Review

Randomized Controlled Trials on Chronic Obstructive Pulmonary Disease in Africa: A Systematic Review

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Running Head: Randomized Controlled Trials on COPD in Africa

Keywords: non-communicable diseases; chronic lung diseases; pulmonology; systematic review; randomized controlled trials

Abbreviations:
AVAPS – Average volume-assured pressure support
BiPAP – Biphasic positive airway pressure
COPD – Chronic obstructive pulmonary disease
ED – Emergency department
GOLD – Global initiative for chronic obstructive lung disease
ICU – Intensive care unit
RCT – Randomized-controlled trial
PACTR – Pan African Clinical Trials Registry
WHO – World Health Organization
PEN – Package of essential noncommunicable diseases

**Funding Support:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Date of Acceptance:** July 9, 2023  |  **Published Online Date:** July 12, 2023

**Citation:** Kroeber ES, Frese E, Kantelhardt J, et al. Randomized controlled trials on chronic obstructive pulmonary disease in Africa: a systematic review. *Chronic Obstr Pulm Dis.* 2023; Published online July 12, 2023. [https://doi.org/10.15326/jcopdf.2023.0387](https://doi.org/10.15326/jcopdf.2023.0387)

**Note:** This article has an online supplement.
Abstract

**Background:** The rising burden of chronic obstructive pulmonary disease (COPD) in African countries is attributed to the growing and ageing of the populations, lifestyle, and environmental changes. This systematic review aims to map the available evidence on interventions on COPD in Africa.

**Methods:** We performed a systematic search in six (including local African) databases and registries with updates until January 2022. We included randomized controlled trials (RCTs) the included patients diagnosed with COPD that were conducted in Africa, studying outcomes on acute respiratory episodes and rates, physical and functional abilities, and adverse events. We followed the PRISMA guidelines. The study quality was assessed using the Cochrane Risk of Bias tool. We primarily summarized the results in a narrative way.

**Results:** Out of 1594 identified publications we included 18 studies with altogether 1504 participants, conducted in Egypt, South Africa, and Tunisia. Eight studies investigated interventions for patients in stable phases treated in outpatient settings and ten included patients with acute COPD exacerbation treated in emergency or intensive care settings. The interventions mainly include ventilatory support, pharmacological and rehabilitative interventions. Reported treatment effects were heterogeneous ranging from no beneficial effects to clinically relevant benefits.

**Conclusions:** The included studies were conducted in countries with high infrastructural development and half of them were set in intensive care units. Despite the paucity of RCTs on COPD management, research activities have been increasing over the last years.
1 Introduction
Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide\(^1,2\). Of the 3.23 million COPD-related deaths in 2019, 80 % occurred in low- and middle income countries\(^3\). With a mean prevalence of 11.7 \(^4\), COPD affects the lives of over 150 million people in Africa\(^5\). The reported prevalence of COPD greatly varies across the continent ranging from 8.4 % in Cape Verde to 24.8 % in South Africa\(^6\). These variations are attributed to differing local determinants, risk factors, diagnostic criteria and procedures\(^7\).

The varying and increasing burden of non-communicable diseases such as COPD in African countries is attributed to the ageing of the populations and lifestyle changes\(^8\). Major risk factors for COPD are cigarette smoking\(^9\) and air pollution\(^10\). Despite several measures on awareness and tobacco control policies\(^11,12\), cigarette consumption is increasing\(^2,13-15\) and COPD prevalence is high even in non-smoking young people\(^7,14,16,17\). Major contributing factors are the use of biomass fuels for cooking and heating in enclosed spaces, environmental pollution, dust in occupational settings, tuberculosis, childhood respiratory infections\(^7,16,18\) and exposure to ambient air pollution in the mega-cities\(^19\).

COPD is an umbrella term describing chronic lung diseases that cause limitations in pulmonary airflow with common symptoms as shortness of breath, a 'need for air', excessive sputum production and a chronic cough\(^20\). These symptoms are persistent with only small day-to-day variations, usually starting in middle age and slowly worsening over time\(^21\). Due to high individual health and financial burdens of acute exacerbations, interventions in stable phases and effective tertiary prevention are crucial\(^21,22\). Currently, there are no national guidelines on diagnosis and treatment of COPD in African countries except for South Africa\(^7,8,23\). Well-established international
guidelines \textsuperscript{24,25} are rarely applicable, due to low availability of diagnostic tools and affordable treatment, especially in rural areas\textsuperscript{14,17}.

The main aim of this systematic review is to map the best available evidence of interventions on secondary and tertiary prevention, diagnosis, and treatment to achieve symptom control and to prevent exacerbations for African patients with COPD.

2 Methods
We registered a protocol for a systematic review to summarize evidence on chronic obstructive respiratory diseases created in Africa on PROSPERO (CRD42020145057). This systematic review summarizes a subsample of studies on patients diagnosed with COPD from studies found in the systematic search. All steps were based on the PRISMA guideline for systematic reviews (see checklist S1)\textsuperscript{26}.

2.1 Inclusion and exclusion criteria
We included full-text publications of randomized controlled trials (RCTs) with COPD patients from African countries in stable or acute phases of COPD, that reported results on our predefined primary or secondary outcomes. Included RCTs focused on any preventive, diagnostic, or treatment intervention for patients with COPD. Studies on primary COPD prevention that included participants without COPD, as well as international multi-center studies with less than 50 % of centers in African countries were excluded. Table 1 details our inclusion criteria.

Insert table 1: Inclusion and exclusion criteria
2.1 Systematic search

We performed a systematic search in electronic databases (MEDLINE [Ovid], Cochrane Central Register of Controlled Trials [CENTRAL], the Cumulative Index to Nursing & Allied Health Literature [CINAHL]), specialized African databases (African Journals Online, African Index Medicus) without time restrictions until January 2022. Furthermore, we checked publications from studies registered in the Pan African Clinical Trials Registry (PACTR), screened reference lists, and contacted corresponding authors of included studies as well as members of the Guidelines International Network (GIN) African Community. Search strings based on Medical Subject Headings (MeSH) and terms on chronic obstructive lung diseases including COPD, Africa, a list of all 54 African countries, and terms related to RCTs (see full search strategy in the supplement).

