

**PICO5: Should opioids be used to reduce symptoms in people with serious illness related to lung disease?**

P	Adults with serious illness related to lung disease
I	Oral, subcutaneous or intravenous opioids
C	No opioids
O	Critical: breathlessness Important: cough, health-related quality of life, adverse events

**Types of studies:** We will include randomised controlled trials and randomised crossover trials.

Where a high-quality, relevant systematic review has been published (e.g. Cochrane Collaboration), this will be utilised in order to increase the efficiency of the guideline development process. The AMSTAR-2 checklist (Shea et al, BMJ 2017) will be used to appraise the quality of these existing reviews.

Where RCTs are not available or are few in number we may consider other types of evidence.

**Types of participants:** We will include adults with serious illness related to lung disease. Serious illness is defined as a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress (Kelley AS. J Palliat Med. 2014;17:985.)

For mixed studies (eg studies including those with malignant disease) we will ask the authors for data related to the participants with non-malignant disease only. If separate data are unable to be obtained then we will include studies only if  $\geq 80\%$  of participants have non-malignant disease.

**Types of interventions:** Any opioid drug, given by intravenous, sub-cutaneous or oral routes in any dose, for the treatment of breathlessness or cough.

**Types of comparisons:** we will include studies that report the effects of opioids compared to placebo (i.e. usual care), or any other pharmacological or non-pharmacological interventions that were directly compared with the opioid treatment.

**Outcomes:**

Critical:

- Breathlessness, using relevant and validated tool. This may include measures at rest or during exercise, but exercise measures obtained before and after an intervention must be obtained at iso-workload.

Important:

- Health related quality of life, using any validated tool
- Cough, using any validated tool
- Arterial blood gas
- Adverse events, defined according to the investigators' definition

Reporting one of more of the outcomes listed here in the trial is not an inclusion criterion for the review.

**Search methods:** We will identify trials from searches of the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library) (latest issue);
- MEDLINE (Ovid) (1950 to date);
- EMBASE (Ovid) (1974 to date).

The search strategy will be developed by the medical librarian.

Key words to consider for inclusion are:

opioid

analgesic

narcotic

morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone or opioid\* or opiate\* or codeine or dextromoramide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine

Dyspnea

dyspnoea\* or breathless\* or (short\* near/2 breath\*)

exercise

endurance

cough

randomised controlled trial

controlled clinical trial

randomized

placebo

drug therapy

random

random allocation

trial

crossover

controlled clinical trial

double-blind

single Blind

quantitative studies

quality of life

placebo

human

exclude: (animal/ or nonhuman/) not human

We will first search for any systematic reviews. Where a relevant systematic review is identified but has been published more than 1 year ago we will update the search to ensure more recent data are included.

**Searching other resources:** We will check reference lists of all primary studies and review articles for additional references. We will search for errata or retractions from included studies published in full-text on PubMed and report the date this was done within the review.

**Assessment of risk of bias:** Two authors will independently assess risk of bias for each study using the Cochrane Collaboration's Risk of Bias (1) tool.

**Measures of treatment effect:** We will analyse dichotomous data as odds ratios (ORs). For continuous data, we will use mean differences (MDs) or standardised mean differences (SMDs). Where it is reported, we will

use the change from baseline. Where the change from baseline is not reported, we will use the adjusted results or final score. We will enter data presented as a scale with a consistent direction of effect (e.g. health-related quality of life data). We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will narratively describe skewed data reported as medians and interquartile ranges. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

**Dealing with missing data:** We will contact trial investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

**Assessment of heterogeneity:** We will use the  $I^2$  statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis.

**Assessment of reporting biases:** If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

**Data synthesis:** We will perform a pooled quantitative synthesis where the trials are clinically homogeneous. We will pool data using a random-effects model to incorporate between study heterogeneity into the meta-analysis. Where the trials are clinically heterogeneous, we will perform a narrative synthesis.

**Subgroup analysis:** No subgroup analyses will be performed, as there are unlikely to be sufficient data to draw meaningful conclusions.

**Sensitivity analysis:** We will perform sensitivity analyses to examine the effects of methodological quality on the pooled estimate by removing studies that are at high or unclear risk of bias for the domains of blinding and incomplete outcome data.

