METHODOLOGICAL APPENDIX

Guideline for Chronic Obstructive Pulmonary Disease, 2017
Literature Review Methods and Results

Section 1. Overview

This document details the methods and results of the systematic literature review performed for the 2017 update of the UMHS clinical guideline for ambulatory care for Chronic Obstructive Pulmonary Disease (COPD).

We reviewed and accepted the literature search and its results performed for the VA/DoD Clinical Practice Guideline on Chronic Obstructive Pulmonary Disease, published in December 2014. That search reviewed evidence from January 2005 to February 2014.

We performed a search of subsequent publications in order to check for better evidence publishes since the VA/DoD search. The search included publications:
- Indexed in the Medline (Ovid) database and the Cochrane Database of Systematic Reviews
- Addressing humans and in the English language
- Categorized as clinical guidelines, controlled trials or meta-analyses, and cohort studies
- From 1/1/14 – 9/8/16

The searched addressed 23 topics. The topics are listed in Section II. The detailed search specifications are listed in Section III.

The search identified a total of 1,886 potentially relevant publications. Section IV lists the number of publications identified by topic and type of publication. Additional articles were identified by searching references in retrieved publications. Very recent publications known to expert members of the guideline team were also considered.

Members of the guideline team reviewed these publications, excluding those found not to be relevant to our population or topic (e.g., study population, measures/outcomes) or not to be the best evidence (e.g., studies with better methodology already available). This process is summarized in Section V.

The review process resulted in 56 studies identified as presenting best evidence on a topic by either the VA/DoD literature review or our review of more recent evidence. For each topic for which "best evidence" was identified, the evidence was synthesized in an evidence table was prepared that describes for each article the key aspects of methods, results, and issues (e.g., benefits and harms). The 19 evidence tables are presented in Section VI.

Section II. Search Framework and Topics

Presented below is the outline for a systematic search on specific topics relevant to the diagnosis and treatment of COPD in the ambulatory care setting. For each topic, searches were performed for (a) guidelines, (b) controlled trials and meta-analyses, and (c) cohort studies. The searches are not mutually exclusive. This approach assumes that each topic will be reviewed by a different individual and that the search on a topic has to include all references relevant to it.

Recent Systematic Search and Review

A relatively recent systematic search and review of literature concerning the diagnosis and treatment of COPD was performed in preparing the VA/DoD Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease. December 2014. That search included evidence since the publication of the preceding VA/DoD guideline on the same topic and included publications from Jan 2005 through Feb 2014. We accepted the literature search, review, and results for best evidence from that search. To identify best evidence since that search, we initiated a systematic search and review of evidence with evidence published starting January 1, 2014.

Inclusion and Exclusion Criteria for Systematic Search of More Recent Literature

To search perform a search of relevant literature published since the VA/DoD search, we developed the following framework of inclusion and exclusion criteria.

Domain	Inclusion	Exclusion
Language:	English	Not written in English
Time frame	Systematic literature search of articles published from 1/1/14– 9/8/16.	Studies published previous to or following these dates.*
Study type/design	Meta-analyses, controlled trials, cohort studies, guidelines	Opinion, letter, commentary
Study population	Adult, inpatient	Not adult, not inpatient
Medical condition	Acute exacerbation of COPD	Chronic, not acute; new onset COPD not exacerbation
Setting	Ambulatory care	Inpatient
Interventions/ indicators	Diagnosis Etiology: Smoking, particulate inhalation exposures, alpha-1-antitrypsin deficiency, life expectancy based on FEV1/BODE Screening: Questionnaires, pulmonary function testing/spirometry Diagnosis: History (risk factors, symptoms), physical exam Diagnostic studies: PFTs, alpha-1-antitrypsin level, chest X-ray, 6 minute walk test, chest CT Diagnostic classification: GOLD classes, MRC or MMRC dyspnea scale, BODE index Definition and diagnosis: Acute exacerbation Treatment: Prevention: Smoking cessation, vaccination (influenza, pneumococcus) Prevention: Irritant avoidance	Interventions/indicators not relevant to ambulatory care for COPD in adults; Interventions/indications that are out of scope for guideline.

	Pharmacologic treatment: Bronchodilators, inhaled corticosteroids Treatment: Supplemental oxygen Treatment: Pulmonary rehabilitation Nutrition Treatment: Complementary and alternative medicine Treatment: Mental health, psychosocial support Treatment: Acute exacerbation – outpatient management, hospitalization Referral to pulmonary sub-specialist Surgical treatment: Lung volume reduction surgery, lung transplantation Treatment: Follow up care, monitoring, chronic disease management Treatment: Palliative care	
Outcomes	For diagnosis test, studies that report associations (including predictive sensitivity / specificity) reflecting accuracy of diagnosis of COPD, COPD severity, and likely COPD progression. For treatment, studies that effect of interventions on clinical aspects of COPD (e.g., disease severity, disease progression, morbidity, mortality), on quality of life, or costs and cost/benefit of treatment.	

* In addition to the results of the search from 2/1/14 to 9/8/16, also considered for inclusion in reviewing studies for best evidence were studies published before or after this timeframe that met the other inclusion and exclusion criteria above and were:

- Best evidence identified by the systematic review of literature published from January 2005 to February 2014 prepared for the Veterans Health Administration, U.S. Department of Veterans Affairs, and the U.S. Department of Defense clinical practice guideline Management of Chronic Obstructive Pulmonary Disease, Dec. 2014: The Lewin Group & ECRI Institute. Management of Chronic Obstructive Pulmonary Disease: Evidence Synthesis Report, Clinical Practice Guideline. Falls Church, Virginia: The Lewin Group, April 10, 2014.

- References in articles identified by the literature search from 1/1/14 to 9/8/16 (not searched systematically).

- Publications since the literature search – from September 2016 to December 2016 – known to members of the guideline team and references in them (not searched systematically).

Search of Literature from 2/1/14 to 9/8/16

An initial search was performed 8/11-14/15 for the time period from 1/1/14 through 8/11/15. A second search using the same search terms was performed 9/8-21/16 for the period from 8/11/15 through 9/8/16.

The general specifications for the search are outlined below. The detailed search terms and specifications are reproduced in Section III.

Within the Medline (Ovid) database, chronic obstructive pulmonary disease was searched as a major descriptor. COPD and "chronic obstructive pulmonary" were also searched in titles of articles to pick up articles about COPD that weren't indexed with the COPD subject heading. The search was not limited to adults because adult was not routinely used in indexing relevant articles. The MEDLINE In-Process database was also searched, using a keyword search. The strategy is available in Section III.

The Cochrane Database of Systematic Reviews was searched using the terms listed in Section III.

Overall specification terms

- Major topic area: chronic obstructive pulmonary disease (COPD)
- Time frame: 1/1/14 – 8/11/15 and 8/11/15 – 9/8/16
- Population: humans
- Language: English

Content terms for specific searches

A. Etiology: Smoking, particulate inhalation exposures, alpha-1-antitrypsin deficiency, life expectancy based on FEV1/BODE
B. Screening: Questionnaires, pulmonary function testing/spirometry
C. Diagnosis: History (risk factors, symptoms), physical exam
D. Diagnostic studies: PFTs, alpha-1-antitrypsin level, chest X-ray, 6 minute walk test, chest CT
E. Diagnostic classification: GOLD classes, MRC or MMRC dyspnea scale, BODE index
F. Definition and diagnosis: Acute exacerbation
G. *Other "diagnosis" not included in C–F above*
H. Comorbid diseases (increased risk)
I. Prevention: Smoking cessation, vaccination (influenza, pneumococcus)
J. Prevention: Irritant avoidance
K. Pharmacologic treatment: Bronchodilators, inhaled corticosteroids
L. Treatment: Supplemental oxygen
M. Treatment: Pulmonary rehabilitation
N. Nutrition
O. Treatment: Complementary and alternative medicine
P. Treatment: Mental health, psychosocial support
Q. Treatment: Acute exacerbation – outpatient management, hospitalization
R. Referral to pulmonary sub-specialist
S. Surgical treatment: Lung volume reduction surgery, lung transplantation
T. Treatment: Follow up care, monitoring, chronic disease management
U. Treatment: Palliative care
V. *Other "treatment" not in I–U above*
W. *Other not in A–V above*

Note: The three "other" searches in italics were performed to check for articles not adequately labeled with specific key words.]

Section III. Detailed Search Terms and Strategy

The searches were performed by informationists at the Taubman Health Sciences Library, University of Michigan.

Overall searches were performed for the period from 1/1/14 – 9/8/16. Two sequential searches were performed. The initial searches were run August 11-14, 2015 for the period 1/1/14 – 8/11/15. The searches were rerun run 9/8, 9/9, 9/21 and 9/22, 2016 for the period 8/11/15 – 9/8/16.

The search strategies are listed below. The only change between the two searches is the timeframe listed in #2 of the first information block, immediately below. Both time frames are shown.