2.1 Study selection and data extraction

Two authors independently screened titles and abstracts of all references as well as potentially eligible full text articles. Data extraction was done by one author and checked by another author. Disagreements were solved via discussion.

2.1 Risk of Bias Assessment

Two authors independently judged the risk of bias for each study using the Cochrane risk of bias tool in seven specific categories (sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias) as 'low', 'high', or 'unclear'. Discrepancies were resolved by discussion.

We defined risk of bias due to incomplete outcome data as high, if over 10% of randomized participants dropped out from analysis. We judged the risk of bias due to selective outcome reporting as low if study protocols with pre-defined primary and secondary outcomes were available and high if any result of pre-planned outcomes were missing. Other sources of bias were...
judged as high risk in the case of missing descriptions of or relevant deviations from a pre-planned sample size calculation, no description of a primary endpoint, or relevant differences of main baseline characteristics between intervention and control groups.

2.1 Data synthesis
We initially subdivided interventions according to the included patients’ condition (stable vs. acute) and then narratively summarized studies according to the type of intervention. We did not perform a pre-planned meta-analysis due to substantial heterogeneity of interventions and outcomes. We produced forest plots with Revman\textsuperscript{28} to visualize treatment effects.

3 Results
We identified 1819 references, screened 1594 references, read 161 potentially eligible articles and included 18 studies (reported in 19 articles) on African patients diagnosed with COPD. We excluded 51 articles reporting on asthma patients and 5 on patients with other chronic obstructive diseases (Figure 1 and table of detailed description of included studies in the supplementary material). We grouped patients into stable patients in outpatient settings and patients with acute exacerbation treated in intensive care units or emergency care. The interventions mainly included ventilatory support, pharmacological and rehabilitative interventions.

Insert figure 1: Flow chart of the systemic search

2.1 Study characteristics

2.1.1 Setting
All studies were either conducted in Egypt\textsuperscript{29-37}, Tunisia\textsuperscript{38-44} or South Africa\textsuperscript{45,46}. Ten studies were conducted in intensive care units (ICUs)\textsuperscript{29-31,36,38,43,44}, emergency units\textsuperscript{40} or specialized chest
disease departments\textsuperscript{37} of tertiary hospitals including patients in acute conditions and eight studies were set in outpatient departments and included patients in stable condition\textsuperscript{32-35,39,41,42,45,46}.

### 2.1.2 Population

A total of 17 RCTs involved 1480 participants and one crossover-RCT randomized an additional number of 24 participants to six diagnostic procedural variants\textsuperscript{46}. Eleven studies reported the inclusion of women (between 9 and 45\%). The mean age of the participants ranged from 47 to 69 years. Over 90\% of the participants had a smoking history, three studies excluded recent smokers\textsuperscript{29,39,41}. Most studies named the Global initiative for chronic obstructive lung disease (GOLD) criteria\textsuperscript{47} to diagnose COPD\textsuperscript{30,38,40,41} and classified airflow limitation as moderate\textsuperscript{35,46}, moderate to severe\textsuperscript{32,34,36,37}, or severe\textsuperscript{42}. Others based the diagnosis on the criteria\textsuperscript{48} of the American Thoracic Society\textsuperscript{35,36}, pulmonary function testing\textsuperscript{39}, or a clinical diagnosis and pulmonary function testing\textsuperscript{29,31,33,43-45}.

### 2.1.3 Interventions and results

Two studies\textsuperscript{34,44} reported results on our planned primary outcomes acute respiratory episodes and exacerbation rate. Magdy 2020 compared the effect of two nightly ventilation support regimes (spontaneously timed average volume-assured pressure support (AVAPS) vs. biphasic positive airway pressure (BiPAP)) in stable outpatients with hypercapnic respiratory failure over 6 months. The interventions showed no difference in treatment effects on the change in number of exacerbations (mean difference [MD] -0.9; 95\% CI -0.9 to 0.7), hospitalizations (MD -0.1; 95\% CI -0.6 to 0.4), or hospital days (MD -1.5; 95\% CI -5 to 2) over a 6-month period with different support systems. Nevertheless, patients in the AVAPS group showed slightly better exercise tolerance with a higher change in the 6-minute-walk-distance (6-MWD) of 9.2 m (95\% CI -1 to 15) and quality
of life scores\textsuperscript{34}. Nouira 2010 compared the effects of antibacterial agents trimethoprim-sulfamethoxazole vs. ciprofloxacin in the treatment of severe exacerbations in ICUs, stating no difference in exacerbation-free intervals (14 days; 95 %CI -15 to 43)\textsuperscript{44}.

### 2.1.4 Interventions for patients in stable phases of COPD

Nine Eight studies included stable patients COPD\textsuperscript{32,34,35,37,39,41,42,46} with, if reported, moderate to severe COPD\textsuperscript{34,35,37,41,46} (details see table 12) where interventions were prescribed and conducted in outpatient settings or home-based (Magdy 2020).

#### Insert table 2: Characteristics of studies involving stable patients in stable phases of COPD

### 2.1.5 Rehabilitative interventions

Six studies tested rehabilitative interventions including physical activity, balance training, home-based pulmonary rehabilitation, neuromuscular electrical stimulation, inspiratory muscle training and nightly spontaneous timed average volume-assured pressure support ventilation\textsuperscript{32,35,39,41,42} and compared these interventions to a usual care or another active component (see figure 2). All these studies reported on exercise tolerance (all studies reported on 6-MWD) showing beneficial, yet very heterogeneous treatment effects with a MD between 5.3 m (95 %CI -14.0 to 24.6) and MD 73.2 m (95 %CI 54.0 to 92.2) (see figure 2). A clinically relevant difference in 6-MWD of over 25 m which was judged as clinically relevant for patients with COPD\textsuperscript{49} was gained in three studies (Ghanem 2010, Mekki 2019, Mehani 2017).