Search strategy: RCTs for Opioids and Lung diseases (minus PHT and CF)

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions** 1946 to July 07, 2022

Search Strategy:

#	Searches	Results
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/	146162
2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/ or respiratory tract diseases/ or respiration disorders/ or dyspnea/	274683
3	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s or bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s or airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.	383508
4	((((chronic or severe* or unrelenting or obstructive) adj asthma*) or (chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory))))).mp.	90549

5	1 or 2 or 3 or 4	565554
6	exp narcotics/ or exp analgesics, opioid/ or exp Analgesics/ or exp morphine derivatives/ or morphine/ or fentanyl/ or alfentanil/ or sufentanil/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/	573427
7	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.	321908
8	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanil or sulfentanil or sulfentanil or alfentanil or remifentanil or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodeinone or dihydrohydroxydodeinone or dihydrone or oxiconona or oxicone or oxicontin or oxikodon or oxycodoinonhydrochloride or oxycodon or pentacozone or pentazocin? or methadon or codein or methyl morfine or methylmorfine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethedine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.	96301
9	6 or 7 or 8	709051
10	5 and 9	9816
11	(randomized controlled trial or controlled clinical trial).pt.	662415
12	(randomi?ed or placebo).ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1328662
13	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.	76937
14	11 or 12 or 13	1514519
15	10 and 14	1494
16	exp animals/ not humans.sh.	5024857
17	15 not 16	1429

18	limit 17 to yr="2020 -Current"	132
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Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** June 2022  
Search Strategy:

#	Searches	Results
1	lung diseases/ or "cystic adenomatoid malformation of lung, congenital"/ or hepatopulmonary syndrome/ or lung abscess/ or lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/	4231
2	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/ or respiratory tract diseases/ or respiration disorders/ or dyspnea/	21069
3	(lung disease* or pulmonary disease* or cystic fibrosis or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma* or bronchial disease* or bronchiectas?s or bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s or airway obstructive	36604

	disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.	
4	((((chronic or severe* or unrelenting or obstructive) adj asthma*) or (chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory))))).mp.	21431
5	1 or 2 or 3 or 4	51353
6	exp narcotics/ or exp analgesics, opioid/ or exp Analgesics/ or exp morphine derivatives/ or morphine/ or fentanyl/ or alfentanil/ or sufentanil/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/	58946
7	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.	85939
8	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanyl or sulfentanil or sulfentanyl or alfentanyl or remifentanyl or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodone or dihydrohydroxydodeinone or dihydrone or oxiconone or oxiconone or oxiconone or oxiconone or oxycodone or oxycodone or pentacozine or pentazocin? or methadon or codein or methyl morfine or methylmorfine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethedine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.	21625
9	6 or 7 or 8	116868
10	5 and 9	1407
11	limit 10 to yr="2020 -Current"	140

RCTs for chronic obstructive and bronchi 2015 plus Embase

Database(s): **Embase Classic+Embase** 1947 to 2022 July 07

Search Strategy:

#	Searches	Results
1	exp opiate agonist/ or exp opiate/ or exp analgesic agent/ or exp narcotic agent/ or exp fentanyl derivative/ or exp alfentanil/ or exp fentanyl/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/ or exp morphine derivative/ or exp narcotic analgesic agent/	1216205
2	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.	590408
3	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanil or sulfentanil or sulfentanil or alfentanil or remifentanil or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodone or dihydrohydroxydodeinone or dihydrone or oxiconone or oxiconone or oxiconone or oxiconone or oxycodone or oxycodone or pentacozine or pentazocin? or methadon or codein or methyl morfine or methylmorfine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethidine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.	180704
4	1 or 2 or 3	1302550
5	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/	1796872
6	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.	1418543
7	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.	73389
8	5 or 6 or 7	2171182

9	lung diseases, obstructive/ or asthma/ or asthma-chronic obstructive pulmonary disease overlap syndrome/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/ or bronchitis, chronic/ or pulmonary disease, chronic obstructive/ or pulmonary emphysema/ or plasma cell granuloma, pulmonary/ or bronchial diseases/ or bronchiectasis/ or respiratory tract diseases/ or respiration disorders/ or dyspnea/	605549
10	((chronic or severe* or unrelenting or obstructive) adj asthma*) or (chronic* obstruct* adj3 (lung* or airway* or pulmon* or bronch* or alveolit* or respiratory))).mp.	192567
11	(airway obstructive disease* or obstructive airway disorder* or obstructive respiratory disease* or obstructive respiratory disorder* or pneumatosis pulmonum or interstitial syndrome).mp.	1301
12	bronchiectasis/ or (bronchiolitis obliterans or constrictive bronchiolit* or exudative bronchiolit* or chronic bronchitis or emphysema* or bronchial disease* or bronchiectas?s).mp.	118204
13	9 or 10 or 11 or 12	729160
14	4 and 13	38844
15	8 and 14	5446
16	limit 14 to (randomized controlled trial or controlled clinical trial)	1836
17	15 or 16	5653
18	(exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not exp human/	7772986
19	17 not 18	5586
20	limit 19 to (conference abstract or editorial or letter or note)	705
21	19 not 20	4881
22	limit 21 to yr="2015 -Current"	1783

## RCTs for interstitial 2019 plus Embase

Database(s): **Embase Classic+Embase** 1947 to 2022 July 07

Search Strategy:

#	Searches	Results
1	exp opiate agonist/ or exp opiate/ or exp analgesic agent/ or exp narcotic agent/ or exp fentanyl derivative/ or exp alfentanil/ or exp fentanyl/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/ or exp morphine derivative/ or exp narcotic analgesic agent/	1216205
2	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.	590408
3	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanil or sulfentanil or sulfentanil or alfentanil or remifentanil or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodone or dihydrohydroxydodeinone or dihydrone or oxiconone or oxiconone or oxiconone or oxiconone or oxycodone or oxycodone or pentacozine or pentazocin? or methadon or codein or methyl morfine or methylmorfine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethedine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.	180704
4	1 or 2 or 3	1302550
5	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/	1796872
6	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.	1418543
7	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.	73389
8	5 or 6 or 7	2171182

9	lung diseases, interstitial/ or alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/ or anti-glomerular basement membrane disease/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or asbestosis/ or berylliosis/ or byssinosis/ or caplan syndrome/ or siderosis/ or silicosis/ or silicotuberculosis/ or pulmonary fibrosis/ or idiopathic pulmonary fibrosis/ or hamman-rich syndrome/ or idiopathic interstitial pneumonias/ or cryptogenic organizing pneumonia/ or sarcoidosis, pulmonary/	313355
10	(lung disease* or pulmonary disease* or interstitial pneumoni* or extrinsic allergic alveolit* or hypersensitivity pneumoniti* or pneumoconios?s or anthracos?s or anthracosilicos?s or asbestos?s or beryllios?s or byssinos?s or beryllium disease* or caplan syndrome or bird fancier* lung or farmer* lung or silo filler* disease or trichosporonos?s or sideros?s or silicos?s or silicotuberculos?s or fibrosing alveolit* or pulmonary fibros?s or fibrocystic pulmonary dysplasia* or hamman-rich disease or hamman-rich syndrome or cryptogenic organizing pneumonia* or pulmonary sarcoidos?s or pulmonary inflammatory pseudotumo?r or pulmonary plasma cell granuloma*).mp.	436362
11	(bronchopulmonary disease* or lung granulomatos?s or pneumopath* or pulmonary disorder* or acute pneumonitis or chronic fibrous pneumonia* or fibroid phthisis or interstitial cell pneumonia or interstitial plasma cell pneumonia or interstitial pneumocystic pneumonia or phthisis fibroidea or pneumonia interstitialis or interstitial fibros?s or lung fibros?s or interstitial fibros?s or alveolar fibros?s or respiratory granulomatos?s or pulmonary granulomatos?s or lung conios?s or pneumoconiotic lesion or pneumokonios?s or pneumono?onios?s).mp.	72328
12	9 or 10 or 11	571944
13	4 and 8 and 12	2389
14	4 and 12	17954
15	limit 14 to (randomized controlled trial or controlled clinical trial)	736
16	13 or 15	2478
17	(exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not exp human/	7772986
18	16 not 17	2457
19	limit 18 to (conference abstract or editorial or letter or note)	299
20	18 not 19	2158
21	limit 20 to yr="2019 -Current"	516





9	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.	73389
10	7 or 8 or 9	2171182
11	6 and 10	326
12	limit 6 to (randomized controlled trial or controlled clinical trial)	64
13	11 or 12	343
14	limit 13 to yr="2019 -Current"	51

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** June 2022 Search Strategy:

#	Searches	Results
1	cystic fibrosis.mp.	6048
2	exp narcotics/ or exp analgesics, opioid/ or exp Analgesics/ or exp morphine derivatives/ or morphine/ or fentanyl/ or alfentanil/ or sufentanil/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/	58946
3	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.	85939
4	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanyl or sulfentanil or sulfentanyl or alfentanyl or remifentanyl or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodone or dihydrohydroxydodeinone or dihydrone or oxycodona or oxicone or oxicontin or oxikodon or oxycodonehydrochloride or oxycodon or pentazocine or pentazocin? or methadon or codein or methyl morfine or methylmorphine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethedine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.	21625

5	2 or 3 or 4	116868
6	1 and 5	38
7	limit 6 to yr="2019 -Current"	4

## RCTs for PHT and Opioids

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions** 1946 to July 07, 2022

Search Strategy:

#	Searches	Results
1	hypertension, pulmonary/ or familial primary pulmonary hypertension/ or pulmonary arterial hypertension/ or Pulmonary Heart Disease/	43858
2	((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomas or veno-occlusive or venoocclusive or parenchyma* disease*)).mp.	44298
3	(corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*).mp.	4338
4	1 or 2 or 3	62339
5	exp narcotics/ or exp analgesics, opioid/ or exp Analgesics/ or exp morphine derivatives/ or morphine/ or fentanyl/ or alfentanil/ or sufentanil/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/	573427
6	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.	321908
7	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanil or sulfentanil or sulfentanil or alfentanil or remifentanil or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodone or dihydrohydroxydodeinone or dihydrone or oxiconone or oxiconone or oxiconone or oxiconone or oxycodone or oxycodone or pentazocine or pentazocin? or methadon or codein or methyl morphine or methylmorphine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethidine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.	96301
8	5 or 6 or 7	709051

