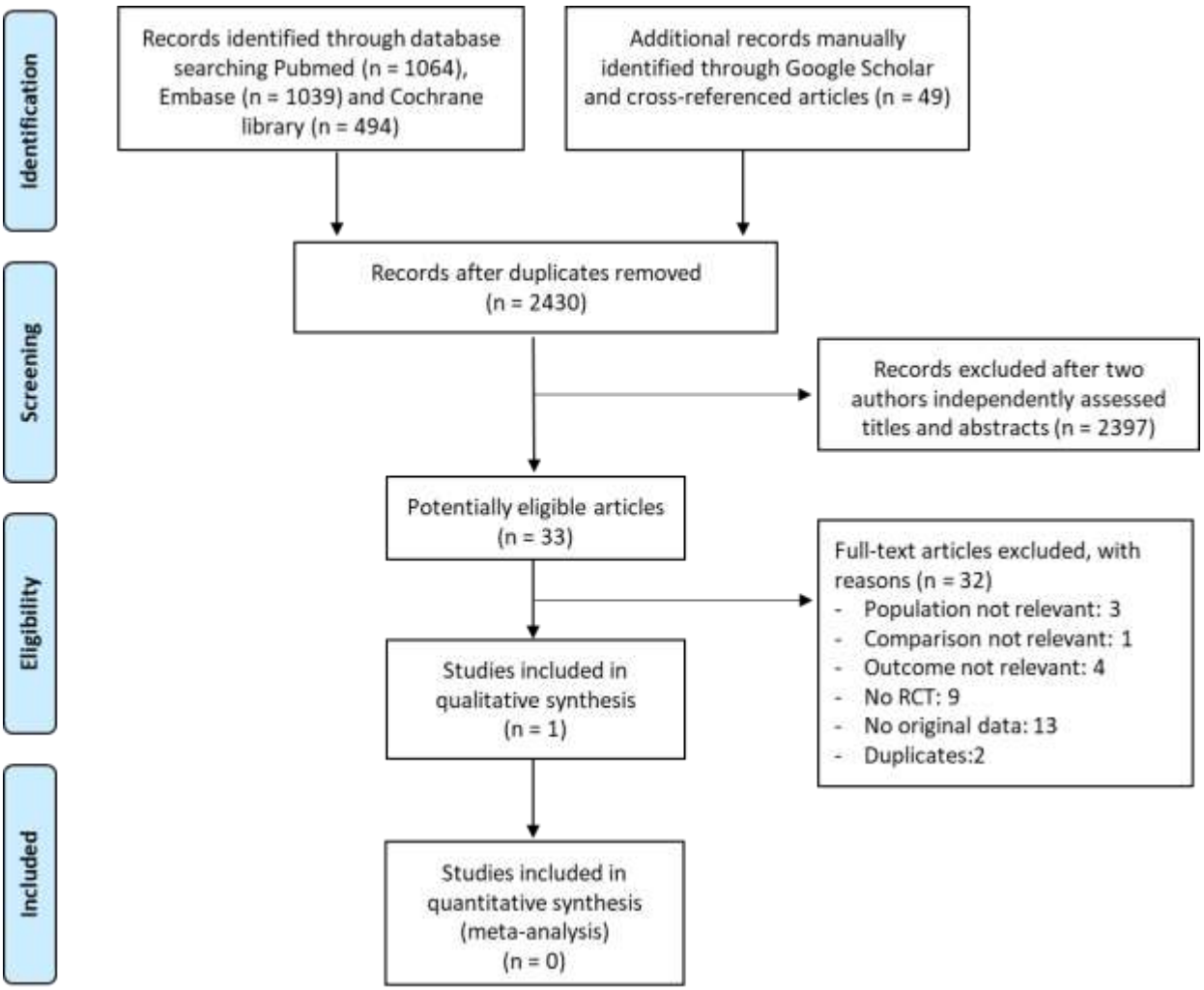
Question 7: Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

Last search: June 2018



Question 8: Should a trial of antibiotics be used in children with chronic wet cough with normal chest x ray, normal spirometry and no warning signs?

Last search: June 2018



5. Evidence GRADE profiles

Question 1: Should chest CT be routinely performed on chronic cough patient with normal chest X-ray and physical examination?

Summary of finding table including GRADE assessment (GRADE Evidence Profile).

Quality assessment							Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic yield									
4 [1,2,3,4]	Observational	serious [a]	serious [b]	serious [c]	serious [d]	none	**Prospective study:** - Kastelik 2005: 3 out of 46 (6.5%) CT findings despite normal chest X-rays (specific findings were not described; causal relationship of each finding was not specified) **Retrospective studies:** - McGarvey 1998: 20 out of 34 (58%) CT findings despite normal chest X-rays (specific findings were not described; causal relationship of each finding was not specified) - Barnes 2004: 9 out of 21 (43%) CT findings despite normal chest X-rays (none were likely to explain cough) - Truba 2018: 21 out of 59 (36%) CT findings despite normal chest X-rays. (Causal relationship of each finding was not specified)	⊕◯◯◯ **VERY LOW**	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

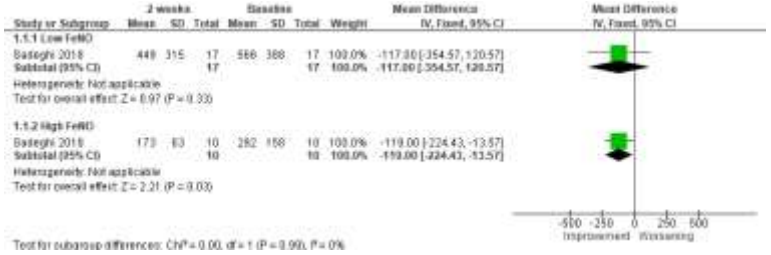
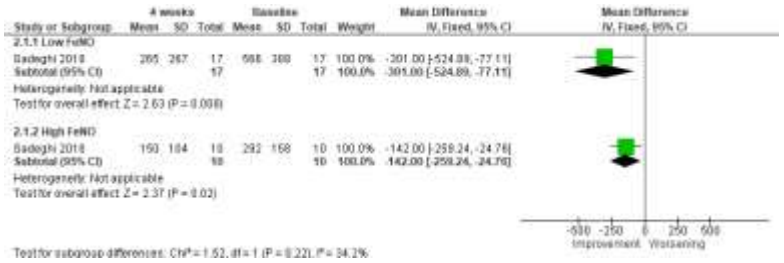
a. In most of studies CT scan was only performed in a subgroup of patients (about half of them)
b. Rate of positive findings varied broadly (from 6.5% to 58%)
c. Diagnostic yield / diagnostic accuracy are indirect findings of the effectiveness of CT scan on patients' important outcomes
d. Specific findings o causal relationship not described or not likely to explain the cough, the impact on final patient management and outcomes in comparison to not performing CT is not known.