COPD Main Search (referred to as Main)
1. exp *Pulmonary Disease, Chronic Obstructive/ or (COPD or chronic obstructive pulmonary).ti.
2. limit 1 to (english language and humans and *[for initial search]* yr="2014 -Current" *[for second search]* ed-20150811-Current)
3. remove duplicates from 2

Clinical Trials Search Hedge
1. randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or meta-analysis/ or clinical trial, phase iv/
2. clinical trial/
3. limit 2 to humans
4. 1 or 3

Cohort Studies Search Hedge
1. randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or meta-analysis/ or clinical trial, phase iv/
2. clinical trial/
3. limit 2 to humans
4. 1 or 3
5. exp cohort studies/ not 4

Guideline Search Hedge
1. clinical protocols/ or physician's practice patterns/ or algorithms/ or "Outcome and Process Assessment (Health Care)"/ or consensus development conference, nih/ or consensus development conference/ or practice guideline/ or guideline/
2. randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or meta-analysis/ or clinical trial, phase iv/
3. clinical trial/
4. limit 3 to humans
5. 2 or 4 or exp cohort studies/
6. 1 not 5

A. Etiology: Smoking, particulate inhalation exposures, alpha-1-antitrypsin deficiency, life expectancy based on FEV1/BODE
1. exp *Pulmonary Disease, Chronic Obstructive/et [Etiology]
2. Smoking/ or exp Particulate Matter/ or exp alpha 1-Antitrypsin Deficiency/
3. (bode.mp. or exp Forced Expiratory Volume/) and Life Expectancy/
4. or/1-3
5. 4 and Main

B. Screening: Questionnaires, pulmonary function testing/spirometry
1. exp Mass Screening/ or screen*.ti,ab.
2. 1 and Main

C. Diagnosis: History (risk factors, symptoms), physical exam

1. exp Risk Factors/ or exp Physical Examination/ or exp Medical History Taking/
2. (di or du).fs. or exp Diagnosis/
3. 1 and 2
4. 3 and Main

D. Diagnostic studies: PFTs, alpha-1-antitrypsin level, chest X-ray, 6 minute walk test, chest CT
1. exp Respiratory Function Tests/ or exp Alpha-1-Antitrypsin/ or Radiography, Thoracic/ or exp Tomography, X-Ray Computed/ or Exercise Test/
2. ((("6" or six) and "walk* test*") or 6MWT).mp.
3. 1 or 2
4. exp Pulmonary Disease, Chronic Obstructive/di, ra, ri, us [Diagnosis, Radiography, Radionuclide Imaging, Ultrasonography]
5. 3 and 4
6. 5 and Main

E. Diagnostic classification: GOLD classes, MRC or MMRC dyspnea scale, BODE index
1. exp Pulmonary Disease, Chronic Obstructive/cl
2. ((Global Initiative adj2 Chronic Obstructive Lung Disease) or gold stag* or gold class*).mp.
3. (dyspnea scal* or bode).mp.
4. 1 or 2 or 3
5. 4 and Main

F. Definition and diagnosis: Acute exacerbation
1. exacerbat*.ti,ab.
2. (cl or di or du).fs. or exp Diagnosis/
3. 1 and 2
4. 3 and Main

G. Other "diagnosis" not included in C–F above
1. exp Risk Factors/ or exp Physical Examination/ or exp Medical History Taking/
2. (di or du).fs. or exp Diagnosis/
3. 1 and 2
4. exp Respiratory Function Tests/ or exp Alpha-1-Antitrypsin/ or Radiography, Thoracic/ or exp Tomography, X-Ray Computed/ or Exercise Test/
5. ((("6" or six) and "walk* test*") or 6MWT).mp.
6. 4 or 5
7. exp Pulmonary Disease, Chronic Obstructive/di, ra, ri, us [Diagnosis, Radiography, Radionuclide Imaging, Ultrasonography]
8. 6 and 7
9. exp Pulmonary Disease, Chronic Obstructive/cl
10. ((Global Initiative adj2 Chronic Obstructive Lung Disease) or gold stag* or gold class*).mp.
11. (dyspnea scal* or bode).mp.
12. 9 or 10 or 11
13. exacerbat*.ti,ab.
14. (cl or di or du).fs. or exp Diagnosis/
15. 13 and 14
16. 3 or 8 or 12 or 15
17. exp *Pulmonary Disease, Chronic Obstructive/di
18. 17 not 16
19. 18 and Main

H. Comorbid diseases (increased risk)
1. Comorbidity/
2. 1 and Main

I. Prevention: Smoking cessation, vaccination (influenza, pneumococcus)
1. exp Smoking Cessation/ or exp Vaccination/ or Influenza Vaccines/ or Pneumococcal Vaccines/

2. 1 and Main

J. Prevention: Irritant avoidance
1. exp irritants/ or irritant*.ti,ab.
2. 1 and Main

K. Pharmacologic treatment: Bronchodilators, inhaled corticosteroids
1. exp Pulmonary Disease, Chronic Obstructive/dt or exp Bronchodilator Agents/ or exp Adrenal Cortex Hormones/
2. 1 and Main

L. Treatment: Supplemental oxygen
1. exp Oxygen Inhalation Therapy/ or exp oxygen/tu or supplement* oxygen*.mp.
2. 1 and Main

M Treatment: Pulmonary rehabilitation
1. exp Pulmonary Disease, Chronic Obstructive/rh or pulmonary rehab*.ti,ab.
2. 1 and Main

N. Nutrition
1. exp Pulmonary Disease, Chronic Obstructive/dh
2. exp diet/ or exp nutrition processes/ or exp nutritional requirements/ or nutritional status/ or nutritive value/ or exp Nutrition Therapy/
3. 1 or 2
4. 3 and Main

O. Treatment: Complementary and alternative medicine
1. exp Complementary Therapies/ or Integrative Medicine/
2. 1 and Main

P. Treatment: Mental health, psychosocial support
1. exp Pulmonary Disease, Chronic Obstructive/px or exp *Social Support/ or exp *Mental Disorders/dt, th or exp *Psychotherapy/ or *Mental Health/ or exp *Anxiety/ or exp Adaptation, Psychological/ or exp *Behavioral Symptoms/
2. 1 and Main

Q. Treatment: Acute exacerbation – outpatient management, hospitalization
1. exacerbat*.ti. or acute disease/
2. exp *Pulmonary Disease, Chronic Obstructive/co, dh, dt, mo, nu, pc, rt, rh, su, th
3. 1 and 2
4. 3 and Main

R. Referral to pulmonary sub-specialist
1. Pulmonary Medicine/ or exp "Referral and Consultation"/
2. 1 and Main

S. Surgical treatment: Lung volume reduction surgery, lung transplantation
1. exp Pulmonary Surgical Procedures/ or exp lung/su or exp Pulmonary Disease, Chronic Obstructive/su
2. 1 and Main

T. Treatment: Follow up care, monitoring, chronic disease management
1. patient care planning/ or "continuity of patient care"/ or progressive patient care/ or disease management/ or Patient Education as Topic/
2. (ongoing care or "patient follow-up").ti,ab.
3. 1 or 2
4. 3 and Main

U. Treatment: Palliative care

1. palliative care/ or exp terminal care/ or end-of-life.ti.
2. 1 and Main

V. Other "treatment" not in I–U above
1. exp Smoking Cessation/ or exp Vaccination/ or Influenza Vaccines/ or Pneumococcal Vaccines/
2. exp irritants/ or irritant*.ti,ab.
3. exp Pulmonary Disease, Chronic Obstructive/dt or exp Bronchodilator Agents/ or exp Adrenal Cortex Hormones/
4. exp Oxygen Inhalation Therapy/ or exp oxygen/tu or supplement* oxygen*.mp.
5. exp Pulmonary Disease, Chronic Obstructive/rh or pulmonary rehab*.ti,ab.
6. exp Pulmonary Disease, Chronic Obstructive/dh or exp diet/ or exp nutrition processes/ or exp nutritional requirements/ or nutritional status/ or nutritive value/ or exp Nutrition Therapy/
7. exp Complementary Therapies/ or Integrative Medicine/
8. exp Pulmonary Disease, Chronic Obstructive/px or exp *Social Support/ or exp *Mental Disorders/dt, th or exp *Psychotherapy/ or *Mental Health/ or exp *Anxiety/ or exp Adaptation, Psychological/ or exp *Behavioral Symptoms/
9. exacerbat*.ti. or acute disease/
10. exp *Pulmonary Disease, Chronic Obstructive/co, dh, dt, mo, nu, pc, rt, rh, su, th
11. 9 and 10
12. Pulmonary Medicine/ or exp "Referral and Consultation"/
13. exp Pulmonary Surgical Procedures/ or exp lung/su or exp Pulmonary Disease, Chronic Obstructive/su
14. patient care planning/ or "continuity of patient care"/ or progressive patient care/ or disease management/ or Patient Education as Topic/
15. (ongoing care or "patient follow-up").ti,ab.
16. palliative care/ or exp terminal care/ or end-of-life.ti.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11 or 12 or 13 or 14 or 15 or 16
18. exp Pulmonary Disease, Chronic Obstructive/dh, dt, mo, nu, pc, ra, rt, rh, su, th
19. 18 not 17
20. 19 and Main

W. Other not in A–V above
1. exp *Pulmonary Disease, Chronic Obstructive/et [Etiology]
2. Smoking/ or exp Particulate Matter/ or exp alpha 1-Antitrypsin Deficiency/
3. (bode.mp. or exp Forced Expiratory Volume/) and Life Expectancy/
4. or/1-3
5. exp Mass Screening/ or screen*.ti,ab.
6. exp Risk Factors/ or exp Physical Examination/ or exp Medical History Taking/
7. (di or du).fs. or exp Diagnosis/
8. 6 and 7
9. exp Respiratory Function Tests/ or exp Alpha-1-Antitrypsin/ or Radiography, Thoracic/ or exp Tomography, X-Ray Computed/ or Exercise Test/
10. ((("6" or six) and "walk* test*") or 6MWT).mp.
11. 9 or 10
12. exp Pulmonary Disease, Chronic Obstructive/di, ra, ri, us [Diagnosis, Radiography, Radionuclide Imaging, Ultrasonography]
13. 11 and 12
14. exp Pulmonary Disease, Chronic Obstructive/cl
15. ((Global Initiative adj2 Chronic Obstructive Lung Disease) or gold stag* or gold class*).mp.
16. (dyspnea scal* or bode).mp.
17. 14 or 15 or 16
18. exacerbat*.ti,ab.
19. (cl or di or du).fs. or exp Diagnosis/
20. 18 and 19
21. 8 or 13 or 17 or 20
22. exp *Pulmonary Disease, Chronic Obstructive/di
23. Comorbidity/
24. exp Smoking Cessation/ or exp Vaccination/ or Influenza Vaccines/ or Pneumococcal Vaccines/
25. exp irritants/ or irritant*.ti,ab.