The highest benefit exercise tolerance benefit was reported from a home-based pulmonary rehabilitation program including educational lectures and muscle training (MD 73.2 m (95 %CI 54.1 to 92.2). The study furthermore described improved health-related quality of life scores (Ghanem 2010)\textsuperscript{32}. Two studies trialing neuromuscular electrical stimulation (Acheche 2020, Mekki
in addition to standard pulmonary rehabilitation programs improved balance and exercise parameters. Finally, a comparison of training inspiratory and expiratory muscles (Mehani 2017) improved pulmonary function parameters and 6-MWT in both groups but showed little to no between group differences. Magdy 2020 tested two nightly breathing support regimes in stable COPD outpatients with chronic hypercapnic failure. Both interventions had beneficial outcomes with AVAPS showing additional improvements in exercise tolerance and in several domains of quality of life.

Insert figure 2: Summary of treatment effects of rehabilitative interventions for stable patients on 6-minute-walk-distance

2.1.6 Other Pharmacological interventions and diagnostic interventions

Two studies compared pharmacological interventions (Bateman 2008, Mostafa 2021) with comparable results in pulmonary function and dyspnea parameters. The last study (Calligaro 2014) tested ways to provoke dynamic hyperinflation showing the feasibility of metronome-paced tachypnea as an alternative to exercise testing.

2.1.7 Treatment of patients in acute exacerbation phases of COPD

Ten studies studied patients with acute exacerbation set in ICUs, emergency departments (ED) requiring mechanical ventilation or included outpatients. Seven studies investigated the efficacy of medication and three studies compared different ventilation treatments. They reported results on ventilation support outcomes, length of ICU or hospital stay, mortality and adverse events.
including hyperglycemic episodes, ventilator-associated pneumonia, nausea, tremor, headache\textsuperscript{29,36,38,40,43,44} (table 2 3 and supplemental figures S1 to S4).

**Insert table 3: Characteristics of studies involving stable patients in acute phases of COPD**

### 2.1.8 Pharmacological interventions

Three studies\textsuperscript{33,43,44} investigated the effects of antibiotics. Two of them stated the benefit of antibiotic therapy for patients with exacerbations. Nouira 2001 compared ofloxacin to placebo and stated reduced mortality, time on mechanical ventilation and hospital stay. Additional treatment with quinolone or amoxicillin resulted in a shorter treatment time and a higher treatment success rate (Hassan 2015). No differences were shown between distinct antibacterial agents (trimethoprim-sulfamethoxazole and ciprofloxacin) (Nouira 2010).

Only one of the other pharmacological studies (Abroug 2014, El-Attar 2009, Beltaif 2018) showed some benefit for patients with exacerbations. A small study including 80 patients with COPD exacerbations showed that intravenous supplementation of trace elements Selenium, Manganese and Zinc during mechanical ventilation can reduce the length of ventilation by 8.4 days (95 %CI 5.1 to 11.7) and slightly reduce mortality and adverse events on ICU (El-Attar 2009) (see table 2).

### 2.1.9 Breathing Ventilatory support

Weaning was more often successful in proportionally assisted ventilation than pressure support ventilation with resulting duration of mechanical ventilation and hospital stay (RR 1.35; 95 %CI 1.02 to 1.79) (Elganady 2014). Due to the importance of successful weaning in patients mechanical ventilations, El-Daim 2020 investigated different predictors of successful weaning and stated...
sensitive parameters. A last study (Mohamed 2018) investigated the therapeutic utility of fibre-optic bronchoscopy to suction retained secretions in patients with noninvasive ventilation as an alternative to intubation and was able to reduce stay in ICU by 30.5 hours (95 %CI 14.4 to 46.6) without major complications (Mohamed 2018).

2.1.10 Risk of bias

Adequate information on sequence generation, and allocation concealment were reported for eight studies. Most studies analyzed more than 90 % of randomized participants in their primary analyses. The risk of selective outcome reporting was checked in seven studies with published protocols and judged as low. Other sources of bias were identified in ten studies either due to missing description of a primary endpoint or a pre-planned sample size, relevant deviation from the pre-planned sample size or a missing description of main baseline characteristics (see table 34).

Insert table 4: Risk of bias

3 Discussion

This systematic review aims to map the available high-quality evidence on management options for patients with COPD conducted in Africa. The included studies investigated patients in stable phases of COPD treated in outpatient settings and in acute exacerbation treated in emergency or intensive care settings. The interventions involved ventilatory support, pharmacological as well as rehabilitative interventions. At present, RCTs are sparse and heterogeneous, but the number of studies and the frequency of publications have grown over the last two decades. As of today, all RCTs were conducted in three countries with a comparably high infrastructural development. No studies have been conducted in Central, East or West Africa.
3.1 Early detection, diagnosis and initial assessment and diagnosis of COPD

Reliable diagnostic interventions are crucial to initiate adequate treatment, inform patients on their condition, monitor the disease and prevent exacerbations\(^5\). Diagnostic studies with patient-related outcomes are generally rare\(^5\). We identified only one small cross-over trial that tested a simple standardized alternative to usual exercise testing for early diagnosis and assessment\(^4\). The WHO recommends spirometrically measuring the peak expiratory flow rate for patients presenting typical symptoms of COPD. Underutilization due to high costs and the need of trained staff is a major reason of under- and overdiagnosis of COPD\(^5\). There is a need of implementation research on how to effectively implement high quality diagnostic infrastructure especially spirometry for chronic lung diseases in Africa\(^5\).\(^3\).

3.2 Treatment of patients in stable phases of COPD

The six included studies that tested rehabilitative interventions in the management of COPD\(^3\) all showed some beneficial results as an additional component to usual care. Even though studies were very heterogenous in both intervention type as well as outcomes these rehabilitative efforts are diverse and are showing promising results offering a first glimpse into a future where COPD interventions that have been trialed in African countries can be used in continent specific guidelines. Stating this positive trend, is has to be said that these six studies are only currently conducted in Tunisia and Egypt and the four of them were conducted solely with male participants in urban areas\(^3\), leaving out vulnerable groups like women and people living in rural areas, who have a higher exposure to indoor air pollution and the associated increased COPD risk\(^5\). This leaves a big leap to be taken to implement research structures that represent different African populations more distinctly.