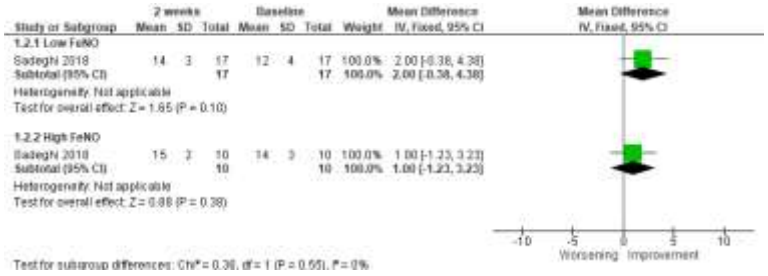
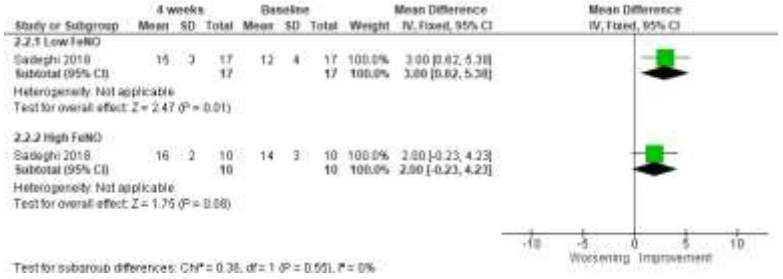
References

1. Kastelik JA, Aziz I, Ojoo JC, Thompson RH, Redington AE, Morice AH. Investigation and management of chronic cough using a probability-based algorithm. Eur Respir J. 2005 Feb;25(2):235-43.
2. Barnes TW, Afessa B, Swanson KL, Lim KG. The clinical utility of flexible bronchoscopy in the evaluation of chronic cough. Chest. 2004 Jul;126(1):268-72.
3. Truba O, Rybka A, Klimowicz K, Grabczak EM, Żukowska M, Dąbrowska M, Krenke R. Is a normal chest radiograph sufficient to exclude pulmonary abnormalities potentially associated with chronic cough? Adv Respir Med. 2018;86(3).
4. McGarvey LP, Heaney LG, Lawson JT, Johnston BT, Scally CM, Ennis M, Shepherd DR, MacMahon J. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. Thorax. 1998 Sep;53(9):738-43.

Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - ANTI-LEUKOTRIENES

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FeNO measurement**	**no FeNO measurement**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cough frequency: 24-hours cough count at 2 weeks												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	24-hours cough count at 2 weeks decreased in both groups (low and high FeNO at baseline) without differences between them: -117.00 [95%CI -354.57 to 120.57] and -119.00 [95%CI -224.43, -13.57] respectively 				⊕⊕◯◯ **LOW**	CRITICAL
Cough frequency: 24-hours cough count at 4 weeks												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	24-hours cough count at 4 weeks decreased in both groups (low and high FeNO at baseline) without differences between them: -301.00 [95%CI -524.89 to -77.11] and -142.00 [95%CI -259.24 to -24.76] respectively 				⊕⊕◯◯ **LOW**	CRITICAL

Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points; Follow up: 2 weeks									
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	LCQ score at 2 weeks improved in both groups (low and high FeNO at baseline) without differences between them: 2.00 [95%CI -0.38 to 4.38] and 1.00 [95%CI -1.23 to 3.23] respectively 	⊕⊕◯◯ **LOW**	CRITICAL
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points; Follow up: 4 weeks									
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	LCQ score at 4 weeks improved in both groups (low and high FeNO at baseline) without differences between them: 3.00 [95%CI 0.62 to 5.38] and 2.00 [95%CI -0.23 to 4.23] respectively 	⊕⊕◯◯ **LOW**	CRITICAL

CI: Confidence interval

Explanations

a. Patients with low FeNO levels (<20ppb) received montelukast 10 mg (28 days); patients with high FeNO levels (>30ppb) were randomised to receive prednisolone+montelukast or montelukast 10 mg (28 days). Only patients receiving montelukast were considered in the analysis, thus one arm was not randomised. Baseline characteristics were not similar between groups (higher percentage of females in low FeNO levels)

b. Very limited sample size, wide 95%CI making difficult to detect subgroup differences.

References

1. Sadeghi MH, Wright CE,Hart S,Crooks M,Morice A.. Phenotyping patients with chronic cough: evaluating the ability to predict the response to anti-inflammatory therapy.. Ann Allergy Asthma Immunol; 2018.

Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - CORTICOSTEROIDS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Responders**	**Non-responders**	**Relative (95% CI)**	**Absolute (95% CI)**		
FeNO levels (follow up: range 4 weeks to 24 weeks; assessed with: difference between responders and non responders)												
3 [1,2,3]	observational studies	not serious	not serious [a]	very serious [b,c]	serious [d]	none	113	86	-	MD **23.31 ppb fewer** (39.35 fewer to 7.27 fewer)	⊕◯◯◯ **VERY LOW**	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Although the analysis shows significant variability among effect estimates one study (Prieto 2009) contributes to most of the heterogeneity. This study assessed treatment response using he most objective score (>50% reduction in daily cough symptom score)
b. Studies show considerable heterogeneity in definition of 'high' versus 'low' FeNO (thresholds range from 16.3 to 38.0 ppb); ICS prescribing criteria, dose, and duration; and definition of treatment response
c. Indirect measure for predictive value of FeNO
d. Lower 95%CI (-7.27 ppb) probably does not allow discriminate populations and is not clinically meaningful.

References

1. Watanabe K, Shinkai M,Shinoda M,Hara Y,Yamaguchi N,Rubin BK. Measurement of eNO with portable analyser might improve the management of persistent cough at primary care practice in Japan. Clin Respir J; 2016.

2. Prieto L, Ferrer A,Ponce S,Palop J,Marin J.. Exhaled nitric oxide measurement is not useful for predicting the response to inhaled corticosteroids in subjects with chronic cough. Chest; 2009.