26. exp Pulmonary Disease, Chronic Obstructive/dt or exp Bronchodilator Agents/ or exp Adrenal Cortex Hormones/
27. exp Oxygen Inhalation Therapy/ or exp oxygen/tu or supplement* oxygen*.mp.
28. exp Pulmonary Disease, Chronic Obstructive/rh or pulmonary rehab*.ti,ab.
29. exp Pulmonary Disease, Chronic Obstructive/dh or exp diet/ or exp nutrition processes/ or exp nutritional requirements/ or nutritional status/ or nutritive value/ or exp Nutrition Therapy/
30. exp Complementary Therapies/ or Integrative Medicine/
31. exp Pulmonary Disease, Chronic Obstructive/px or exp *Social Support/ or exp *Mental Disorders/dt, th or exp *Psychotherapy/ or *Mental Health/ or exp *Anxiety/ or exp Adaptation, Psychological/ or exp *Behavioral Symptoms/
32. exacerbat*.ti. or acute disease/
33. exp *Pulmonary Disease, Chronic Obstructive/co, dh, dt, mo, nu, pc, rt, rh, su, th
34. 32 and 33
35. Pulmonary Medicine/ or exp "Referral and Consultation"/
36. exp Pulmonary Surgical Procedures/ or exp lung/su or exp Pulmonary Disease, Chronic Obstructive/su
37. patient care planning/ or "continuity of patient care"/ or progressive patient care/ or disease management/ or Patient Education as Topic/
38. (ongoing care or "patient follow-up").ti,ab.
39. palliative care/ or exp terminal care/ or end-of-life.ti.
40. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 34 or 35 or 36 or 37 or 38 or 39
41. exp Pulmonary Disease, Chronic Obstructive/dh, dt, mo, nu, pc, ra, rt, rh, su, th
42. 4 or 5 or 21 or 22 or 23 or 40 or 41
43. Main not 42

MEDLINE In-Process
1. (COPD or chronic obstructive pulmonary).ti.
2. limit 1 to (english language and yr="2014 -Current")

Search hedges used for MEDLINE In-Process
Clinical Trials
1. ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab.

Cohort Studies
1. (cohort or longitudinal or prospective or retrospective).ti,ab.

Practice Guidelines
1. guideline*.ti. or ((practice adj3 parameter*) or guidance or care pathway* or (clinical adj3 pathway*)).ti,ab.

Cochrane Database of Systematic Reviews
ID   Search
#1   MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
#2   #1 Publication Year from 2014 to 2015

Section IV. Number of Search Results by Topic and Type of Publication

The first search (literature published 1/1/14 through 8/11/15) identified 841 unique indexed publications in Medline and 8 Cochrane reviews. The second search (published 8/11/15 through 9/8/16) identified 1,031 unique indexed publications in Medline and 6 Cochrane reviews. The Medline In-Process publications were not reviewed because all that were initially in process were included in the second review and working with indexed articles was more efficient for the review process.

The results by topic and type of publication are summarized below for the first and second searches, respectively. Note that a publication may be relevant to more than one topic, so the sum of entries by topic is greater than the number of unique publications overall.

Results for First Search, 1/1/14 – 8/11/15

Specific Topic	Guidelines	Clinical Trials & Meta-analyses	Cohort Studies
Main	39	403	396
A. Etiology: Smoking, particulate inhalation exposures, alpha-1-antitrypsin deficiency, life expectancy based on FEV1/BODE.	3	51	69
B. Screening: Questionnaires, pulmonary function testing/spirometry	2	18	6
C. Diagnosis: History (risk factors, symptoms), physical exam	4	93	112
D. Diagnostic studies: PFTs, alpha-1-antitrypsin level, chest X-ray, 6 minute walk test, chest CT	16	80	90
E. Diagnostic classification: GOLD classes, MRC or MMRC dyspnea scale, BODE index	5	48	50
F. Definition and diagnosis: Acute exacerbation	6	104	79
G. Other "diagnosis" not included in C–F above	1	4	6
H. Comorbid diseases (increased risk)	0	24	42
I. Prevention: Smoking cessation, vaccination (influenza, penumocus)	0	7	10
J. Prevention: Irritant avoidance	0	4	11
K. Pharmacologic treatment: Bronchodilators, inhaled corticosteroids	6	151	42
L. Treatment: Supplemental oxygen	2	7	14
M Treatment: Pulmonary rehabilitation	2	43	28
N. Nutrition	0	0	5
O. Treatment: Complementary and alternative medicine	0	9	0
P. Treatment: Mental health, psychosocial support	1	47	19
Q. Treatment: Acute exacerbation – outpatient management, hospitalization	2	50	27

R. Referral to pulmonary sub-specialist	2	5	6
S. Surgical treatment: Lung volume reduction surgery, lung transplantation	5	14	30
T. Treatment: Follow up care, monitoring, chronic disease management	3	14	7
U. Treatment: Palliative care	0	2	4
V. Other "treatment" not in I–U above	11	55	78
W. Other not in A–V above	5	26	50
Medline In-Process (not by topic)	27	230	300
Cochrane reviews (not by topic)	8		

Results for Second Search, 8/11/15 – 9/8/16

Specific Topic	Guidelines	Clinical Trials & Meta-analyses	Cohort Studies
Main	55	500	476
A. Etiology: Smoking, particulate inhalation exposures, alpha-1-antitrypsin deficiency, life expectancy based on FEV1/BODE.	5	48	73
B. Screening: Questionnaires, pulmonary function testing/spirometry	6	37	24
C. Diagnosis: History (risk factors, symptoms), physical exam	10	90	118
D. Diagnostic studies: PFTs, alpha-1-antitrypsin level, chest X-ray, 6 minute walk test, chest CT	12	102	111
E. Diagnostic classification: GOLD classes, MRC or MMRC dyspnea scale, BODE index	3	56	69
F. Definition and diagnosis: Acute exacerbation	6	131	109
G. Other "diagnosis" not included in C–F above	2	6	9
H. Comorbid diseases (increased risk)	7	26	62
I. Prevention: Smoking cessation, vaccination (influenza, pneumococcus)	6	14	6
J. Prevention: Irritant avoidance	0	0	0

K. Pharmacologic treatment: Bronchodilators, inhaled corticosteroids	7	176	54
L. Treatment: Supplemental oxygen	8	14	17
M Treatment: Pulmonary rehabilitation	1	70	30
N. Nutrition	2	10	3
O. Treatment: Complementary and alternative medicine	2	20	0
P. Treatment: Mental health, psychosocial support	1	49	30
Q. Treatment: Acute exacerbation – outpatient management, hospitalization	4	42	37
R. Referral to pulmonary sub-specialist	2	6	6
S. Surgical treatment: Lung volume reduction surgery, lung transplantation	4	18	35
T. Treatment: Follow up care, monitoring, chronic disease management	1	23	11
U. Treatment: Palliative care	1	4	7
V. Other "treatment" not in I–U above	8	54	100
W. Other not in A–V above	8	31	51
Medline In-Process	5	30	47
Epub ahead of print	4	45	92
Cochrane	6		

Section V. Evidence Review and Identification of Best Evidence

Criteria for Best Evidence

In order to identify best evidence, team members were assigned topics, then team members reviewed publications to identify studies that had the overall best methods ("best evidence") taking into consideration:

Study setting: reflects care and care settings that are similar to outpatient care in the U.S.

Study population and sample(s): represents adult patients typically seen related to COPD in outpatient care in the U.S.

Study design: strength of design in the ability to identify causal relationships using the following categories.
  A = systematic reviews of randomized controlled trials with or without meta-analysis,
  B = randomized controlled trials,
  C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control),
  D = individual observation studies (case study/case series),
  E = expert opinion regarding benefits and harm

Size of study sample: larger size generally reflecting more stable results

Variables: Extent to which the variables studied matched topics of interest in the inclusion criteria

Measures: Extent to which the measures likely reflected the conceptual variables

Data collection: Extent to which data collection procedures were likely to collect data appropriate for the measures

Intervention appropriateness: Extent to which an intervention was likely to produce the desired condition

Intervention execution: Extent to which interventions were carried out as planned

Analysis appropriateness: Appropriateness of analyses to address the questions of interest

Clarity of description: Extent to which the above information was communicated to readers

Assessment of Included Evidence

Team members used the preceding criteria to identify the "best evidence" on a topic. The intent was not to produce a review of all relevant literature, just to identify the study or few studies that have the strongest overall methodology in providing evidence.

The review proceeded in three steps:

- VA/DoD best evidence. Team members began their assessment by looking at the best evidence on a topic that was previously identified by the literature search performed for the VA/DOD Clinical Practice Guideline on Chronic Obstructive Disease (2014).

- More recent systematically searched literature. Then guideline team members reviewed the 1,886 publications from 1/1/14 to 9/8/16 that were identified in the recent search in order to determine whether better evidence was now available. (Team members had the option of adding to their review any earlier studies cited in these publications that appeared likely to have better evidence than the publication being reviewed. This occurred rarely.)

- Very recent literature known to team members. Then guideline team members had the option of adding to their review any publications since 9/8/16 known to the team member that were likely to be or through citations lead to new best evidence.

Best Evidence Identified and Organized into Evidence Tables
Section VI presents the synthesis of the best evidence identified. It is organized into 19 evidence tables that include a total of 56 publications.

Section VI. Evidence Synthesis: Tables Describing Best Evidence

Evidence identified by the literature review for the VA/DOD Clinical Practice Guideline on Chronic Obstructive Disease (2014) was carried forward as best evidence unless the subsequent search for this guideline identified better evidence/

  * Search performed to check for articles not indexed to specific topics.
** Systematic review of comorbid disease and increased risk is beyond scope of this review, but recent literature monitored.