3.3 Treatment of patients in acute exacerbation phases of COPD
Most of the included studies stated at least one beneficial change in clinically relevant outcomes in the intervention group \(^{29,31-36,39,41,43}\). The existing evidence is mainly concentrated on different pharmacological interventions (see table 23). Since ICU treatment is cost- and infrastructure intensive, there are considerable hurdles of implementation and utilization in many low resource settings. Self-management interventions with prescribed drugs for acute exacerbations are proven to reduce the delay to seek treatment and the risk of hospitalization, as well as improving quality of life \(^{22,58}\).

3.4 Association between prevalence and research

The geographic distribution of the randomized studies we included does not reflect the distribution of COPD prevalence with highest rates in the Southern and Eastern African regions \(^{4}\). Only two of the included studies were conducted in South Africa, where it is known that prevalence rates are high, while most studies were conducted in Tunisia and Egypt in which prevalence rates are comparably low \(^{4,59}\). Despite COPD prevalence research becoming more frequent in recent years and COPD being considered a relevant health problem there is a lack of awareness of the ongoing burden in many African countries \(^{4,6,60,61}\). Research activities are affected by infrastructural conditions including access to essential medications, ICU capacities, research supportive environments, funding or trained personnel rather than the burden of disease \(^{62-64}\).

3.5 Infrastructural aspects of COPD research

Hospital care for COPD is often costly due to acute medical treatment in ICUs \(^{65}\). Egypt, South Africa and Tunisia rank 2\(^{\text{nd}}\), 4\(^{\text{th}}\) and 6\(^{\text{th}}\) on the 2018 African Infrastructure Development Index (AIDI) \(^{66}\). About half the studies were set in ICUs, studying acute exacerbation interventions. On average, there are 3.1 ICU beds per 100,000 capita all over the African continent \(^{64}\) whereas the European mean is 11.5. Egypt, South Africa, and Tunisia have an estimated 11.2, 5.7, and 4.3 ICU
beds per 100,000 capita. Other African countries have much lower ICU capacities (e.g., Nigeria: 0.2; Ethiopia: 0.5). Moreover, the availability of standard treatment options like salbutamol in public health facilities varies greatly on the African continent from 81 to 100% availability in Tunisia and below 5% (e.g., in Mali and Nigeria)\textsuperscript{63}. Improvement of medical infrastructure including ICU capacities, access to medication, funding and training of research personnel are requirements to support high quality research\textsuperscript{62,67,68}.

### 3.6 Low resource contexts

Six out of seven studies trialing pharmacological treatments\textsuperscript{33,38,40,43-45} tested management options from the WHO essential medicines list\textsuperscript{69} and on the WHO Package of Essential Noncommunicable (WHO PEN) Disease Interventions for Primary Health Care\textsuperscript{50} that can be used in low-resource settings. There is a strong need to provide effective and affordable long-term treatment through primary care to prolong the duration of stable clinical periods, management, and rehabilitation from acute exacerbation and prevention of adverse events\textsuperscript{50}.

### 3.7 Strengths and Limitations

Main aim of this review was to map, describe and discuss characteristics and results of all RCTs on prevention, diagnosis and treatment of chronic obstructive respiratory diseases in African countries. We initiated, registered and used all methods of a systematic review and visualized treatment effects. Due to this broad question, a scoping review with no synthesis of findings from individual studies might have been an alternative\textsuperscript{70}. We therefore decided to visualize, but not synthesize treatment effects.

This review is the first to summarize RCTs on the management of patients with clinically diagnosed COPD in African countries. We did not include studies on individual and community-based primary prevention of COPD, since these are generally not COPD-specific\textsuperscript{71-73}. Nevertheless,
these interventions clearly have a large impact on tackling the burden and should be considered when implementing COPD care. However, the more specific focus on RCTs maps the current research landscape on high-quality quantitative research for COPD patients.

This review aims to emphasize research primarily initiated, planned, and conducted in African countries. We excluded several multinational studies with few African centers which provide training for researchers to improve skills in scientific methodology, study design, and study conduction. The small number of included studies as well as the heterogeneity of interventions and outcomes limit the current possibility of building specifically adapted COPD guidelines in African countries.

4 Conclusion

This systematic scoping review summarizes heterogeneous COPD interventions with a wide range of outcomes and results. The available evidence was compiled in three countries with a comparably high infrastructural development, highlighting the urgent need comprehensive, and comprehensive technical infrastructure implementation and capacity building in African countries. Due to the increasing COPD burden, studies on early identification approaches, preventive primary care for high-risk populations are highly needed.

5 Acknowledgements

SU, BN, EJK, TF, MT and AS contributed to the conception and design of this systematic review. SU guarantees the methodological quality. SU organized and performed the systematic search and updates with support from ESK and BN. SU, ESK, AS and BN contributed to the title-, abstract-, and full-text screening and data extraction. SU and ESK built the tables. SU and ESK wrote the first draft and EN wrote sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.
Kathleen Denny corrected and proofread the manuscript.

Data availability statement

No additional data available.