9	4 and 8	955
10	(randomized controlled trial or controlled clinical trial).pt.	662415
11	(randomi?ed or placebo).ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1328662
12	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.	76937
13	10 or 11 or 12	1514519
14	9 and 13	103
15	limit 14 to yr="2015 -Current"	22

Database(s): **Embase Classic+Embase** 1947 to 2022 July 07

Search Strategy:

#	Searches	Results
1	pulmonary hypertension/ or chronic thromboembolic pulmonary hypertension/ or cor pulmonale/ or pulmonary capillary hemangiomatosis/ or pulmonary vascular obstructive disease/ or pulmonary veno-occlusive disease/	110118
2	((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)).mp.	114660
3	(corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*).mp.	11627
4	1 or 2 or 3	123420
5	exp opiate agonist/ or exp opiate/ or exp analgesic agent/ or exp narcotic agent/ or exp fentanyl derivative/ or exp alfentanil/ or exp fentanyl/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/ or exp morphine derivative/ or exp narcotic analgesic agent/	1216205
6	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide	590408

	or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.	
7	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanyl or sulfentanil or sulfentanyl or alfentanyl or remifentanyl or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodone or dihydrohydroxydodeinone or dihydrone or oxycodona or oxicone or oxicontin or oxikodon or oxycodone or oxycodon or pentacozine or pentazocin? or methadon or codein or methyl morphine or methylmorphine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethedine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.	180704
8	5 or 6 or 7	1302550
9	4 and 8	5498
10	limit 9 to (randomized controlled trial or controlled clinical trial)	162
11	randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/	1796872
12	(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.	1418543
13	((cross over or crossover) adj (clinical study or clinical trial or design or method or study or trial or studies)).mp.	73389
14	11 or 12 or 13	2171182
15	9 and 14	649
16	10 or 15	679
17	limit 16 to yr="2015 -Current"	252

#	Searches	Results
1	hypertension, pulmonary/ or familial primary pulmonary hypertension/ or pulmonary arterial hypertension/ or Pulmonary Heart Disease/	1307
2	((lung or pulmonary) adj (arter* hypertens* or hypertens* or fixed hypertens* or capillary hemangiomatosis or veno-occlusive or venoocclusive or parenchyma* disease*)).mp.	3699
3	(corpulmonale or cor pulmonale or pulmonary cardiac disease* or pulmonary vascular obstructive disease* or obstructive pulmonary vascular disease*).mp.	233
4	1 or 2 or 3	4171
5	exp narcotics/ or exp analgesics, opioid/ or exp Analgesics/ or exp morphine derivatives/ or morphine/ or fentanyl/ or alfentanil/ or sufentanil/ or exp remifentanil/ or exp sufentanil/ or exp hydromorphone/ or exp oxycodone/ or exp pentazocine/ or exp methadone/ or exp codeine/ or exp dextromoramide/ or exp fentanyl citrate/ or exp diamorphine/ or exp dihydrocodeine/ or exp dextropropoxyphene/ or exp meptazinol/ or exp nalbuphine/ or exp meptazinol/ or exp dipipanone/ or exp pethidine/ or exp tramadol/ or exp buprenorphine/	58946
6	(opiate* or opioid* or analgesic* or morphine or narcotic* or fentanyl or alfentanil or remifentanil or sufentanil or hydromorphone or oxycodone or pentazocine or methadone or codeine or dextromoramide or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.	85939
7	(opiat or analgetic or morfin? or morphia or morphin* or fentamyl or fentanil or duragesic or sufentanyl or sulfentanil or sulfentanyl or alfentanyl or remifentanyl or dihydromorphinone or dihydromorphone or hydromorph contin or hydromorphinone or hydromorphon? or dihydrohydroxycodone or dihydrohydroxydodeinone or dihydrone or oxiconone or oxiconone or oxicontin or oxikodon or oxycodone or oxycodone or pentacozine or pentazocin? or methadon or codein or methyl morfine or methylmorphine or methylmorphine or dextro moramide or dextromoramine or actiq or fenodid or fentabbott or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or heroin? or codhydrin? or dihydroneopine or hydrocodin? or propoxyphen? or propoxyphenhydrochloride or propoxyphine or nalbufin? or piperidyl amidone or meperidin? or meperidol or methylphenylcarbethoxypiperidine or pethidine or tramadolhydrochlorid or buprenorfin or buprenorphin).mp.	21625
8	5 or 6 or 7	116868
9	4 and 8	96
10	limit 9 to yr="2015 -Current"	38