Topic A, Etiology

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Ryu JY, Sunwoo YE, Lee SY, Lee CK, Kim JH, Lee JT, Kim DH. Chronic obstructive pulmonary disease (COPD) and vapors, gases, dusts, or fumes (VGDF): A meta-analysis. COPD. 2015 Aug;12(4):374-80 PMID: 25255043	Meta-analysis of epidemiologic studies (C)	11 studies Combined N of 26,959	Epidemiologic studies of COPD for exposure to VGDF.	The pooled OR for exposure to VGDF was 1.43 for COPD (95% CI: 1.19-1.73) compared with no exposure to VGDF.	There was moderate heterogeneity among the included studies (I(2) = 54.3%). Publication bias was not observed.
Fischer F, Kraemer A. Meta-analysis of the association between second-hand smoke exposure and ischaemic heart diseases, COPD and stroke. BMC Public Health. 2015 Dec 1;15:1202. PMID: 26627181	Meta analysis of cohort studies (c)	5 cohort studies Combined N of 28,965 participants	Cohort studies investigating the association between SHS exposure and COPD	Effect size for the association between SHS exposure and COPD: RR = 1.66, 95 % CI: 1.38–2.00.	More than half of the participants (n = 15 379) were investigated in one Chinese cohort study.
Thabut G; Mornex JF; Pison C; Cuvelier A; Balduyck M; Pujazon MC; Fournier M; AitIlalne B; Porcher R. Performance of the BODE index in patients with alpha1-antitrypsin deficiency-related COPD. European Respiratory Journal, 2014, 44, 1, 78-86 PMID: 24525449	Cohort (C)	191 French patients with A1ATD	followed from 2006 to 2012 3-year survival data compared by subgroups divided by BODE index: 0-2, 3-4, 5-6 and 7-10	20 patients died during follow-up. 22 underwent lung transplantation. Survival discrimination of the BODE index was better than with both forced expiratory volume in 1 s and Global Initiative for Chronic Obstructive Lung Disease classification: 3-year survival was 97.4% (96.6-98.2%), 98.0% (96.7-99.3%), 87.7% (84.5-90.9%) and 75.3% (66.0-84.6%) for patients with BODE index 0-2, 3-4, 5-6 and 7-10, respectively.	Confirms that BODE provides very good survival discrimination for A1ATD patients, not just for smokers, which is relevant for pre-transplantation assessment Limitation: expected survival by BODE index was noticeably lower than observed survival
Vestbo J; Agusti A; Wouters EF; et al; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Study Investigators. Should we view chronic obstructive pulmonary disease differently	Cohort (C)	2,164 patients with clinically stable COPD and history of at least 10	3 years follow up with measurement of lung function, exercise tolerance, biomarkers, and amount of emphysema by CT.	Continued smoking and presence of emphysema were the strongest predictors of FEV1 decline progression.	There was heterogeneity noted among patients with COPD, with poor correlations between

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after ECLIPSE? A clinical perspective from the study team. American Journal of Respiratory & Critical Care Medicine, 2014, 189, 9, 1022-1030 PMID: 24552242		pack-years of smoking 337 smokers with normal lung function 245 never-smokers with normal lung function	Comparison of outcomes between stable COPD patients v. smoker and nonsmoker groups with normal lung function	Continued smoking and female sex were the strongest predictors of progression of emphysema by CT	FEV1, symptoms, quality of life, functional outcomes, and biomarkers. Details of effect size and statistical significance were deferred to other referenced papers.
Forey BA, Thronton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulm Med. 2011 Jun 14;11:36 PMID: 21672193	Meta-analysis (C)	218 studies: 20 case-control, 39 prospective, 134 cross-sectional, 25 subsidiary investigations	Relative risk of COPD for current smokers, ever smokers, or ex smokers as compared with never smokers. Dose related indices included amount smoked, age at starting, pack-years exposure, duration of smoking, duration of cessation. Results were adjusted for age and confounders as possible.	Relative risk of COPD was found to be elevated for ever smoking (RR 2.89, CI 2.63-3.17, n = 129 RRs), current smoking (RR 3.51, CI 3.08-3.99) and ex smoking (RR 2.35, CI 2.11-2.63).	Original studies depended on variable definitions of COPD, as they were performed prior to development of consensus definitions.
Hurst JR, Vestbo J, Anzueto A, et al; Evaluatoin of COPD Longitudinality to Itendify Predictive Surrogate Endpoints (C=ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010 Sep 16;363(12):1128-38. PMID: 20843247	Cohort (C)	2138 patients with COPD enrolled in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints)	3 year observation for exacerbation events. A "frequent exacerbation phenotype" was defined by persons experiencing 2 or more exacerbations in a year.	Exacerbations became more frequent and more severe as severity of COPD increased. 22% of patients with stage 2 disease, 33% with stage 3, and 47% with stage 4 had frequent exacerbations. The best predictor of exacerbations was a prior history of exacerbations. The frequent-exacerbation phenotype was associated with more severe disease and prior exacerbations, a history of gastroesophageal reflux or heartburn, poorer quality of life, and elevated white-cell count.	Frequent exacerbations appear to reflect an independent susceptibility phenotype.

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  D = individual observation studies (case study/case series),
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Topic B. Screening for COPD

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Guirguis-Blake JM, Senger CA, Webber EM, et al. Screening for chronic Obstructive pulmonary Disease: Evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2016;315(13):1378-1393. doi:10.1001/jama.2016.2654	Systematic review: randomized controlled trials and cross-sectional studies, depending on the question (A, C)	33studies	Asymptomatic adults 40 years and older for screening outcomes. Asymptomatic adults ≥ 40 years and diagnosed with mild to moderate COPD for relationships to improved health-related quality of life, to reduced morbidity or mortality, and to adverse effects of COPD treatments.	There was no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based screening pulmonary function testing or to determine the benefits of treatment in screen-detected populations. All screening questionnaires were based on symptoms as well as risk factors such as age and smoking history. The COPD Diagnostic Questionnaire was the most extensively studied (5 studies, n = 3048), with moderate overall performance for COPD detection: area under the receiver operating characteristic curve (AUC), 0.65 to 0.72; sensitivity, 80% to 93%; and specificity, 24% to 49%, at a threshold of greater than 16.5. Positive predictive value and NPV ranged from 17% to 45% and 76% to 98%, respectively. For pulmonary function–based screening tools, FEV_1/FEV_6 was the best studied (3 studies, n = 1587), with AUC ranging from 0.84 to 0.85. Sensitivity ranged from 51% to 80%. Specificity (range, 90%-95%) and PPV	

				(range, 63%-75%) appeared better than questionnaires. There was not strong evidence to support that screening and supplying smokers with spirometry results improves smoking cessation rates. Treatment trials were unavailable for screen-detected patients. Trials that reported outcomes in patients with mild to moderate COPD included 2 trials of long-acting β-agonists (LABAs) (n = 3174), 1 RCT of LABAs and inhaled corticosteroids (ICS) (n = 1097), 5 RCTs of the long-acting muscarinic antagonist tiotropium (n = 4592), and 6 RCTs of ICS (n = 3983). They suggested no benefit in all-cause mortality, but a decrease in annual rates of exacerbations with pharmacologic treatments. Few trials reported harms for any individual drug class. Adverse effects were generally mild (eg, dry mouth and cough).	

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Topic C. Diagnosis: History, Physical Exam

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Kohansal R, Martinez-Camblor P, Agusti A et al. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. Am J respire Crit Care Med, 2009; 180(1):3-10. PMID: 19342411	Prospective Cohort Study (C)	Framingham Offspring cohort who had two or more valid spirometry measures N – 4,391, age range at baseline 13 to 71 years	Median follow up time of 23 years describing FEV(1) changes with age.	Lung function changes from adolescence to old age differ in males and females, smoking has similar deleterious effects in both sexes, and quitting earlier is better. (1) healthy never-smoker females achieve full lung growth earlier than males, and their rate of decline with age was slightly, but not significantly, lower. (2) smoking increases the rate of lung function decline, both in males and in females (3) there is a range of susceptibility to the effects of smoking. The presence of respiratory symptoms at baseline and/or a respiratory diagnosis during follow-up appears to identify a group of susceptible smokers/ (4) quitting smoking has a beneficial effect at any age, but it is more pronounced in earlier quitters.	
Miravitlles M, Worth H, Soler Cataluna JJ, et al. Observational study to characterize 24-	Cohort Study (C)	Patients with stable COPD.	Recorded baseline night-time, early morning and daytime symptoms	In each part of the 24-hour day, >60% of patients reported	

hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res 2014; 15:122. 		727 patients	(symptom questionnaire), severity of airflow obstruction (FEV_1), dyspnoea (modified Medical Research Council Dyspnoea Scale), health status (COPD Assessment Test), anxiety and depression levels (Hospital Anxiety and Depression Scale), sleep quality (COPD and Asthma Sleep Impact Scale) and physical activity level (sedentary, moderately active or active)	experiencing ≥1 symptom in the week before baseline. Symptoms were more common in the early morning and daytime versus night-time (81.4%, 82.7% and 63.0%, respectively). Symptom severity was comparable for each period assessed. Overall, in the week before baseline, 56.7% of patients had symptoms throughout the whole 24-hour day (3 parts of the day); 79.9% had symptoms in ≥2 parts of the 24-hour day. Symptoms during each part of the day were inter-related, irrespective of disease severity (all $p < 0.001$). Early morning and daytime symptoms were associated with the severity of airflow obstruction ($p < 0.05$ for both). Night-time, early morning and daytime symptoms were all associated with worse dyspnea, health status and sleep quality, and higher anxiety and depression levels (all $p < 0.001$ versus patients without symptoms in each corresponding period). In each part of the 24-hour day, there was also an association between symptoms and a patient's physical activity level ($p < 0.05$ for each period).	
Cho SH, Lin HC, Ghoshal AG et al. Respiratory disease in the Asia-Pacific region: Cough as a key symptom. Allergy Asthma Proc 2016;37(2): 131-40	Cross-sectional study (C)	Patients ages ≥ 18 years who presented to a physician with symptoms that met the diagnostic criteria for a primary diagnosis of	Association of disease with symptoms	Patients with a primary diagnosis of COPD (73%), followed by asthma (61%), rhinosinusitis (59%), and AR (47%) most frequently reported cough as a symptom.	