6 Declaration of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
References


Table 1: Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Design/Setting</th>
<th>Randomized controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adult Patients &gt; 18 years from African countries with a COPD diagnosis (ICD-10 code: J44) in stable or acute phases (treatment of exacerbation) from African countries in secondary and tertiary prevention, diagnosis and treatment of COPD</td>
</tr>
<tr>
<td>Intervention</td>
<td>All secondary or tertiary prevention interventions (e.g., rehabilitation)ve, diagnostic interventions or curative treatment options interventions (e.g., pharmacological interventions, ventilation support)</td>
</tr>
<tr>
<td>Control</td>
<td>Another or no intervention</td>
</tr>
<tr>
<td>Outcome</td>
<td><strong>Primary outcomes:</strong></td>
</tr>
</tbody>
</table>

- Acute exacerbations: Acute respiratory episodes (reported as rate, number or frequency of acute exacerbation respiratory episodes or COPD-related hospitalizations or emergency care)
- Exacerbation rate

**Secondary outcomes:**

- Results of Pulmonary functioning test (reported as e.g., FEV1, FVC, FEV1/FVC ratio, PEF)
- Level of dyspnea (reported as validated measures related to dyspnea, e.g. Modified Borg Scale) (shortness of breath)
- Functional capacity (reported as walking tests, e.g., 6-MWD)
- Quality of life (assessed using validated scales on health-related or general quality of life)
- Duration of mechanical ventilation, length of ICU stay, hospital stay and mortality (reported as number of all-cause or disease-specific deaths)
| Publication | Full-text publication (no protocols, conference abstracts or preliminary results) in English or German language |

**COPD**: Chronic obstructive pulmonary disease; **FEV₁**: Forced expiratory flow in the first second; **FVC**: Forced vital capacity; **ICU**: Intensive care unit; **6-MWD**: 6 minutes walk difference distance; **PEF**: Peak expiratory flow;

- Adverse events (as defined by the trial authors) and adverse events
- **Only for patients in acute COPD exacerbation**: reported duration of treatment (e.g., lengths of mechanical ventilation, intensive-care-unit, stay in-hospital stay)

Within the longest reported follow-up period
### Table 2: Characteristics of studies involving patients in stable phases of COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Place and time</th>
<th>Inclusion criteria</th>
<th>Baseline characteristics</th>
<th>Intervention (IG) vs. Control (CG)</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Rehabilitative interventions</strong></td>
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<tr>
<td>Acheche 2020</td>
<td>RCT</td>
<td>01/2016 to 09/2016</td>
<td>Tunisia n.r. Outpatients</td>
<td>Clinically stable COPD diagnosed by pulmonary function testing, recent fall or fall in the past five years, 40 to 70 yrs</td>
<td>n=49 (100 % m) Age (yrs): 63±5 Ex-smokers: 100 % Pack yrs: 48±6</td>
<td>IG (n=25):</td>
</tr>
<tr>
<td>Ghanem 2010</td>
<td>RCT</td>
<td>07/2008 to 03/2009</td>
<td>Egypt Urban (44 vs. 14.3%) Home-based</td>
<td>Outpatients, recovery from acute exacerbation, moderate to severe COPD (GOLD), local district residency, ability to complete the CRQ in one session, first language Arabic, age &gt; 40 yrs</td>
<td>n=39 (n.r.) age (yrs): 56.7±10.76 Non-smokers: 5.13%</td>
<td>IG (n=25):</td>
</tr>
<tr>
<td>Magdy 2020</td>
<td>RCT</td>
<td>02/2018 to 11/2019</td>
<td>Egypt Urban Outpatients</td>
<td>Stable COPD stage III or IV (GOLD), chronic hypercapnic respiratory failure; age &gt; 18 yrs; sufficient social support for initiation NPPV at home</td>
<td>n=40 (55 % m) Age (years): 65.6±9.1 Ex + current smokers: 97.5 %</td>
<td>IG (n=20):</td>
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<tr>
<td>Mehani 2017</td>
<td>RCT</td>
<td>03/2015 to 08/2015</td>
<td>Tunisia Urban Outpatients</td>
<td>Outpatients with COPD (GOLD criteria), postbronchodilator FEV/FVC &lt; 0.7</td>
<td>n=45 (n.r.) age (yrs): 59.6±4.1 100 % males</td>
<td>IG (n=25):</td>
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<td>Mekki 2017</td>
<td>RCT</td>
<td>03/2015 to 08/2015</td>
<td>Tunisia Urban Outpatients</td>
<td>Clinically stable COPD (GOLD), recent fall or fall in the last 5 years</td>
<td>n=68 (100 % m) Age (yrs): 60±4</td>
<td>IG (n=25):</td>
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<td>Mkhacher 2015</td>
<td>RCT</td>
<td>03/2015 to 08/2015</td>
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<td>03/2008</td>
<td>South Africa n.r. Outpatients</td>
<td>Outpatient, clinical diagnosis moderate to severe COPD, airflow limitation, smoking history of &gt; 10 pack-yrs, age ≥40 years</td>
<td>n=107 (71 % m) age (years): 62±8.1 Pack-yrs: 42.8±19.2</td>
<td>IG (n=56):</td>
</tr>
<tr>
<td>Mostafa 2021</td>
<td>RCT</td>
<td>11/2016 to 12/2018</td>
<td>Egypt n.r. Chest Disease Department</td>
<td>Moderate to severe COPD, age ≥ 50 yrs, FEV1/forced vital capacity &lt; 0.70, FEV1 30% to 80% of predicted</td>
<td>n=60 (76 % m) Age (yrs): 63±8.60 Ever smokers: 73 % Smoking (yrs): 22.7±8.2</td>
<td>IG 1: (n=20): inhaled corticosteroid IG 2: (n=20): inhaled corticosteroid + budesonide IG 3: (n=20): Long acting β-agonist + Long-acting muscarinic antagonist + tiotropium</td>
</tr>
</tbody>
</table>
| Calligaro 2014 Crossover-RCT | South Africa n.r. Outpatients | Moderate COPD (stage ≤ II, GOLD criteria), smoking history of ≥ 10 pack-years, total lung capacity (TLC) > 80% of predicted, age ≥ 40 years | n=24 (67% m) age (yrs): 61±8 Packs-yrs: 37.7±18.9 | IG (n=24): Salbutamol + ipratropium CG (n=24): placebo MPT (n=24): metronome-paced breathing Exercise testing (n=24): cycle ergometry | Dynamic hyperinflation: greater decline of total lung capacity (in mL) during MPT with higher breathing frequencies and I:E ratio of 1:1 versus 1:2 (p=0.032):