3. Hahn PY, Morgenthaler TI,Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. Mayo Clin Proc; 2007.

Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - LTRA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Placebo**	**LTRA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cough severity and frequency 'combined': mean change at 2 weeks in cough score from baseline (patient completed score: 0 [no cough] - 10 [cough as bad as it has ever been1 or as bad as at the first visit2])												
2 [1,2]	randomised trials	very serious [a]	serious [b]	serious [c]	very serious [d]	none	16	27	-	MD **3.10 lower** (6.20 lower to 0.01 higher)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Cough frequency (number of coughs/day): mean change at 1 week of daily cough frequency from baseline; assessed with: recorded objectively with an audio cough meter.												
1 [3]	randomised trials	not serious	not serious	not serious	very serious [d]	none	6	8	-	MD **29.63 lower** (93.73 lower to 34.47 higher)	⊕⊕◯◯ **LOW**	CRITICAL
Cough frequency (number of coughs/day): mean change at 4 week of daily cough frequency from baseline; assessed with: recorded objectively with an audio cough meter.												
1 [3]	randomised trials	not serious	not serious	not serious	serious [e]	none	6	8	-	MD **144.06 lower** (219.39 to 68.73 lower)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Improvement in quality of life (not further specified)												
1 [3]	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/6 (33%)	8/8 (100%)	**OR 2.64** (0.97 to 7.23)	**547 more per 1.000** (10 fewer to 2.077 more)	⊕⊕◯◯ **LOW**	IMPORTANT
Any adverse events: (any adverse or unusual experiences) documented by patients on a diary card at each visit												
1 [3]	randomised trials	not serious	not serious	not serious	very serious [d]	none	0/6 (0%)	0/8 (0%)	-	-	⊕⊕◯◯ **LOW**	IMPORTANT

CI: confidence interval; **CVA**: cough-variant asthma; **LTRA**: leukotriene receptor antagonist; **MD**: mean difference; **RD**: risk difference; **RR**: risk ratio.

Explanations

a. Very high risk of selection bias and probably lack of blinding in one study.
b. Confidence intervals show only minimal overlap and high I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large).
c. Regarding the population of interest, the study population also includes patients with CVA and chronic atopic cough.
d. Low number of patients and 95% CI consistent with the possibility for benefit and the possibility of harm (dichotomous outcome)
e. Very low number of patients
f. Low number of patients and no events in both groups.

References

1. Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma.* 2002;39(4):291-297.
2. Kita T, Fujimura M, Ogawa H, et al. Antitussive effects of the leukotriene receptor antagonist montelukast in patients with cough variant asthma and atopic cough. *Allergology international : official journal of the Japanese Society of Allergology.* 2010;59(2):185-192.
3. Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2004;93(3):232-236.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – BRONCHODILATORS, ADULT POPULATION

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Placebo**	**Bronchodilator**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cough severity: mean cough score at 52 weeks (patient completed daily score: 0 [no cough] - 3 [severe cough], recording of the previous 24 h before visit at week 52)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	372	-	MD **0.08 lower** (0.16 lower to 0.00 higher)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Day-time cough severity: at 3 weeks; assessed with different scales. Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [2,3]	randomised trials	not serious	serious [b]	not serious	serious [a]	none	43	43	-	SMD **1.63 lower** (3.84 lower to 0.59 higher)	⊕⊕◯◯ **LOW**	IMPORTANT
Night-time cough severity: at 3 weeks; assessed with different scales. Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [2,3]	randomised trials	not serious	serious [b]	not serious	serious [a]	none	43	43	-	SMD **0.98 lower** (1.78 lower to 0.18 lower)	⊕⊕◯◯ **LOW**	IMPORTANT
Generic Quality of life questionnaires - St. George's Respiratory Questionnaire (SGRQ). At 52 weeks. Scores range from 0 to 100, with higher scores indicating more limitations. MID: Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	372	-	MD **2.70 lower** (5.08 lower to 0.32 lower)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Night interruptions: mean change from baseline												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	372	-	MD **0.07 less** (0.93 less to 0.79 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Skin bruises: number of bruises on the volar side of the forearm with a diameter >5 cm												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	22/361 (6.1%)	20/372 (5.4%)	**RR 0.88** (0.49 to 1.59)	**7 Fewer per 1.000** (31 fewer to 36 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Any adverse events: (treatment related adverse events)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	49/361 (13.6%)	46/372 (12.4%)	**RR 0.91** (0.63 to 1.33)	**12 Fewer per 1.000** (50 fewer to 45 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT

CI: confidence interval; **MD**: mean difference; **SMD**: standardized mean difference; **RR**: risk ratio.

Explanations

a. 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect (continuous outcome).
b. Confidence intervals show no overlap and high I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large).

References

4. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet (London, England). 2003;361(9356):449-456.
5. Ellul-Micallef R. Effect of terbutaline sulphate in chronic "allergic" cough. British medical journal (Clinical research ed). 1983;287(6397):940-943.
6. Holmes PW, Barter CE, Pierce RJ. Chronic persistent cough: use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. Respiratory medicine. 1992;86(5):425-29

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – BRONCHODILATORS, CHILDREN POPULATION

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	Bronchodilator	Relative (95% CI)	Absolute (95% CI)		
Cough severity – parent assessment: at 5-7days of treatment; assessed with VAS; Range 0 to 10 points; higher scores indicate better higher severity.												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [a]	none	22	21	-	MD **0.4 lower** (1.93 lower to 1.13 higher)	⊕⊕◯◯ **LOW**	IMPORTANT
Cough severity – parent assessment: at 5-7days of treatment; assessed with VAS; Range 0 to 10 points; higher scores indicate better higher severity.												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [a]	none	22	21	-	MD **0.3 higher** (1.19 lower to 1.79 higher)	⊕⊕◯◯ **LOW**	IMPORTANT
Response to treatment ("treatment success") defined as a ≥70% reduction in cough frequency at 5-7-days.												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [a]	none	5/22 (22.7%)	4/21 (19.0%)	**RR 0.84** (0.26 to 2.70)	**36 Fewer per 1.000** (168 fewer to 386 more)	⊕⊕◯◯ **LOW**	CRITICAL

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio.

Explanations

a. Confidence intervals show no overlap and high I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large).