				Cough was the main reason for seeking medical care among patients with a primary diagnosis of COPD (43%), asthma (33%), rhinosinusitis (13%), and AR (11%).	
Allinson JP, Hardy R, Donaldson GC, et al. The presence of chronic mucus hypersecretion across adult life in relation to Chronic Obstructive Pulmonary Disease Development. Am J Respir Crit Care Med 2016; 193(6): 662-72	Longitudinal cohort study (C)	4427 individuals providing data between ages of 20 and 64 years.	Association of chronic mucus hypersecretion (CMH) with COPD development and progression	The longer CMH was present across three occasions (ages 43, 53, and 60-64 yr), the greater the concurrent FEV1 decline, corresponding to an additional decrement of 3.6 ± 2.5 ml/yr per occasion that CMH was present (P = 0.005). CMH among middle-aged smokers represents an early developmental phase of chronic obstructive pulmonary disease. Smoking-related CMH usually resolves following smoking cessation but the longer its duration the greater the FEV1 lost, suggesting the course of CMH across adult life may reflect the underlying course of airway disease activity.	
Holleman DR, Jr., Simel DL. Does the clinical examination predict airflow limitation? JAMA 1995; 274(4): 313-319. PMID: 7815660	Review (C) (predates systematic reviews)	Several relationships examined with 1 to 6 studies depending on the relationship	Examination of relationship of history, symptoms, signs (physical exam), and overall clinical impression for predicting airflow limitation.	The number pf positive findings (trachea! descent during inspiration, sternomastoid contraction, scalene contraction, supraclavicular fossae excavation, supraclavicular fossae recession, intercostal recession, or costal margin movement) predicted the severity of airflow limitation in patients with known disease. These findings tended to be present only if the FEVj was less than 50% of the predicted value. The number of positive findings (barrel chest, low diaphragm,	Not a systematic review.

| | | | | decreased diaphragmatic excursion, decreased breath sounds, prolonged expiratory phase, wheezing, noisy inspiration, or crackles) predicted the severity of airflow limitation (r=.6). | |

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Topic D. Diagnostic Studies

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Walker PP1, Mitchell P, Diamantea F, Warburton CJ, Davies L. Effect of primary-care spirometry on the diagnosis and management of COPD. *Eur Respir J.* 2006 Nov;28(5):945-52. Epub 2006 Jul 26. PMID: 16870668	Retrospective case review (C)	N=1508 patients referred for open-access spirometry and reversibility in a local primary area	All patients received spirometry.	91 new cases of COPD diagnosed. Primary-care spirometry not only increases rates of COPD diagnosis, but it also leads to improvements in chronic obstructive pulmonary disease treatment. The use of bronchodilator reversibility testing in this setting may be important to avoid misdiagnosis. A total of 797 (53%) had pre-bronchodilator airflow obstruction (AFO). Of the subjects who underwent reversibility testing, 19.3% were no longer obstructed post-bronchodilator. Of 235 subjects with post-bronchodilator AFO, 130 received a new diagnosis, most commonly COPD. The patients with COPD were significantly undertreated before spirometry and testing led to a significant increase in the use of anticholinergics (37 versus 18%), long-acting beta-agonists (25 versus 8%) and inhaled steroids (71 versus 52%).	
Rahaghi FF1, Sandhaus RA, Brantly ML, et al. The prevalence of alpha-1 antitrypsin deficiency among patients found to have airflow obstruction. *COPD.* 2012 Aug;9(4):352-8.	Cohort (C)	3457 in 19 medical centers were tested with 3152 eligible.	Eligible patients (> GOLD II, FEV(1)/FVC ratio < 0.7, with post-bronchodilator FEV(1)<80% predicted) were offered testing for AATD.	The prevalence of A1AT of patients undergoing spirometry was 0.63% and 10.88% carriers..	Recommendations are weak but multiple studies support testing if there is concern.

PMID: 22506682					
Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J 2014; **44**: 1447–1478. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J.* 2014 Dec;44(6):1428-46. doi: 10.1183/09031936.00150314.	Systematic Review (C)	Examined a number of different relationships with the number of studies examined for each relationship ranging from 2 to 23.	This systematic review examined the measurement properties of the 6-min walk test (6MWT), incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT) in adults with chronic respiratory disease.	The 6-min walking distance (6MWD) is a reliable measure (intra-class correlation coefficients ranged from 0.82 to 0.99 in seven studies). There is a learning effect, with greater distance walked on the second test (pooled mean improvement of 26 m in 13 studies). Reliability was similar for ISWT and ESWT, with a learning effect also evident for ISWT (pooled mean improvement of 20 m in six studies). The 6MWD correlates more strongly with peak work capacity (r=0.59–0.93) and physical activity (r=0.40–0.85) than with respiratory function (r=0.10–0.59). Methodological factors affecting 6MWD include track length, encouragement, supplemental oxygen and walking aids. Supplemental oxygen also affects ISWT and ESWT performance. Responsiveness was moderate to high for all tests, with greater responsiveness to interventions that included exercise training.	

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Topic E. Staging

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Han MK, Muellerova H, Curran-Everett D,, et al. Implications of the GOLD 2011 disease severity classification in COPDGene cohort: a prospective cohort study. *Lancet Respir Med.* 2013 Mar;1(1):43-50. doi: 10.1016/S2213-2600(12)70044-9. Epub 2012 Sep 3. PMCID: PMC4105297 DOI: 10.1016/S2213-2600(12)70044-9	Prospective cohort study (C)	4484 analyzed from COPDGene study.	Using all subjects to determine the effect of symptom instrument (Medical Research Council Dyspnea – mMRC vs. Saint George's Respiratory Questionnaire – SGRQ) on: • GOLD category membership • prospective exacerbation risk	Category assignment was similar but not identical (kappa = 0.77) In the highest risk category (D), the prospective exacerbation rates (exacerbations/person-year) varied with the risk factor that determined category assignment: lung function, 0.89; priori exacerbation history, 1.34; or both 1.86; p < .001.	(Several staging systems have been proposed and none found superior than another. GOLD staging is most widely used.)

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Topic F. Definition/Diagnosis of Acute Exacerbation

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2014). *www.goldcopd.org/uploads/users/files/GOLD_Report_2014_Jan23.pdf*. 2014.	Expert opinion (E)	N/A	N/A	N/A	No single definition exists. Generally accepted definition is an acute change in symptoms beyond day to day variability leading to change in medication.

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Topic I. Smoking Cessation

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Dhariwal J; Tennant RC; Hansell DM; Westwick J; Walker C; Ward SP; Pride N; Barnes PJ; Kon OM; Hansel TT. Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution CT imaging. Chest. 2014 May;145(5):1006-15. PMID: 24522562	Cohort, single-center study (C)	(N = 358). . screening spirometry in a group of heavy smokers aged 40 to 80 years.	Effect of smoking cessation in three comparison groups: • 38 met postbronchodilator spirometric criteria for being smokers with COPD • 55 were healthy smokers with normal spirometry • 19 never smoked.	.those with COPD showed a significant increase from baseline in FEV_1 of 184 mL at 6 weeks (n = 17, $P < .01$) Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution CT imaging.	
Romieu GL, Wheaton AG, Malarcher AM, Croft JG. Health-care Provider Screening and Advice for Smoking Cessation Among Smokers With and Without COPD: 2009-2010 National Adult Tobacco Survey. Chest. 2016 Mar;149(3):676-84 PMID: 26291388	Observational study (C)	N= 20,012 adult past-year cigarette smokers in the 2009-2010 National Adult Tobacco Survey, a nationally representative telephone survey of US adults 18 years of age and older	Among smokers with COPD were more likely than smokers without COPD to report being: • asked about tobacco use (95.4% vs 85.8%), • advised to quit (87.5% vs 59.4%), • assessed for readiness to quit (63.8% vs 37.9%), • offered any assistance to quit (58.6% vs 34.0%), • offered follow-up (14.9% vs 5.2%). In adjusted logistic regression models, those with COPD were significantly more likely than those without COPD to receive each of the 5As.	Health professionals should continue to prioritize tobacco cessation counseling and treatment to smokers with COPD	

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Topic J. Irritant Avoidance

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2002 Oct 15;156(8):738-46. PMID: 12370162	Cross-sectional (C)	US population-based Third National Health and Nutrition Examination Survey, conducted from 1988 to 1994: 9,823 subjects aged 30-75 years who underwent lung function tests.	Data were used to estimate the population prevalence, prevalence odds ratios, and attributable fractions for the association of chronic obstructive pulmonary disease (COPD) with employment by industry and occupation. The aim was to identify industries and occupations at increased risk of COPD. COPD was defined as forced expiratory volume in 1 second (FEV(1))/forced vital capacity <70% and FEV(1)<80% predicted.	Adjusting for age, smoking status, pack-years of smoking, body mass index, education, and socioeconomic status, Odds ratios were increased for the following industries: rubber, plastics, and leather manufacturing; utilities; office building services; textile mill products manufacturing; the armed forces; food products manufacturing; repair services and gas stations; agriculture; sales; construction; transportation and trucking; personal services; and health care. Occupations associated with increased odds ratios for COPD were freight, stock, and material handlers; records processing and distribution clerks; sales; transportation-related occupations; machine operators; construction trades; and waitresses. The fraction of COPD attributable to work was estimated as 19.2% overall and 31.1% among never smokers.	
Atkinson RW; Carey IM; Kent AJ; van Staa TP; Anderson HR; Cook DG. Long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort. Occup Environ Med. 2015 Jan; 72(1): 42–48.	Cohort (C)	812,063 patients aged 40-89 years registered with 205 English general practices in 2002 without a COPD diagnosis	Exposure by geographic area was estimated in 2002 for annual average concentrations for particulate matter, nitrogen dioxide, ozone and sulfur dioxide.	This large population-based cohort study found limited, inconclusive evidence for associations between air pollution and COPD incidence.	Further work, utilizing improved estimates of air pollution over time and enhanced socioeconomic

PMC4283678		was followed from 2003 to 2007		Adjusted hazard ratios for diagnosis were: • No difference for particulate matter (two sizes) and nitrogen dioxide • Positive for sulfur dioxide (HR=1.07 (95% CI 1.03 to 1.11) per 2.2 µg/m^3) • Negative for ozone (HR=0.94 (0.89 to 1.00) per 3 µg/m^3). For hospital admissions hazard ratios were positive for particulate matter and nitrogen dioxide (HRs=1.05 (0.98 to 1.13) and 1.06 (0.98 to 1.15) per 1.9 µg/m^3 and 10.7 µg/m^3, respectively).	indicators, is required to clarify the association between air pollution and COPD incidence
Romieu I, Riojas- Rodriguez H, Marron-Mares AT, et al. Improved biomass stove intervention in rural Mexico: impact on the respiratory health of women. Am J Respir Crit Care Med. 2009 Oct 1;180(7):649-56 PMID:19556519	Randomized controlled trial (B)	552 women in the Central Mexican state of Michoacán	Intervention group given Patsari stove (lower biomass release) Control group kept traditional open fire for cooking	Women who reported using the Patsari stove most of the time compared with those using the open fire had significantly lower risk of respiratory symptoms (relative risk [RR], 0.77; 95% confidence interval [CI], 0.62-0.95 for cough and RR, 0.29; 95% CI, 0.11-0.77 for wheezing) adjusted for confounders. Similar results were found for other respiratory symptoms as well as for eye discomfort, headache, and back pain. Actual use of the Patsari stove was associated with a lower FEV(1) decline (31 ml) compared with the open fire use (62 ml) over 1 year of follow-up (P = 0.012) for women 20 years of age and older, adjusting for confounders.	Adherence to the intervention was low (50%).
Liu S, Zhou Y, Wang X, et al. Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. Thorax 2007, 62(10): 889-97 PMID:17483137	Observational study (C)	A cluster disproportional random sampling survey was performed in populations aged over 40 years in urban (Liwang) and rural (Yunyan)	COPD was defined as a post-bronchiodilator ratio of FEV1 < 70. Indoor and outdoor air pollutant measurements were performed.	Indoor pollutants from biomass fuels may be an important risk factor for COPD in rural South China. The prevalence of COPD in both the whole population and a subpopulation of non-smoking women in rural Yunyan was significantly	

| | | areas in Guangdong, China | | higher than in urban Liwang (12.0% vs 7.4%, and 7.2% vs 2.5%, respectively). The use of biomass fuel was higher in rural Yunyan than in urban Liwang (88.1% vs 0.7%). Univariate analysis showed a significant association between COPD and exposure to biomass fuel for cooking. Multivariate analysis showed a positive association between COPD and urban/rural area (surrogate for fuel type and local exhaust ventilation in kitchen) after adjustment for several variables; similar results were found in non-smoking women. | |