AUC: Area under curve; CG: Control group; COPD: Chronic obstructive pulmonary disease; CRQ: Chronic respiratory disease questionnaire; FEV<sub>1</sub>: Forced expiratory flow in the first second; FVC: Forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IG: Intervention group; m: male; MD: Mean difference; 6-MWD: 6-minute walk distance; n: Number of randomized participants, n.r.: not reported; RCT: Randomized controlled trial; wk: week; yr: year
<table>
<thead>
<tr>
<th>Study name</th>
<th>Setting</th>
<th>Population</th>
<th>Intervention (IG) vs. Control (CG)</th>
<th>Primary Outcome Results</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Abroug 2014</td>
<td>Tunisia, Urban ICU</td>
<td>ICU admission, acute exacerbation of COPD, hypercapnic ARF requiring ventilatory support, &gt; 10 pack-yr, known or strongly suspected COPD (GOLD criteria), age ≥40 yrs</td>
<td>n=217 88 % males age (yrs): 70 (IQR 63-75) vs. 68 (IQR 63-75)</td>
<td>IG (n=111): daily prednisone CG (n=100): usual care.</td>
<td>ICU mortality: no differences shown 15.3 vs. 14.2%</td>
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<tr>
<td>El-Daim 2020</td>
<td>Tunisia, Urban ICU</td>
<td>COPD (GOLD criteria) with exacerbation, cough, sputum production or dyspnea and/or history of exposure to risk factors</td>
<td>n=322 81.9 % males age (yrs): 63.5±11 smokers: 75.9 %</td>
<td>IG (n=115): terbutaline + ipratropium bromide + saline solution CG (n=117): terbutaline sulfate + saline solution</td>
<td>No difference shown in Admission to hospital: 65.2 vs. 59.8%. ICU: 32.2 vs. 25.6%</td>
</tr>
<tr>
<td>Hassan 2015</td>
<td>Egypt, Urban Outpatients</td>
<td>type 1 exacerbation of COPD (defined as increase in dyspnea, sputum purulence and increased sputum volume)</td>
<td>n=100 83 % males age (yrs): 61.8±6.5 (39-77) Active smoker: 43 % Ex-smokers: 38 %</td>
<td>bronchodilators &amp; corticosteroids + IG (n=50): antibiotic treatment group quinolone or amoxicillin. CG (n=50): placebo.</td>
<td>Primary not defined; Exemplary outcome Treatment success rate: 88 vs. 70 % (p=0.006) No differences in adverse events including nausea (10 vs. 8 %), vomiting, abdominal cramps, diaphoresis or skin rash</td>
</tr>
<tr>
<td>El-Attar 2009</td>
<td>Egypt, Urban ICU</td>
<td>respiratory failure due to COPD exacerbation, required &gt; 48 hrs of mechanical ventilation, ex-smokers, smoked ≥ 3 months, age:18-65 yrs</td>
<td>n=80 76.2 % males age (yrs): 46.9±8.2 (24-60)</td>
<td>Usual care + IG (n=40): trace elements (sodium selenite, zinc and manganese) CG (n=40): placebo.</td>
<td>Length of stay on mechanical ventilation (days): benefit for IG 9.4±7.5 vs. 17.8±7.6 (p=0.013) ICU-Mortality: 2.9 vs. 5.6 % No differences in adverse events including ventilator-associated pneumonia (13.9 vs. 20.6 %)</td>
</tr>
<tr>
<td>El-Daim 2020</td>
<td>Egypt, Urban ICU</td>
<td>ventilated COPD (GOLD criteria) with acute respiratory failure diagnosis</td>
<td>N=90</td>
<td>IG (n=15): rapid shallow breathing index, respiratory rate, IWI CG (n=15): respiratory rate, vital capacity, Pimax</td>
<td>MIP and IWI were the most sensitive parameters Length of stay (days): mechanical ventilation: Successful weaning: 8.1±1.45 vs. 9.0±3.0 Failed weaning: 15.4±4.2 vs. 17.7±3.2 In-hospital: Successful weaning: 11.8±1.93 vs. 13.2±3.0 Failed weaning: 32.6±1.8 vs. 29.0±7.9</td>
</tr>
<tr>
<td>Hassan 2015</td>
<td>Egypt, Urban ICU</td>
<td>type 1 exacerbation of COPD (defined as increase in dyspnea, sputum purulence and increased sputum volume)</td>
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</tr>
</tbody>
</table>

Table 3: Characteristics of studies involving acute patients of in acute exacerbation phases of COPD
### Inclusion: severe acute exacerbation of COPD (history of COPD with clinical evidence of a purulent bronchitis + ARF requiring mechanical ventilation max 24 h after ICU admission)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Intervention</th>
<th>Age (yrs)</th>
<th>Pack-yrs</th>
<th>Length of stay (days): mechanical ventilation</th>
<th>Mortality</th>
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</thead>
<tbody>
<tr>
<td>Nouira 2010</td>
<td>Tunisia n.r.</td>
<td>IG1 (n=85): trimethoprim-sulfamethoxazole</td>
<td>67.5±9.9</td>
<td>58.25±25.35</td>
<td>6±4.2 vs. 5.6±4.3</td>
<td>ICU: 10.2±7 vs. 9.4±4.8</td>
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<tr>
<td></td>
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<td>IG2 (n=85): ciprofloxacin</td>
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<td>In-hospital: 12.9±7.4 vs. 13.1±8.4</td>
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<td></td>
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<td></td>
<td>91.2 % males</td>
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<td></td>
<td>Mortality: no differences shown</td>
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</table>

### Diagnostic studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>ICU</th>
<th>Inclusion: ventilated COPD (GOLD criteria) with acute respiratory failure diagnosis</th>
<th>N=30</th>
<th>IG (n=15): rapid shallow breathing index, respiratory rate, IWI</th>
<th>MIP and IWI were the most sensitive parameters</th>
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<tr>
<td>El-Daim 2020</td>
<td>Egypt Urban ICU</td>
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### Ventilatory supportion support studies