References

1. Chang AB, Phelan PD, Carlin JB, Sawyer SM, Robertson CF. A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. Archives of disease in childhood. 1998;79(1):6-11.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – ICS, Adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Placebo**	**ICS**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cough severity at 2 weeks– patient with chronic cough; assessed with VAS; Range 0 to 100 points; higher scores indicate better higher severity.												
2 [5,6]	randomised trials	not serious	not serious	not serious	serious [d]	none	111	109	-	MD **8.42 lower** (15.5 lower to 1.34 lower)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Cough frequency at 2 weeks– patient with chronic cough; assessed with patient completed score: 0 [no cough] - 4 [constant cough].												
1 [2]	randomised trials	serious [a]	not serious	not serious	serious [f]	none	20	44	-	MD **1 lower** (1.6 lower to 0.4 lower)	⊕⊕◯◯ **LOW**	CRITICAL
Cough severity – patient with chronic cough: mean cough symptom score up to 8 weeks. Assessed with: different scales. Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.												
3 [1,2,3]	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	none	104	128	-	SMD **0.28 lower** (0.79 lower to 0.23 higher)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Cough severity – patient with chronic bronchitis: mean change in daily cough score (patient completed) from baseline (at 12 weeks): 0 (none), 1 (few coughs every day), 2 (repeated cough attacks, but only in the morning or during the day), 3 (persistent cough attacks during the night and day)												
1 [4]	randomised trials	not serious	not serious	serious [e]	very serious [f]	none	18	18	-	MD **0.03 lower** (0.68 lower to 0.63 higher)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Night interruptions– patient with chronic cough**:** mean change from baseline												
1 [2]	randomised trials	serious [a]	not serious	not serious	very serious [f]	none	20	44	-	MD **0.31 less** (0.81 less to 0.19 more)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Any adverse events– patient with chronic cough												
3 [2,3,6]	randomised trials	serious [a]	not serious	serious [c]	serious [d]	none	44/113 (38.9%)	50/135 (37.0%)	**RR 1.07** (0.83 to 1.38)	**27 more per 1.000** (66 fewer to 148 more)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Any adverse events– patient with chronic bronchitis												
2 [7,8]	randomised trials	very serious [g]	not serious	not serious	very serious [h]	none	0/44 (0%)	1/43 (2.3%)	**RR 3.40** (0.15 to 77.34)	**-**	⊕◯◯◯ **VERY LOW**	IMPORTANT
Major adverse events– patient with chronic cough												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	ICS	Relative (95% CI)	Absolute (95% CI)		
2 [2,3]	randomised trials	serious [a]	not serious	serious [c]	very serious [h]	none	6/90 (6.7%)	5/114 (4.4%)	**RR 0.83** (0.27 to 2.60)	**11 fewer per 1.000** (49 fewer to 107 more)	⊕◯◯◯ **VERY LOW**	IMPORTANT

CI: confidence interval; **ICS**: inhaled corticosteroids; **SMD**: standardized mean difference; **MD**: mean difference; **RD**: risk difference; **RR**: risk ratio.

Explanations

a. High risk of selective reporting.
b. High I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large, I^2 >50%).
c. Patients with airway symptoms suggestive of asthma, without fulfilling the functional criteria of asthma included.
d. 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect.
e. All patients in the study were smokers with bronchitis.
f. Small number of patients; 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect.
g. Very high risk of selection bias.
h. Small number of patients and events; 95% CI was consistent with the possibility of large benefit or large harm.

References

1. Boulet LP, Milot J, Boutet M, St Georges F, Laviolette M. Airway inflammation in nonasthmatic subjects with chronic cough. *American journal of respiratory and critical care medicine.* 1994;149(2 Pt 1):482-489.
2. Ribeiro M, Pereira CA, Nery LE, Beppu OS, Silva CO. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2007;99(1):61-68.
3. Rytila P, Ghaly L, Varghese S, Chung W, Selroos O, Haahtela T. Treatment with inhaled steroids in patients with symptoms suggestive of asthma but with normal lung function. *The European respiratory journal.* 2008;32(4):989-996.
4. Engel T, Heinig JH, Madsen O, Hansen M, Weeke ER. A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. *The European respiratory journal.*1989;2(10):935-939.
5. Chaudhuri R, McMahon AD, Thomson LJ, et al. Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. *The Journal of allergy and clinical immunology.* 2004;113(6):1063-1070.
6. Pizzichini MM, Pizzichini E, Parameswaran K, et al. Nonasthmatic chronic cough: No effect of treatment with an inhaled corticosteroid in patients without sputum eosinophilia. *Canadian respiratory journal.* 1999;6(4):323-330.
7. Kozak-Szkopek EU, W. T. Inhalative Budesonid-Therapie bei chronischer Bronchitis. *Atemwegs- und Lunkenkrankheiten.* 1997;23(9):542-546.
8. Wesseling GJ, Quaedvlieg M, Wouters EF. Inhaled budesonide in chronic bronchitis. Effects on respiratory impedance. *The European respiratory journal.* 1991;4(9):1101-1105.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – ICS, COPD POPULATION

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	ICS	Relative (95% CI)	Absolute (95% CI)		
Cough severity: mean cough score at 52 weeks (patient completed daily score: 0 [no cough] - 3 [severe cough], recording of the previous 24 h before visit at week 52)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	374	-	MD **0.06 lower** (0.14 lower to 0.02 higher)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Generic Quality of life questionnaires - St. George's Respiratory Questionnaire (SGRQ). At 52 weeks. Scores range from 0 to 100, with higher scores indicating more limitations. MID: Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	374	-	MD **3.50 lower** (5.80 lower to 1.20 lower)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Night interruptions: mean change from baseline												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	374	-	MD **0.56 less** (1.35 less to 0.23 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Skin bruises: number of bruises on the volar side of the forearm with a diameter >5 cm												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	22/361 (6.1%)	26/374 (7.0%)	**RR 1.14** (0.66 to 1.98)	**9 more per 1.000** (21 fewer to 60 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Response to treatment ('treatment success'): at 24 weeks; defined as: no cough symptoms												
1 [2]	randomised trials	not serious	not serious	not serious	serious [a]	none	11/139 (7.9%)	26/142 (18.3%)	**RR 2.31** (1.19 to 4.50)	**104 more per 1.000** (15 to 277 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Exacerbations: number of patients with exacerbations up to 52 weeks.												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious [a]	none	70/500 (14.0%)	55/516 (10.7%)	**RR 0.74** (0.46 to 1.20)	**36 fewer per 1.000** (76 fewer to 28 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Any adverse events: up to 52 weeks												
2 [1,2]	randomised trials	not serious	serious [b]	not serious	serious [a]	none	144/500 (28.8%)	161/516 (31.2%)	**RR 1.11** (0.73 to 1.68)	**32 more per 1.000** (78 fewer to 196 more)	⊕⊕◯◯ **LOW**	IMPORTANT

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio.

Explanations

c. 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect (continuous outcome).
d. confidence intervals show only minimal overlap and high I² (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large,

I^2 >50%).

References

7. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet (London, England). 2003;361(9356):449-456.
8. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo- controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. Lancet (London, England). 1998;351(9105):773-780.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – BRONCHODILATORS +ICS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	Bronchodilators +ICS	Relative (95% CI)	Absolute (95% CI)		
Cough severity: mean cough score at 52 weeks (patient completed daily score: 0 [no cough] - 3 [severe cough], recording of the previous 24 h before visit at week 52)												
1 [1]	randomised trials	not serious	not serious	serious [a]	serious [b]	none	361	358	-	MD **0.09 lower** (0.17 lower to 0.01 lower)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Generic Quality of life questionnaires - St. George's Respiratory Questionnaire (SGRQ). At 52 weeks. Scores range from 0 to 100, with higher scores indicating more limitations. MID: Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	358	-	MD **2.20 lower** (4.55 lower to 0.15 higher)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Night interruptions: mean change from baseline												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	358	-	MD **0.00 less** (0.8 less to 0.8 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Skin bruises: number of bruises on the volar side of the forearm with a diameter >5 cm												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	22/361 (6.1%)	29/358 (8.1%)	**RR 1.33** (0.78 to 2.27)	**20 more per 1.000** (13 fewer to 77 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Any adverse events: (treatment related adverse events)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	49/361 (13.6%)	58/358 (16.2%)	**RR 0.48** (0.22 to 1.04)	**27 Fewer per 1.000** (41 fewer to 2 more)	⊕⊕⊕◯ **MODERATE**	IMPORTANT

CI: confidence interval; **MD**: mean difference; **SMD**: standardized mean difference; **RR**: risk ratio.