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     studies (cohort, cross-sectional, case-control),
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Topic K. Pharmacologic Treatment

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance	Reviewer notes • Methodological issues, • Noteworthy harms • Other
B-2-agonists Sestini P, Renzoni E, Robinson S, Poole P. Short Acting beta-2 agonists for stable COPD. *Cochrane Database Syst Rev.* 2002;(4):CD001495	Systematic Review (A)	13 RCTs of at least 1 week of duration	All studies used crossover design.	Use of SABA for at least 7 days produced improvements in lung function and decrease in breathlessness. Patients preferred use of SABA vs placebo. Comparing SABA to placebo: • Spirometry post-bronchodilator showed a slight but significant increase in FEV1 and FVC (WMD=0.14 L; 95%CI=0.04,0.25 & WMD=0.30 L; 95%CI=0.02,0.58, respectively). • Morning and evening PEFR were significantly better (WMD=29.17 L/min; 95%CI=0.25,58.09 & WMD=36.75 L/min; 95%CI=2.56,70.94, respectively). • Daily breathlessness score improved (SMD=1.33; 95%CI=1.0,1.65). • Patients preferred beta-2 agonists almost 10 times more frequently (OR=9.04; 95%CI=4.64,17.61). • One study that used a validated questionnaire for 'quality of life' assessment, found highly significant improvements in the scores for dyspnea (p=0.003) and fatigue (p=0.0003).	Methods high quality. No studies reported serious side effects during treatment with inhaled beta-agonists. However, none of the studies were of sufficient length or size in order to allow any meaningful information on long-term occurrence of side effects

| Inhaled corticosteroids

Nannini LJ, Poole P. Milan SJ, Kesterson A. Combined corticosteroid and long acting beta-agonist in one inhaler for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004;(3):CD003794.

PMID: 15266502 | Systematic Review of Randomized Controlled Trials (A) | 6 RTCs

4,118 participants | Studies that compared a combined inhaled corticosteroids and long-acting beta-agonist preparation with either component preparation or placebo. | Combination treatment was more effective than placebo for mean exacerbation rates, quality of life and lung function.
No trials were found comparing the combination of drugs in a single inhaler with the same drugs both given in separate inhalers.
Exacerbations: Fluticasone/ salmeterol did not significantly reduce exacerbations compared with either of its component treatments in one large study. There was no significant difference when budesonide/formoterol was compared with budesonide. Budesonide/formoterol was more effective than formoterol in reducing exacerbations (Rate ratio: 0.78 [0.68 to 0.90], two studies). A pooled analysis of both combination therapies indicated that exacerbations were less frequent when compared with either placebo or long-acting beta-agonist (versus placebo Rate ratio: 0.76 [0.68, 0.84], three studies, versus beta-agonist, Rate ratio: 0.85 [0.77, 0.95], three studies), but not when compared with steroid. The clinical impact of this effect depends on the frequency of exacerbations experienced by patients.
Quality of Life: There were conflicting findings in quality of life and symptoms when fluticasone/salmeterol was compared with inhaled steroids alone (three studies). There was no significant difference between fluticasone/salmeterol and long-acting beta-agonist in quality of life scores (three | |

				studies). Budesonide/ formoterol improved symptoms when compared with budesonide but not with formoterol. There were conflicting findings in quality of life scores when budesonide/formoterol was compared with component inhaled corticosteroid or beta-agonist. These may be accounted for by different study design. Lung Function: Treatment with either combination led to small, significant differences in lung function compared with component steroid medication.	
Anticholinergic Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. _Cochrane Database Syst Rev._ 2012 Jul 11;(7):CD009285. PMID: 22786525 doi: 10.1002/14651858.CD009285.pub2	Systematic Review (A)	22 studies Total of 22,309 patients	RCTs ≥ 3 months in length comparing tiotropium to placebo on patients with COPD	Tiotropium significantly: • improved mean quality of life (mean difference (MD) -2.89; 95% confidence interval (CI) -3.35 to -2.44) • increased the number of participants with a clinically significant improvement (odds ratio (OR) 1.52; 95% CI 1.38 to 1.68) • reduced the number of participants with a clinically significant deterioration (OR 0.65; 95% CI 0.59 to 0.72) in quality of life (measured by the St George's Respiratory Questionnaire (SGRQ)). reduced the number of participants suffering from exacerbations (OR 0.78; 95% CI 0.70 to 0.87) • led to fewer hospitalizations due to exacerbations (OR 0.85; 95% CI 0.72 to 1.00) • had improved lung function at the end of the study (trough forced expiratory volume in one second	Difference in death rate by delivery device/dose: • dry powder inhaler had fewer deaths in the tiotropium group (Peto OR 0.92; 95% CI 0.80 to 1.05) than in the placebo group (yearly rate 2.8%) • soft mist inhaler had significantly more deaths in the tiotropium group (Peto OR 1.47; 95% CI 1.04 to 2.08) than in the placebo group (yearly rate 1.8%).

					(FEV(1)) MD 118.92 mL; 95% CI 113.07 to 124.77).
PD4 inhibitors Calverly P, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease. *Lancet.* 2009 Aug 29;374(9691):685-94 PMID:19716960	2 separate RCT (A/B)	14 countries, 14 centers, N = 3,091 patients total. Studies analyzed separately and together	Pts < 40 years with clinical diagnosis of COPD and 1+ exacerbation per year requiring steroids or hospitalization. Randomized to placebo vs treatment.	Compared to placebo roflumilast: • Increased prebronchodilator FEV(1) by 48 mL (p<0.0001). • Decreased exacerbations that were moderate or severe per patient per year 1.14 vs. 1.37 (reduction 17% [95% CI 8-25], p<0.0003)	Adverse events were more common with roflumilast (1040 [67%]) than with placebo (963 [62%]); 219 (14%) patients in the roflumilast group and 177 (12%) in the placebo group discontinued because of adverse events.

Antibiotics Yao GY, Ma YL, Zhang MQ, Gao ZC. Macrolide therapy decreases chronic obstructive pulmonary disease exacerbation: a meta analysis. *Respiration.* 2013;86(3) 254-260 PMID: 23817204	Systemic review (A)	6 studies 1,485 patients total	RCTs of COPD patients Four studies compared macrolide with placebo (erythromycin n=2; azithromycin n=1; clarithromycin n=1), one compared macrolide (erythromycin) with riboflavin (10.0 mg/d), and one compared macrolide (azithromycin) with standard therapy. Course of therapy ranged from 3 to 12 months. Patients in 5 of 6 studies were taking other medication (e.g., inhaled corticosteroids, bronchodilators) for COPD. One trial did not report on patient medication use.	Macrolide reduced the frequency of acute exacerbations of COPD [risk ratio (RR) = 0.62; 95% CI 0.43-0.89, p = 0.01]. Subgroup analysis: • Only erythromycin might be associated with decreased COPD exacerbations (erythromycin: p = 0.04, azithromycin: p = 0.22, clarithromycin: p = 0.18). • Macrolide therapy for 3 months did not significantly reduce the number of exacerbations (p = 0.18), but a beneficial effect occurred in the 6-month (p = 0.009) and 12-month (p = 0.03) treatment subgroups.	Nonfatal adverse events were more frequent in the macrolide treatment groups than in the controls (RR = 1.32; 95% CI 1.06-1.64, p = 0.01).
Donath E, Chaudhry A, Hernandez-Aya LF, Lit L. A meta –analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with chronic obstructive pulmonary disease. *Respiratory Medicine.* Sept 2013:107(9):1385-1392.	Systemic Review (A)	6 studies 1,485 patients total (Same as Yao GY et al, 2013 above)	(Same as Yao GY et al, 2013 above)	Compared to placebo, macrolides resulted in: • A 37% relative risk reduction (RR = 0.63, 95% CI: 0.45-0.87, p value = 0.005) in COPD exacerbations	Lack of consistent adverse event reporting

| PMID: 23768735 | | | | • A 21% reduced risk of hospitalization (RR = 0.79, 95% CI: 0.69-0.90, p-value = 0.01)
• A 68% reduced risk of having at least one COPD exacerbation (RR = 0.34, 95% CI 0.21-0.54, p-value = 0.001)
• Trends toward decreased mortality and increased adverse events that were not statistically significant. | |