<table>
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<tr>
<th>Study</th>
<th>Country</th>
<th>ICU</th>
<th>Inclusion: acute exacerbation of COPD, indicated for invasive mechanical ventilation</th>
<th>N=60</th>
<th>IG (n=30): Weaning with proportional assist ventilation</th>
<th>Length of stay (days): benefit for IF</th>
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<tbody>
<tr>
<td>Elganady 2014</td>
<td>Egypt Urban ICU</td>
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<tr>
<td>Mohamed 2018</td>
<td>Egypt n.r. ICU</td>
<td>Inclusion: moderate to severe COPD (ATS/ERS &amp; GOLD), acute exacerbation due to respiratory tract infection, hypercapnic ARF, dyspnea at rest, bronchial hypersecretion, loose cough, inability to clear airways</td>
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### ARF: Acute respiratory failure; ATS: American Thoracic Society; CG: Control group; COPD: Chronic obstructive pulmonary disease; ERS: European Respiratory Society; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IG: Intervention group; ICU: Intensive care unit; IWI: integrative weaning index; n: Number of randomized participants; n.r.: not reported; MIP: maximal inspiratory pressure; RCT: Randomized controlled trial; RD: Risk difference; RR: Relative risk; wk: week; yr: year
Table 4: Risk of bias assessment based on the Cochrane risk of bias tool 1.

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<tr>
<th>Study</th>
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<th>Blinding of participants/personnel</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
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😊: Low  😐: Unclear  😒: High risk of bias
Figure 1: Study selection flow chart

Legend: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart describing the process of study selection.

References identified through electronic database searching (n=1819) (Medline: N=990, CENTRAL: N=584, CINAHL: N=245)

Additional references identified through other sources (n=235) (Specialized African databases: N=146, PACTR: N=14, Contact of corresponding authors: N=75)

References after duplicates removed (N=1594)

1433 references excluded

161 of full-text articles assessed for eligibility

86 full-text articles excluded:
- < 50% of the participants are from African countries (n=54)
- Other indications (n=9)
- No or other interventions, no control group (n=6)
- Other outcomes (n=7)
- No RCT (n=6)
- Protocols, conference abstracts, preliminary results, no full-text publication available, not in English or German language (n=4)

Inclusion of 75 full-text articles
18 trials (reported in 19 publications) on COPD
51 asthma; 2 HIV-associated chronic lung disease; 1 cystic fibrosis; 2 chronic bronchitis
Figure 2: Summary of treatment effects of rehabilitative interventions for stable patients on 6-minute-walk-distance

Legend: Visualization of treatment effects without meta-analysis due to substantial heterogeneity of both interventions and outcomes.
Online Supplement

Figure S1: Summary of treatment effects in patients with acute exacerbation of COPD on length of mechanical ventilation (not included: Abroug 2014 and El Daim 2020 due to missing information, see table 3)

Figure S2: Summary of treatment effects in patients with acute exacerbation of COPD on length of stay in ICU (not included: El Daim 2020 due to missing information, see table 3)
Figure S3: Summary of treatment effects in patients with acute exacerbation of COPD on mortality on length of in-hospital stay (not included: Abroug 2014 due to missing information, see table 3)

Figure S4: Summary of treatment effects on mortality in patients with acute exacerbation of COPD on mortality in the longest follow-up period (see table 3)
## Search strategy

### Medline (Ovid)

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<td>Uganda$.tw or exp Uganda/</td>
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**Study design**

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<td>Searches (Last Search: 14.04.2021)</td>
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<tr>
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<td>MESH descriptor Pulmonary Disease, Chronic Obstructive</td>
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<td>MESH descriptor Bronchitis, Chronic</td>
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<td>(Chronic near obstructive near (pulmonary or respiratory or airway))</td>
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<td>(chronic near airway near obstruct*)</td>
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<td>Pulmonary near emphysema*</td>
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<td>asthma*</td>
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<td>Chronic* near Bronchitis</td>
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<td>bronchiolitis or bronchiectasis or alveolitis or mucoviscidosis or (cystic near fibrosis)</td>
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<tr>
<td>12</td>
<td>reduc* near (lung function)</td>
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<td>#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12</td>
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<td>14</td>
<td>#1 and #13</td>
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<td>Trials</td>
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CINAHL

Searches conducted: 8.10.2019 and 14.04.2021

(Africa$ or Africa$ or Algeria$ or Angol$ or Benin$ or Botswana$ or (Burkina Faso) or Burundi$ or Cameroon$ or (Cape Verde) or (Central African Republic) or Chad$ or Comoros$ or Cote d'Ivoire or Congo$ Djibout$ or Egypt$ or (Equatorial Guinea$) or Eritrea$ or Ethiopian$ or Gabon$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Kenya$ or Lesoth$ or Liberia$ or Libya$ or Madagascar$ or Malawi$ or Mali$ or Mauritania$ or Mauritius$ or Morocco$ or Mozambique$ or Namibia$ or Niger$ or Nigeria$ or Rwanda$ or (Sao Tome and Principe) or Senegal$ or Seychelles$ or Sierra Leone or Somalia$ or (South Africa) or (South Sudan$) or Sudan$ or Swasiland or Tanzania$ or Togo$ or Tunisia$ or Uganda$ or Zamb$ or Zimbabwe$ or Somal$ or (Sahrawi Arab Democratic Republic)) in Abstract
AND
(chronic obstructive pulmonary disease) or asthma or (chronic obstructive lung disease) or (pulmonary emphysema) or (chronic bronchitis treatment) or bronchiolitis or bronchiectasis or alviolitis or mucoviscidosis or (cystic fibrosis) in Abstract
AND
In English
AND
Peer-reviewed
And
Humans