Explanations

a. Duration of intervention was
b. 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect (continuous outcome).

References

9. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet (London, England). 2003;361(9356):449-456.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – ICS, Children

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS	Placebo	Relative (95% CI)	Absolute (95% CI)		
Nocturnal cough frequency: mean change from baseline (objectively recorded) - At nights 15/16												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	26	24	-	MD **60 lower** (85.45 lower to 34.55 lower)	⊕⊕◯◯ LOW	
Cough severity: mean change from baseline (VAS score averaged over 1 week, at 4-5 weeks) - Parent completed												
1 [2]	randomised trials	serious [a]	not serious	not serious	serious [c]	none	22	21	-	MD **0.6 higher** (0.6 lower to 1.8 higher)	⊕⊕◯◯ LOW	
Cough severity: mean change from baseline (VAS score averaged over 1 week, at 4-5 weeks) - Child completed												
1 [2]	randomised trials	serious [a]	not serious	not serious	serious [c]	none	22	21	-	MD **0.6 higher** (0.53 lower to 1.73 higher)	⊕⊕◯◯ LOW	
Response to treatment ('treatment succes') - Defined as a ≥75% reduction in nocturnal cough frequencys (at nights 15/16)												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [d]	none	17/26 (65.4%)	8/24 (33.3%)	**RR 1.96** (1.04 to 3.69)	**320 more per 1,000** (from 13 more to 897 more)	⊕⊕◯◯ LOW	
Response to treatment ('treatment succes') - Defined as a ≥70% reduction in 24 h cough frequency (at 4/5 weeks)												
1 [2]	randomised trials	serious [a]	not serious	not serious	very serious [d,e]	none	12/22 (54.5%)	14/21 (66.7%)	**RR 0.82** (0.50 to 1.33)	**120 fewer per 1,000** (from 333 fewer to 220 more)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Potential risk of carry-over effect, uncertainties in missinbg data and randomisation.

b. 95% CI was consistent with the possibility of improving and the possibility of no effect.

c. 95% CI was consistent with the possibility of worsening symptoms or no effect.

d. Low number of events and patients included

e. 95%CI was consistent with appreciable benefit or harm

References

1. Davies MJ, Fuller P, Picciotto A, McKenzie SA. Persistent nocturnal cough: randomised controlled trial of high dose inhaled corticosteroid. Arch Dis Child. 1999 Jul;81(1):38-44.
2. Chang AB, Phelan PD, Carlin JB, Sawyer SM, Robertson CF. A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. Arch Dis Child. 1998 Jul;79(1):6-11.

Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - Adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acid suppression therapy**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cough severity (different scales). Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
4 [1,2,3,4]	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	74	63	-	SMD **0.63 lower** (1.37 lower to 0.1 higher)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Cough frequency (different scales). Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [2,3]	randomised trials	serious [d]	not serious	not serious	serious [c]	none	46	43	-	SMD **0.18 lower** (0.6 lower to 0.23 higher)	⊕⊕◯◯ **LOW**	IMPORTANT
Quality of life specific questionnaires (different scales). Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
3 [2,3,4]	randomised trials	serious [e]	not serious	not serious	serious [c]	none	65	51	-	SMD **0.72 SD lower** (1.3 lower to 0.13 lower)	⊕⊕◯◯ **LOW**	CRITICAL
Tussive response to cough challenge. Assessed with: Citric acid cough challenge												
1 [2]	randomised trials	not serious	not serious	Serious [f]	serious [g]	none	There were no differences between treatment and placebo groups in the change from baseline concentration on inhaled citric acid (to trigger cough). Log C2; between-group p value 0.66 Log C5; between-group p value 0.57.				⊕⊕◯◯ **LOW**	IMPORTANT
Adverse events												
3 [2,3,4]	randomised trials	serious [e]	not serious	not serious	serious [h]	none	3 RCTs reported few adverse events with a similar incidence between intervention and placebo group. Faruqi: treatment 4/24 (17%) versus placebo 2/25 (8%) respiratory tract infection; Shaheen: no serious events/withdrawns in both groups; Park: treatment 2/19 (11%, both from high-dose group) urticaria versus placebo 2/8 (25%) 1 urticaria and 1 palpitation				⊕⊕◯◯ **LOW**	IMPORTANT

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. 3 studies: non-validated subjective outcome measures; 1 study (Kiljander) no description on the number of dropouts according to treatment group or period; 1 study (Park): high drop-out rate (30%); 1 study (Park): significant different baseline characteristics and different dropout rates between groups

b. Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 11.70$, df = 3 (P = 0.008); $I^2 = 74\%$

c. SMD >0.5 and <0.8 representing a moderate difference

d. All studies: non-validated subjective outcome measures

e. 1 study (Park): high drop-out rate (30%); 1 study (Park): significant different baseline characteristics and different dropout rates between groups

f. Indirect (surrogate) measure of efficacy

g. single study with small sample size

h. Low number of patients and events

References

1. Kiljander TO1, Salomaa ER, Hietanen EK, Terho EO. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. Eur Respir J. 2000 Oct;16(4):633-8.
2. Faruqi S, Molyneux ID, Fathi H, Wright C, Thompson R, Morice AH. Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study. Respirology. 2011 Oct;16(7):1150-6.
3. Shaheen NJ, Crockett SD, Bright SD, Madanick RD, Buckmire R, Couch M, Dellon ES, Galanko JA, Sharpless G, Morgan DR, Spacek MB, Heidt-Davis P, Henke D. Randomised clinical trial: high-dose acid suppression for chronic cough - a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011 Jan;33(2):225-34.
4. Park HJ, Park YM, Kim JH, Lee HS, Kim HJ, Ahn CM, Byun MK. Effectiveness of proton pump inhibitor in unexplained chronic cough. PLoS One. 2017 Oct 10;12(10):e0185397