Topic L. Oxygen Therapy

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Cranston JM, Crockett A, Moss J, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD001744. DOI: 10.1002/14651858.CD001744.pub2.	Systematic reviews of randomized controlled trials (A)	Patients with hypoxemia and COPD that compared long term oxygen therapy with a control treatment. 6 RCTs were included in this analysis	Mortality was assessed in 1 trial comparing continuous oxygen therapy vs no oxygen therapy in patients with severe hypoxemia and heart failure. Mortality was assessed in 1 trial comparing continuous vs nocturnal oxygen therapy with severe hypoxia. Mortality was aggregated from 2 trials of continuous oxygen therapy versus no oxygen therapy in patients with mild to moderate COPD.	Significant mortality benefit at 5 years in continuous vs no oxygen therapy (OR 0.42, 95% CI: 0.18 to 0.98). Significant mortality benefit at 2 years in continuous vs nocturnal oxygen therapy (OR 0.45, 95% CI: 0.25 to 0.81). No mortality benefit in continuous oxygen therapy versus no oxygen therapy in patients with mild to moderate COPD.	The methodologic quality of the studies included in this analysis were moderate
COPD Working Group. Long-term oxygen therapy for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. *Ont Health Technol Assess Ser.* 2012;12(7):1-64. PMID: 23074435	Systematic review / meta-analysis (including randomized and observational studies) (A, C)	COPD patients with mild, moderate, or severe hypoxemia. 3 systematic reviews, 3 RCTs and 2 observational studies were included in this review.	Outcomes of Interest for long term oxygen therapy (LTOT): -Mortality/survival -Hospitalizations -End-exercise dyspnea score (Borg scale) -Endurance time -Health related quality of life (HRQOL): St. George's Respiratory Questionnaire (SGRQ) or Chronic Respiratory Questionnaire (CRQ) -Lung Function	Mortality: borderline significance in patients with severe hypoxemia (none in mild/moderate hypoxemia) Hospitalizations: no benefit observed End exercise dyspnea: no benefit observed HRQOL: minimal improvement Lung function: significant improvement in survivors with severe hypoxemia.	Many of the outcomes assessed were based from low quality evidence

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   C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control),
   D = individual observation studies (case study/case series),
   E = expert opinion regarding benefits and harm

Topic M. Pulmonary Rehabilitation

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance	Reviewer notes • Methodological issues, • Noteworthy harms • Other
COPD Working Group. Pulmonary Rehabilitation for Patients with Chronic Pulmonary Disease (COPD): An Evidence-Based Analysis. *Ontario Health Technology Assessment Series*, 2012, *12*(6), 1–75. PMCID: PMC3384375	Systematic Review (A)	20 studies: 1 health technology assessment, 2 systematic reviews, and 17 RCTs. 1,136 patients total	Patients with COPD that compared pulmonary rehabilitation programs of ≥ 6 weeks (including exercise training) with no pulmonary rehabilitation	Effect of Pulmonary Rehabilitation on Outcomes in Stable COPD: • Pulmonary rehabilitation including at least 4 weeks of exercise training leads to clinically and statistically significant improvements in Health Related Quality of Life in patients with COPD.[1] (St. George's Respiratory Questionnaire effect size mean difference -8.4, 95% confidence interval -12.2, -3.5 (also mean differences on Chronic Respiratory Questionnaire subscales) • Pulmonary rehabilitation also leads to a clinically and statistically significant improvement in functional exercise capacity[2] (weighted mean difference, 54.83 m; 95% confidence interval, 35.63–74.03; P < 0.001	Moderate quality of evidence.
		5 RTCs 276 patients total		Effect of Pulmonary Rehabilitation on Outcomes Following an Acute Exacerbation of COPD : • Pulmonary rehabilitation (within 1 month of hospital discharge) after acute exacerbation significantly reduces hospital readmissions (relative risk, 0.50; 95% confidence	Moderate quality of evidence

				interval, 0.33–0.77; P = 0.001) and leads to a statistically and clinically significant improvement in Health Related Quality of Life	
		3 RTC 158 patients total		Effect of Pulmonary Rehabilitation Maintenance Programs on COPD Outcomes: • Maintenance programs have a nonsignificant effect on HRQOL and hospitalizations. • Maintenance programs have a statistically but not clinically significant effect on exercise capacity (P = 0.01). When subgrouped by intensity and quality of study, maintenance programs have a statistically and marginally clinically significant effect on exercise capacity.	Low quality of evidence

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Topic N. Nutrition

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Collins PF, Elia M, Stratton RF. Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respirology*. May 2013;18(4):616-629 PMID:23432923	Systematic review with meta-analysis (A)	12 studies N=448	Stable COPD patients investigating the effects of nutritional support (dietary advice (1 RCT), oral nutritional supplements (10 RCT), enteral tube feeding (1 RCT)) versus control on functional outcomes.	Nutritional support: • Did not improve respiratory function (forced expiratory volume in 1 s, lung capacity, blood gases) • improved both inspiratory and expiratory muscle strength (maximal inspiratory mouth pressure +3.86 standard error (SE) 1.89 cm H_2O, P = 0.041; maximal expiratory mouth pressure +11.85 SE 5.54 cm H_2O, P = 0.032) • Improved handgrip strength (+1.35 SE 0.69 kg, P = 0.05) • Was associated with weight gains of ≥2 kg. • Improved quality of life in some trials, although meta-analysis was not possible. • Improved exercise performance and enhancement of exercise rehabilitation programs.	While several studies were of high quality, many were of lower quality. Despite evidence, referral of COPD patients for nutritional support may not be reimbursed by insurance.

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Topic O. Complementary and Alternative Medicine

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Ngai SP, Jones AY, Tam WW. Tai Chi for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2016 Jun 7;(6):CD009953. PMID: 27272131	Systematic review and meta-analysis of low quality RCTs (C)	12 studies (811 participants)	6 week to 1 year Tai Chi programs compared with a variety of other interventions	No adverse events were reported. No significant benefit for symptoms or physical function or psychosocial function from Tai Chi when compared with other interventions	Study quality very low to moderate
Wu W; Liu X; Wang L; Wang Z; Hu J; Yan J. Effects of Tai Chi on exercise capacity and health-related quality of life in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. International Journal of COPD, 2014, 9, 1253-1263 PMID: 25404855	Systematic review and meta-analysis of low quality studies (C)	11 articles 824 patients	Tai Chi group. Comparisons: non-exercise and/or physical exercise groups. Primary outcome measures were six-minute walking distance (6 MWD), St George's Respiratory Questionnaire (SGRQ), and Chronic Respiratory Disease Questionnaire (CRQ).	Compared with the non-exercise group, the Tai Chi group demonstrated significantly enhanced 6 MWD (mean difference 35.99, 95%CI 15.63-56.35, P=0.0005), decreased SGRQ score (mean difference -10.02, 95% CI -17.59, -2.45, P=0.009), and increased CRQ total score (mean difference 0.95, 95% CI 0.22-1.67, P=0.01). Compared with the physical exercise group, the Tai Chi group showed significantly reduced SGRQ total score (mean difference -3.52, 95% CI -6.07, -0.97, P=0.07), but no difference in 6 MWD.	Studies were of low methodologic quality

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Topic P. Treatment: Mental Health, Psychological Support

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Farver-Vestergaard I[1], Jacobsen D, Zachariae R. Efficacy of psychosocial interventions on psychological and physical health outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Psychother Psychosom. 2015;84(1):37-50. doi: 10.1159/000367635. Epub 2014 Dec 24. PMID: 25547641	(A) Meta-analysis of controlled trials	20 studies (1361 patients) (19 RCTs, 1 nonrandomized CT)	683 received psychosocial intervention v. 394 received active control intervention (non psychosocial) and 284 usual care controls	CBT improved psychological outcomes (g = 0.39, CI = 0.15-0.62; p = 0.001). Mind-body interventions (e.g. mindfulness-based therapy, yoga, and relaxation) improved physical symptoms (g = 0.40; CI = 0.01-0.79; p = 0.042)	Likely positive publication bias Studies on mind-body interventions were of variable quality Effect sizes were larger for psychological than physical outcomes
Blakemore A; Dickens C; Guthrie E; Bower P; Kontopantelis E; Afzal C; Coventry PA. Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis. International Journal of COPD, 2014, 9, 501-512 PMID: 24876770	Meta-analysis of prospective cohort studies (C)	3 studies of COPD patients with depression 2 studies of COPD patients with anxiety	Random effects meta-analysis for correlation between depression at baseline and HRQoL measured at follow-up	Depression: large positive correlation between depression at baseline and HRQoL measured at follow-up (r=0.48, 95% CI 0.37–0.57, P<0.001). anxiety at baseline was associated with a moderate and significant positive correlation with HRQoL at follow-up (r=0.36, 95% CI 0.23–0.48, P<0.001) -	High heterogeneity across studies reported N (individuals) of the meta-analysis was not clearly stated.

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Topic Q. Treatment of Acute COPD Exacerbation

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Walters JAE et al. Different durations of corticosteroid therapy for exacerbations of COPD. Cochrane Database of Systematic Reviews. 2014, Issue 12. No: CD006897 PMID: 25491891	Systematic review and meta-analysis of RCTs (Cochrane review) (A)	Adults with acute exacerbations of COPD receiving systemic corticosteroid treatment 5 RCTs (519 pts)	Short (≤ 7 days) versus long (> 7 days) duration of systemic corticosteroid treatment	No difference was noted in any of the following outcomes: - risk of treatment failure - risk of relapse - time to next COPD exacerbation - adverse events of steroid therapy - length of hospital stay	Studies were at low risk of selection, performance, detection, and attrition bias. Studies were of moderate quality evidence. Patients with mild or moderate COPD were not included in this analysis.
Cheng T, Gong Y, Guo Y, Cheng Q, Zhou M, Shi G, Wan HY. Systemic corticosteroid for COPD exacerbations, whether the higher dose is better? A meta-analysis of randomized controlled trials. *Clin Respir J.* 2013 Oct;7(4):305-18. PMID: 23072733	Systematic review / meta-analysis or RCTs (A)	To compare high dose and low dose systemic corticosteroid treatment in patients with acute exacerbations of COPD 12 RCTs (1,172 pts)	1. Systemic steroids vs placebo 2. Comparing outcomes between low-dose (30-80 mg prednisone equivalent/day) and high-dose (≥80 mg/day) corticosteroid administration.	Exposure to systemic steroids (all doses) demonstrated a significant reduction in the treatment failure rate compared to placebo (RR 0.58; 95% CI: 0.46-0.73) and improvement in FEV1 (0.11 L; 95% CI: 0.08-0.14 L). Low vs high dose corticosteroid regimens: no significant association between dose and risk for treatment failure	Significantly more hyperglycemia in patients receiving systemic corticosteroids (any dose) No significant difference in secondary infection (4 trials), gastrointestinal bleeding (4 trials), and neurologic disorders (5 trials) with corticosteroid use or dose.
Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Dec 12;12:CD010257. PMID: 23235687	Systematic review of RCTs (Cochrane review) (A)	Adult patients with an acute exacerbation of COPD 16 RCTs (2,068 pts)	Antibiotics vs placebo. Analysis was separated into 3 patient groups: outpatients, inpatients, and patients admitted to the ICU.	Treatment failure: antibiotics significantly reduced treatment failure in outpatients (RR 0.75; 95% CI 0.60 to 0.94); inpatients (RR 0.77; 95% CI 0.65 to 0.91); and ICU patients (RR 0.19; 95% CI 0.08 to 0.45). Mortality: no significant difference (except for ICU pts)	The studies for outpatients were of lower quality and treatment failure significance was lost when the meta-analysis was restricted to only currently available drugs . There was a statistically significant higher risk of adverse events with use of antibiotics (eg. Diarrhea)
El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PM. Short-course antibiotic treatment in acute exacerbations of	Systematic review with meta-analysis of double-	Adult patients with an acute exacerbation of COPD	Short course of antibiotics (≤5 days) vs. a longer course (>5 days).	Clinical cure rate: No statistically significant difference in cure rates found between short and conventional course treatments at early and late follow-up.	The average quality of studies was high. Double-blind studies with azithromycin in shorter arm were excluded.

| chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax*. 2008. May;63(5):415-22. PMID: 18234905 | blinded RCTs (A) | 21 RCTs (10,698 pts) | | Sub-analysis by antibiotic class also did not reveal any significant difference. | |

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Topic R. Referral

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
(no entries available)					

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Topic S. Surgical Treatment: Lung Volume Reduction Surgery, Lung Treatment

Reference Citation	Study Design*	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Klooster K, tenHacken NH, Hartman JE, Kerstiens HS, van Rikxoort EM, Siebos DJ. Endobronchial valves for emphysema without interlobar collateral ventilation. N Engl J Med. 2015 Dec 10;373(24):2325-35. PMID:26650153	Randomized controlled trial (B)	68 patients (mean age 59 years; 46 were women)	EBV group (34 patients) v. control group (34) One patient in the EBV group died.	Intention-to-treat analyses: significantly greater improvement in FEV1, FVC, 6-minute walk distance. Increased adverse events in the EBV group at 6 months: 23 serious adverse events, as compared with 5 in the control group (P<0.001).	Serious treatment-related adverse events included 1 death, pneumothorax (18% of patients) and events requiring valve replacement (12%) or removal (15%).
Sciurba FC, Criner GH, Strange C, et al. Effect of endobrachial coils vs usual care on exercise tolerance in patients with severe emphysema: The RENEW randomized clinical trial. JAMA. 2016 May 24-31;315(20):2178-89. PMID: 27179849	Randomized controlled trial (B)	315 patients with emphysema and severe hyperinflation	158 intervention (usual care plus bilateral coil treatment 157 Usual care controls (guideline based, including pulmonary rehabilitation and bronchodilators)	Statistically significant improvement in clinical outcomes was modest and of uncertain clinical significance.	Major complications occurred in 34.8% of coil participants and 19.1% of usual care (P = .002). Pneumonia and pneumothorax occurred more frequently in the coil group
Naunheim KS, Wood De, Mohsenifar, Z, et al; National Emphysema Treatment Trial Research Group. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg. 2006 Aug;82(2):431-43. PMID: 16888872	Randomized controlled trial (B)	1218 patients with severe emphysema from 17 centers	608 underwent lung volume reduction surgery (LVRS) 610 received medical treatment	Overall survival advantage for LVRS, with a 5-year risk ratio (RR) for death of 0.86 (p = 0.02).	Survival advantage was noted in patients with the lowest exercise capacity and upper-lobe predominant emphysema.

Reference	Study Design*	Sample	Intervention	Results	Comments
Ramsey SD, Shroyer AL, Sullivan SD, Wood DE. Updated evaluation of the cost-effectiveness of lung volume reduction surgery. <u>Chest</u> [2007, 131(3):823-832] PMID: 17356099	Randomized controlled trial (B)	1218 patients with severe emphysema from 17 centers	608 underwent lung volume reduction surgery (LVRS) 610 received medical treatment Cost effectiveness was calculated from a societal perspective over the course of the trial and estimated for a projection of 10 years based on observed trends in survival, cost, and quality of life.	Cost-effectiveness of LVRS vs medical therapy for unselected patients with severe emphysema was $140,000 per quality-adjusted life-year (QALY) gained (95% confidence interval, $40,155 to $239,359) at 5 years, and was projected to be $54,000 per QALY gained at 10 years. Cost-effectiveness of LVRS in selected patients with upper-lobe emphysema and low exercise capacity was $77,000 per QALY gained at 5 years, and was projected to be $48,000 per QALY at 10 years.	Projections demonstrated cost effectiveness for a selected subpopulation with upper-lobe emphysema and low exercise capacity, but only if life expectancy surpassed the analyzed survival thresholds of 5-10 years.
Orens JB, Estienne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. <u>J Heart Lung Transplant.</u> 2006 Jul;25(7):745-55. PMID: 16818116	Expert consensus guideline		International guideline for selection of lung transplant candidates: 2006 update		Considerations for lung transplantation candidates require collaboration with a pulmonary specialist for detailed assessment.

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Topic T. Follow up Care, Monitoring, Chronic Disease Management

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Bischoff EW, Akkermans R, Bourbeau J, van Weel C, Vercoulen JH, Schermer TR. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. BMJ. 2012 Nov 28;345:e7642 PMID: 23190905	Randomized controlled trial (B)	Patients with COPD confirmed by spirometry and treated in general practice. Patients with very severe COPD or treated by a respiratory physician were excluded. 165 patients	24 month, multicentre, investigator blinded, three arm, pragmatic, randomised controlled trial with 55 patients allocated to each condition: • self management, • routine monitoring • usual care alone	Comprehensive self management or routine monitoring did not show long term benefits in terms of quality of life or self efficacy over usual care alone in COPD patients in general practice. Patients in the self management group seemed to be more capable of appropriately managing exacerbations than did those in the usual care group. Compared with usual care, more exacerbations in the self management group were managed with bronchodilators (odds ratio 2.81, 95% confidence interval 1.16 to 6.82) and with prednisolone, antibiotics, or both (3.98, 1.10 to 15.58).	

* Levels of evidence are based on study design:
  A = systematic reviews of randomized controlled trials (interventions) with or without meta-analysis,
  B = randomized controlled trials (interventions)
  C = systematic review of non-randomized controlled trials (interventions) or observational studies, non-randomized controlled trials (interventions), group observation analysis studies (cohort, cross-sectional, case-control),
  D = individual observation descriptive studies (case study/case series),
  E = expert opinion regarding benefits and harm

Topic U. Palliative Care for COPD

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Weber C, Stirnemann J, Herrmann FR, Pautex S, Janssens, JP. Can early introduction of specialized palliative care limit intensive care, emergency and hospital admissions in patients with severe and very severe COPD? A randomized study. BMC Palliative Care, 2014, 13:47. DOI: 10.1186/1472-684X-13-47	Review of non-randomized controlled trials and observational studies (C) (Review reported in background and intervention sections for basis of protocol of study to be performed.)	23 studies	Trials and observational studies assessing the relationships between aspects of palliative care are with a variety of outcomes.	Given the trends toward aggressive and costly care near end-of-life among patients with COPD, a timely introduction of palliative care may limit unnecessary and burdensome personal and societal costs, and invasive approaches. The results of this study may provide directions for future palliative care interventions in this particular population.	Methods for performing the review were not described and whether it was systematic is uncertain.
Au DH, Udris EM, Engelberg RA, et al. A randomized trial to improve communication about end-of-life care among patients with COPD. Chest, t2012, 141 (3) : 726-35. doi: 10.1378/chest.11-0362	Randomized controlled trial (B)	Patients with COPD (GOLD definition) treated at outpatient clinics at VA Puget Sound Health Care System. 376 patients and 92 clinicians providing their care	The intervention clinicians and patients received a one-page patient-specific feedback form, based on questionnaire responses, to stimulate conversations. The control group completed questionnaires but did not receive feedback. Patient-reported occurrence and quality of end-of-life communication (QOC) were assessed within 2 weeks of a targeted visit.	Patients in the intervention arm reported nearly a threefold higher rate of discussions about end-of-life care (unadjusted, 30% vs 11%; $P < .001$). Baseline end-of-life communication was poor (intervention group QOC score, 23.3; 95% CI, 19.9-26.8; control QOC score, 19.2; 95% CI, 15.9-22.4). Patients in the intervention arm reported higher-quality end-of-life communication that was statistically significant, although the overall improvement was small (Cohen effect size, 0.21).	

Weingaertner V; Scheve C; Gerdes V; et al. Breathlessness, functional status, distress, and palliative care needs over time in patients with advanced chronic obstructive pulmonary disease or lung cancer: a cohort study. J Pain Symptom Manage. 2014 Oct;48(4):569-81.e1. doi: 10.1016/j.jpainsymman.2013.11.011.	Cohort Study (C)	Patients with COPD (Stage III/IV) or lung cancer. A total of 82 patients (50 COPD and 32 LC), mean (SD) age of 67.2 (7.8), and 36% female were included (8 COPD and 23 LC deceased)	Objective to describe and compare the courses of refractory breathlessness, functional status, distress, and PC needs in patients with advanced chronic obstructive pulmonary disease (COPD) or lung cancer (LC) over time.	The patients with COPD perceived higher levels of breathlessness and distress at lower functional status steadily over time. The LC patients' breathlessness, distress, and palliative care (PC) needs increased, whereas functional status decreased toward death. The PC needs were similar between disease groups. Breathlessness was negatively correlated with functional status (COPD=mean r=-0.20, P=0.012; LC=mean r=-0.277, P=0.029) and positively correlated with PC needs in COPD patients (mean r=0.343, P<0.001). Death was significantly predicted by diagnosis (LC: hazard ratio=7.84, P<0.001) and functional status (10% decline: hazard ratio=1.52, P=0.001). The PC needs of patients with advanced COPD are comparable with LC patients, and breathlessness severity and distress are even higher. The care for COPD patients requires further improvement to address symptom burden and PC needs.	

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     studies (cohort, cross-sectional, case-control),
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