Suchlauf-Alert: "AB ((Africa$ or Africa$ or Algeria$ or Angol$ or Benin$ or Botswana$ or (Burkina Faso) or Burundi$ or Cameroon$ or (Cape Verde) or (Central African Republic) or Chad$ or Comoros$ or Cote d'Ivoire or Congo$ Djibout$ or Egypt$ or (Equatorial Guinea$) or Eritrea$ or Ethiopian$ or Gabon$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Kenya$ or Lesoth$ or Liberia$ or Libya$ or Madagascar$ or Malawi$ or Mali$ or Mauritania$ or Mauritius$ or Morocco$ or Mozambique$ or Namibia$ or Niger$ or Nigeria$ or Rwanda$ or (Sao Tome and Principe) or Senegal$ or Seychelles$ or Sierra Leone or Somalia$ or (South Africa) or (South Sudan$) or Sudan$ or Swasiland or Tanzania$ or Togo$ or Tunisia$ or Uganda$ or Zamb$ or Zimbabwe$ or Somal$ or (Sahrawi Arab Democratic Republic)) AND AB ((chronic obstructive pulmonary disease) or asthma or (chronic obstructive lung disease) or (pulmonary emphysema) or (chronic bronchitis treatment) or bronchiolitis or bronchiectasis or alviolitis or mucoviscidosis or (cystic fibrosis) ) Erscheinungsdatum: 20190101-20211231; In Englisch; Peer-Reviewed; Menschen AND Entsprechende Themen anwenden on 2021-04-14 08:25 AM"

Results (last search): 245 references
African Journals Online
https://www.ajol.info/index.php/ajol

https://www.google.com/search?client=ms-google-coop&q=random+and+COPD+or+Chronic+obstructive+pulmonary+disease&cx=00779754043222069508:kprfz3-g5lc

(search for random and COPD or Chronic obstructive pulmonary disease)

Last Search: 29.04. 2021, 117 results with 1 potentially eligible reference

African Index Medicus

http://indexmedicus.afro.who.int/aim/

Advanced search 29.04.202e
Title, Expression booléenne: (COPD or Chronic obstructive pulmonary disease) AND (randomized or randomized) in Titel
Last Search: 29.04. 2021, 29 results with no potentially eligible references

Pan African Clinical Trials Registry

https://pactr.samrc.ac.za/Search.aspx

Chronic obstructive pulmonary disease or COPD (Last Search: 29.4.2021): 14 studies

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<th>Principal investigator</th>
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<td>202008893896971</td>
<td>HANDLING USI20 Study: Satisfaction assessment and Good Usage Practice of RS01® versus Handihaler® inhalers in patients with COPD, a randomized comparative multicenter study</td>
<td>Tunisia</td>
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<td>202005764510617</td>
<td>Short-term outcome of a home-based rehabilitation program in COPD tunisian patients</td>
<td>Tunisia</td>
<td>Dr. Nidhal Belloumi</td>
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<td>201711002731292</td>
<td>Impact of pulmonary rehabilitation programme for COPD patient (not yet recruiting)</td>
<td>Tunisia</td>
<td>Marwa Mekki</td>
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<td>201804002608316</td>
<td>Comparative Study of Segmental thoracic Spinal versus thoracic epidural anaesthesia for laparoscopic cholecystectomy (early terminated)</td>
<td>Egypt</td>
<td>Hatem El Moutaz Mahmoud</td>
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</table>

Table 1: Completed studies

Included studies
COPD (N=18 RCTs with 19 publications)

Abroug 2014

Acheche 2020

Bateman 2008

Beltaief 2018

Calligaro 2014

El-Attar 2009

El-Daim 2020

Elganady 2014

Ghanem 2010

Hassan 2015

Magdy 2020
Magdy DM, Metwally A. Effect of average volume-assured pressure support treatment on health-related quality of life in COPD patients with chronic hypercapnic respiratory failure: a randomized trial. Respir Res. 2020;21(1):64.

Mehani 2017

Mekki 2019

Mkacher 2015

Mohamed 2018

Mostafa 2021

Nouira 2001

Nouira 2010
Asthma (N=49 RCTs with 51 publications)

Abdel Fattah 2011

Abdelbasset 2018

Abdelhamid 2008

Abroug 1995

Al-Biltagi 2012

Ali 2017

Aloulou 2001

Ammorrha 2020

Anah 1980

Aweto 2017
Badawy 2014a

Badawy 2014b

Bello 2004

Besbes-Ouanes 2000

Biltagi 2009

Buchanan 1981

Dabbous 2017

Dardouri 2020

El-Ghitany 2012

El-Helbawy 2020

Elkharwili 2020

Goldin 1988

Ibrahim 2017

Ibrahim 1993

Ige 2010

Ige 2002
Ige OM, Sogaolu OM. The clinical efficacy of fluticasone propionate (Fluvent) compared with beclomethasone dipropionates (Becotide) in patients with mild to moderate bronchial asthma at the University College Hospital, Ibadan, Nigeria. West Afr J Med. 2002;21(4):297-301.

Ige 2004
Ige OM, Sogaolu OM. A single blinded randomised trial to compare the efficacy and safety of once daily budesonide (400microg) administered by turbuhaler with beclomethasone dipropionate (400microg) given twice daily through a metered-dose inhaler in patients with mild to moderate asthma. African journal of medicine and medical sciences. 2004;33(2):155-60.

Khayyal 2003

Le Roux 1991

Louw 2007

Middle 1993

Middle 2002

Mohamed 2008

Moustafa 2017

Nabil 2014

Nicola 2018

Nouira 1999

Ohaju-Obodo 2005
Radwan 2013

Radwan 2010

Rylance 2021

Sadek 2020
Sadek EM, Tawfik NR, Hussein AK, Abdelhakeem MA. Efficacy and safety of liquorice extract in patients with bronchial asthma: a randomized controlled trial. Indian journal of public health research and development. 2020;11(4):585-90.

Shaw 2011

Shokry 2020

Siddorn 1976

Sobhy 2019

Steinman 1993

Zar 1999
Zar HJ, Brown G, Donson H. Spacers made from sealed cold-drink bottles were as effective as conventional spacers in children with acute asthma: commentary. Evidence-based medicine. 2000;5(3):79-.


Zedan 2009
6.1.1 Other chronic obstructive diseases (N=5 RCTs)

**Ferrand 2020**

**Masekela 2004**

**Milne 2004**

**Tag 1993**

**Yakoot 2010**