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - Children

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acid suppression therapy	Placebo	Relative (95% CI)	Absolute (95% CI)		
Daytime cough frequency. Assessed with : episodes/day												
1 [1]	randomised trials	serious [a]	not serious	not serious	Very serious [b]	none	4	4	-	MD **2.70 fewer** (3.85 fewer to 1.55 fewer)	⊕◯◯◯ **VERY LOW**	CRITICAL
Night-time cough frequency. Assessed with : episodes/night												
1 [1]	randomised trials	serious [a]	not serious	not serious	Very serious [b]	none	4	4	-	MD **0.20 fewer** (0.56 fewer to 0.16 more)	⊕◯◯◯ **VERY LOW**	CRITICAL
Adverse event												
1	randomised trials	serious [a]	not serious	not serious	Very serious [b]	none	No adverse events reported by parents in both treatment and placebo group				⊕◯◯◯ **VERY LOW**	IMPORTANT

CI: Confidence interval

Explanations

a. non-validated subjective outcome measures; observer bias; unknown number of dropouts in treatment group

b. small groups (n=4)

References

1. Adamko DJ, Majaesic CM, Skappak C, Jones AB. A pilot trial on the treatment of gastroesophageal reflux-related cough in infants. Transl Pediatr. 2012 Jul;1(1):23-34.

Question 5: Should drugs with pro-motility activity (reflux inhibitors, prokinetics and macrolides with pro-motility activity) be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Macrolides**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
3 [1,2,3]	randomised trials	not serious	not serious	serious [a]	serious [b]	none	74	77	-	MD **1.27 higher** (2.09 higher to 0.45 higher)	⊕⊕◯◯ **LOW**	CRITICAL
Cough severity (VAS or severity score). Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [1,3]	randomised trials	not serious	not serious	not serious	serious [b]	none	36	36	-	SMD **0.42 lower** (0.89 lower to 0.05 higher)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Cough frequency at 12 weeks (number of coughs/24h)												
1 [1]	randomised trials	not serious	not serious [c]	not serious	serious [d]	none	Mean difference in fold change 1.1 (95% CI 0.7 to 1.5)				⊕⊕⊕◯ **MODERATE**	CRITICAL
Capsaicin C2 at 12 weeks												
1	randomised trials	not serious	not serious [d]	serious [e]	serious [d]	none	Mean difference in fold change 0.7 (95% CI 0.4 to 1.3)				⊕⊕◯◯ **LOW**	IMPORTANT
Capsaicin C5 at 12 weeks												
1	randomised trials	not serious	not serious [d]	serious [e]	serious [d]	none	Mean difference in fold change 1.3 (95% CI 0.9 to 2.0)				⊕⊕◯◯ **LOW**	IMPORTANT
Generic Quality of life questionnaires - St. George's Respiratory Questionnaire (SGRQ). Scores range from 0 to 100, with higher scores indicating more limitations. MID: Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment												
1	randomised trials	not serious	not serious [d]	serious [a]	serious [b]	none	Mean difference in fold change -7.5 (95% CI -12.5 to -2.5)				⊕⊕◯◯ **LOW**	IMPORTANT
Adverse events - Gastrointestinal												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolides	Placebo	Relative (95% CI)	Absolute (95% CI)		
2 [2,3]	randomised trials	not serious	serious [f]	not serious	serious [g]	none	13/58 (22.4%)	11/58 (19.0%)	**OR 1.24** (0.50 to 3.09)	**35 more per 1,000** (from 85 fewer to 230 more)	⊕⊕◯◯ **LOW**	IMPORTANT
Adverse events - Respiratory												
2 [2,3]	randomised trials	not serious	not serious	not serious	serious [g]	none	8/58 (13.8%)	13/58 (22.4%)	**OR 0.56** (0.21 to 1.46)	**85 fewer per 1,000** (from 73 more to 167 fewer)	⊕⊕◯◯ **LOW**	IMPORTANT
Adverse events - CNS												
1 [3]	randomised trials	not serious	not serious [c]	not serious	very serious [d]	none	1/21 (4.8%)	0/21 (0.0%)	**OR 3.15** (0.12 to 81.74)	**-**	⊕⊕◯◯ **LOW**	IMPORTANT
Adverse events - Musculoskeletal												
1 [3]	randomised trials	not serious	not serious [c]	not serious	very serious [d]	none	0/21 (0.0%)	3/21 (14.3%)	**OR 0.12** (0.01 to 2.54)	**123 fewer per 1,000** (from 141 fewer to 155 more)	⊕⊕◯◯ **LOW**	IMPORTANT
Adverse events - Cardiovascular												
1 [2,3]	randomised trials	not serious	not serious [c]	not serious	very serious [d]	none	2/37 (5.4%)	1/37 (2.7%)	**OR 2.06** (0.18 to 23.72)	**27 more per 1,000** (from 22 fewer to 370 more)	⊕⊕◯◯ **LOW**	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **OR:** Odds ratio

Explanations

a. Largest study includes patients with COPD and chronic cough
b. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference.
c. Single study
d. Small study, probably not powered to detect differences.
e. Indirect measure of efficacy
f. Variability (heterogeneity) among effects estimates
g. Very low number of events, 95%CI indicates large benefit or harm.

References

1. Yousaf, N., et al. (2010). "Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial." Thorax65(12): 1107-1110
2. Berkhof, F., et al. (2013) Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: a randomised controlled trial. Respir Res14, 125 DOI: 10.1186/1465-9921-14-125
3. Hodgson, D., et al. (2016). "The Effects of Azithromycin in Treatment-Resistant Cough: A Randomized, Double-Blind, Placebo-Controlled Trial." Chest149(4): 1052-1060

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - OPIATES

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Opioids**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Follow-up: 4 weeks. Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [b]	none	27	27	-	MD **2 higher** (3.07 higher to 0.93 higher)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Cough severity score. Follow-up: 4 weeks. Range 0 to 9 points; higher scores indicate more severity; assessed with: Diary												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [c]	none	27	27	-	MD **1.6 lower** (2.11 lower to 1.09 lower)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Tussive response to cough challenge. Follow up: 4 weeks; assessed with: Citric acid cough challenge.												
1 [1]	randomised trials	not serious	not serious [a]	serious [d]	not serious	none	27	27	-	MD **93 higher** (27.88 lower to 213.88 higher)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Adverse event - constipation												
1 [1]	randomised trials	not serious	not serious [a]	not serious	very serious [e]	none	40% in treatment group (11 patients)				⊕⊕◯◯ **LOW**	CRITICAL
Adverse event – drowsiness												
1 [1]	randomised trials	not serious	not serious [a]	not serious	very serious [e]	none	25% in treatment group (7 patients)				⊕⊕◯◯ **LOW**	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Single study

b. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference

c. Low number of patients included. Lower 95%CI does not exclude a meaningless difference

d. Indirect (surrogate) measure of efficacy

e. No information on control group. Frequency based on very limited number of patients and events. The expected frequency of this adverse events in no-treatment is zero ho wever it is not clear that these figures reflect an accurate measure.

References

1. Morice AH1, Menon MS, Mulrennan SA, Everett CF, Wright C, Jackson J, Thompson R. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007 Feb 15;175(4):312-5.

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - GABAPENTIN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gabapentin**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Follow-up: 8 weeks on treatment. Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [b]	none	32	30	-	MD **1.8 higher** (3.04 higher to 0.56 higher)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Cough frequency at 8 weeks of treatment (number of coughs/h)												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [c]	none	32	30	-	MD **27.31 lower** (51.75 lower to 2.87 lower)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Cough severity at 8 weeks of treatment; assessed with VAS; Range 0 to 100 points; higher scores indicate better higher severity.												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [c]	none	32	30	-	MD **12.23 lower** (23.23 lower to 1.23 lower)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Capsaicin C5 at 8 weeks of treatment												
1 [1]	randomised trials	not serious	not serious [a]	serious [d]	serious [e]	none	32	30	-	MD **3.12 lower** (19.84 lower to 13.6 higher)	⊕⊕◯◯ **LOW**	IMPORTANT
Any adverse reactions												
1 [1]	randomised trials	not serious	not serious [a]	not serious	very serious [f]	none	17/32 (53.1%)	6/30 (20.0%)	**OR 4.53** (1.46 to 14.07)	**331 more per 1,000** (from 67 more to 579 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Blurred vision												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	1/32 (3.1%)	0/30 (0.0%)	**OR 2.90** (0.11 to 74.10)	**-**	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Depression												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	0/32 (0.0%)	1/30 (3.3%)	**OR 0.30** (0.01 to 7.72)	**23 fewer per 1,000** (from 33 fewer to 177 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Disorientation												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/32 (6.3%)	0/30 (0.0%)	**OR 5.00** (0.23 to 108.53)	**-**	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Dizziness												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	3/32 (9.4%)	1/30 (3.3%)	**OR 3.00** (0.29 to 30.56)	**60 more per 1,000** (from 23 fewer to 480 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Dry mouth												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/32 (6.3%)	1/30 (3.3%)	**OR 1.93** (0.17 to 22.50)	**29 more per 1,000** (from 28 fewer to 404 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Fatigue												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	3/32 (9.4%)	1/30 (3.3%)	**OR 3.00** (0.29 to 30.56)	**60 more per 1,000** (from 23 fewer to 480 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Headache												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	1/32 (3.1%)	0/30 (0.0%)	**OR 2.90** (0.11 to 74.10)	**-**	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Memory loss												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	1/32 (3.1%)	0/30 (0.0%)	**OR 2.90** (0.11 to 74.10)	**-**	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Nausea, stomach pain												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gabapentin**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	4/32 (12.5%)	2/30 (6.7%)	**OR 2.00** (0.34 to 11.82)	**58 more per 1,000** (from 43 fewer to 391 more)	⊕⊕◯◯ **LOW**	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Single study

b. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference

c. Low number of patients included. Lower 95%CI does not exclude a meaningless difference

d. Indirect (surrogate) measure of efficacy

e. Low number of patients included. Lower 95%CI includes both benefit or harm

f. Very low number of events.

References

1. Ryan NM1, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet. 2012 Nov 3;380(9853):1583-9.

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - PREGABALIN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pregabalin**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Follow-up: 14 weeks on treatment. Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
1	randomised trials	not serious [a]	not serious [b]	not serious	serious [c]	none	20	20	-	MD **3.5 higher** (5.89 higher to 1.11 higher)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Cough frequency at 14 weeks of treatment (number of coughs/h)												
1	randomised trials	not serious [a]	not serious [b]	not serious	serious [d]	none	20	20	-	MD **2.3 lower** (13.58 lower to 8.98 higher)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Cough severity at 14 weeks of treatment; assessed with VAS; Range 0 to 100 points; higher scores indicate better higher severity.												
1	randomised trials	not serious [a]	not serious [b]	not serious	serious [c]	none	20	20	-	MD **25.1 lower** (39.6 lower to 10.6 lower)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Capsaicin C5 at 14 weeks of treatment												
1	randomised trials	not serious [a]	not serious [b]	serious [e]	serious [d]	none	20	20	-	MD **47 lower** (174.35 lower to 80.35 higher)	⊕⊕◯◯ **LOW**	IMPORTANT
Adverse event - Blurred vision												
1	randomised trials	not serious	not serious [b]	not serious	very serious [f]	none	4/20 (20.0%)	1/20 (5.0%)	**OR 4.75** (0.48 to 46.91)	**150 more per 1,000** (from 25 fewer to 662 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Cognitive changes												
1	randomised trials	not serious	not serious [b]	not serious	very serious [f]	none	6/20 (30.0%)	1/20 (5.0%)	**OR 8.14** (0.88 to 75.48)	**250 more per 1,000** (from 6 fewer to 749 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Dizziness												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious [b]	not serious	very serious [f]	none	9/20 (45.0%)	1/20 (5.0%)	**OR 15.55** (1.73 to 139.65)	**400 more per 1,000** (from 33 more to 830 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Dry mouth												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/20 (10.0%)	1/20 (5.0%)	**OR 2.11** (0.18 to 25.35)	**50 more per 1,000** (from 41 fewer to 522 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Fatigue												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	7/20 (35.0%)	6/20 (30.0%)	**OR 1.26** (0.33 to 4.73)	**51 more per 1,000** (from 176 fewer to 370 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Headache												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	0/20 (0.0%)	2/20 (10.0%)	**OR 0.18** (0.01 to 4.01)	**80 fewer per 1,000** (from 99 fewer to 208 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Weight gain												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	5/20 (25.0%)	1/20 (5.0%)	**OR 6.33** (0.67 to 60.16)	**200 more per 1,000** (from 16 fewer to 710 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Sleep disturbance												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	0/20 (0.0%)	2/20 (10.0%)	**OR 0.18** (0.01 to 4.01)	**80 fewer per 1,000** (from 99 fewer to 208 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Gastrointestinal												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	5/20 (25.0%)	7/20 (35.0%)	**OR 0.62** (0.16 to 2.43)	**100 fewer per 1,000** (from 217 more to 271 fewer)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Respiratory												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pregabalin**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	3/20 (15.0%)	3/20 (15.0%)	**OR 1.00** (0.18 to 5.67)	**0 fewer per 1,000** (from 119 fewer to 350 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Dermatological												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	1/20 (5.0%)	2/20 (10.0%)	**OR 0.47** (0.04 to 5.69)	**50 fewer per 1,000** (from 96 fewer to 287 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Fluid build-up												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/20 (10.0%)	1/20 (5.0%)	**OR 2.11** (0.18 to 25.35)	**50 more per 1,000** (from 41 fewer to 522 more)	⊕⊕◯◯ **LOW**	CRITICAL
Adverse event - Tight leg and muscle cramp												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/20 (10.0%)	1/20 (5.0%)	**OR 2.11** (0.18 to 25.35)	**50 more per 1,000** (from 41 fewer to 522 more)	⊕⊕◯◯ **LOW**	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. No comparison to pregabalin or placebo alone. Mean cough duration is longer in the placebo group (151 months) than in the pregabalin group (94 months). Mean baseline LCQ score is higher in the placebo group (12.3) than in the pregabalin group (10.8).
b. Single study
c. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference
d. Low number of patients included. Lower 95%CI includes both benefit or harm
e. Indirect (surrogate) measure of efficacy
f. Very low number of events

Refetrences

1. Vertigan AE, Kapela SL, Ryan NM, Birring SS, McElduff P, Gibson PG. Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough: A Randomized Controlled Trial. Chest. 2016 Mar;149(3):639-48.

Question 7: Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**speech pathology interventions**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cough frequency at 4 weeks of treatment (number of coughs/h)												
1 [1]	randomised trials	not serious	not serious [a]	not serious	not serious [b]	none	31	40	-	MD **7 less** (8.34 less to 5.66 less)	⊕⊕⊕◯ **MODERATE**	CRITICAL
Cough severity at 4 weeks of treatment (assessed with different scales) Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [1,2]	randomised trials	serious [c]	not serious	not serious	not serious	none	74	84	-	SMD **0,61 less** (1.02 less to 0.20 less)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Cough severity at 4 weeks of treatment												
2 [1,2]	randomised trials	serious [c]	not serious	not serious	not serious	none	Chamberlain (2017): Mean difference between groups at 4 weeks −9.72 (−20.80 to 1.36) P=0.084 (VAS severity). Vertigan (2006): Mean difference between groups at 4 weeks 8.5 (95% CI 4.7 to 14.9) P<0.001 (23-item symptom score).				⊕⊕⊕◯ **MODERATE**	CRITICAL
Capsaicin C2 at 4 weeks of treatment												
1 [1]	randomised trials	not serious	not serious [a]	serious [d]	not serious	none	31	40	-	MD **1.11 C2 higher** (0.76 higher to 1.61 higher)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Follow-up: 4 weeks on treatment. Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
1 [1]	randomised trials	serious [c]	not serious [a]	not serious	serious [e]	none	31	40	-	MD **1.53 LCQ points higher** (0.21 higher to 2.85 higher)	⊕⊕◯◯ **LOW**	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**speech pathology interventions**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events												
1 [1]	randomised trials	not serious	not serious [a]	not serious	not serious	none	None observed				⊕⊕⊕⊕ HIGH	IMPORTANT
Incontinence – not measured												
											-	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Single study

b. Low number of patients included, most probably underpowered to detect differences.

c. Single blinded study (patients were not aware of the intervention assignment), bias cannot be excluded for subjective outcomes

d. Indirect (surrogate) measure of efficacy

e. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference

References:

1. Chamberlain Mitchell, S. A., et al. (2017). "Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomise d control trial." Thorax 72(2): 129-136.
2. Vertigan, A., et al. (2006) Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax 61, 1065-1069

Question 8: Should a trial of antibiotics be used in children with chronic wet cough with normal chest x ray, normal spirometry and no warning signs?

Certainty assessment							N of patients		Effect			Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With no treatment	With antibiotics	Relative (95% CI)	Absolute (95% CI)			
Cough resolution rate: >75% reduction in cough score after 14 days or cessation of coughing for >3 days within the trial (=treatment) period (assessed with VCD score)													
1 [1]	randomized trials	not serious	not serious	serious[a]	serious[b]	none	4/25 (16.0%)	12/25 (48.0%)	**RR 3.00** (1.12 to 8.05)	**320 more per 1.000** (19 more to 1.000 more)		⊕⊕◯◯ **LOW**	CRITICAL
Change in cough score (VCD score) after 14 days (VCD cough score from 0 to 5: 0=no cough, 1=cough for one or two short periods only, 2=cough for more than two short periods, 3=frequent coughing but does not interfere with school and other activities, 4=frequent coughing which interferes with school and other activities, 5=cannot perform most activities due to severe coughing)													
1 [1]	randomized trials	not serious	not serious	serious[a]	serious[b]	none	24[c]	23[c]	-	MD **0.96 lower**[e] (1.88 lower to 0.04 lower)		⊕⊕◯◯ **LOW**	CRITICAL
Adverse event: mild diarrhoea													
1 [1]	randomized trials	not serious	not serious	serious[a]	very serious[f]	none	2/25 (8.0%)	5/25 (20.0%)	**RR 2.50** (0.53 to 11.70)	**120 more per 1.000** (38 fewer to 856 more)		⊕◯◯◯ **VERY LOW**	IMPORTANT
Adverse event: vomiting													
1 [1]	randomized trials	not serious	not serious	serious[a]	very serious[f]	none	0/25 (0.0%)	1/25 (4.0%)	**RR 3.00** (0.13 to 70.30)	**Study population** 0 per 1.000	**0 fewer per 1.000** (from 0 fewer to 0 fewer)[g]	⊕◯◯◯ **VERY LOW**	IMPORTANT
										Low risk population[h] 10 per 1.000	**20 more per 1.000** (from 9 fewer to 693 more)		

CI: Confidence interval; **RR**: Risk Ratio; **MD**: mean difference; **VCD**: verbal category descriptive cough score.

Explanations

a. Children in both groups were very young (median 1.9 years), therefore, the study findings don't apply to the age group which should be addressed according to the ERS; additionally, chest x ray was abnormal in 15 out of 42 children; 8 children did not receive a chest x ray; an abnormal chest x ray also raises concerns about indirectness considering the PICO provided by the ERS; spirometry was not conducted (according to authors, measurement is not valid in children <6 years).

b. Low number of included patients and few events.

c. Outcome addresses change in cough score, which is not a binary outcome; therefore, no event rates can be provided.

d. Change in cough score: in the primary study data were expressed as median and interquartile range (IQR); we calculated the mean change and standard deviation according to the methods described in Wan 2014.[5]

e. Change is in favour of the antibiotic treatment.

f. 95% CI was consistent with the possibility for benefit and the possibility of harm; additionally, (very) few events in both groups and a low number of included patients.

g. Due to zero events in the control group, it was not possible to calculate the risk difference with antibiotics.

h. Assumed baseline risk for a low risk population.

References

1. Marchant J, Masters I, Champion A, Petsky H, Chang A. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax 2012:689-93.