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REVIEW

# Effects of medical and psychological treatment of depression in patients with COPD – A review

Anja Fritzsche [a,*], Annika Clamor [a], Andreas von Leupoldt [a,b]

[a] Department of Psychology, University of Hamburg, Von-Melle-Park 5, 20146 Hamburg, Germany
[b] Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany

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**Summary**
Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory lung disease characterized by progressive and only partially reversible symptoms and by considerable negative consequences such as reductions in functional status and quality of life. Comorbid depression is highly prevalent in patients with COPD and related to a worse course of the disease. Despite its negative impact, depression often remains unrecognized and untreated in COPD patients. This review summarizes the current state of findings from studies examining the effects of antidepressant treatments in patients with COPD. Reviewed treatment options are antidepressant medical therapy and cognitive-behavioral therapy (CBT). Antidepressant medical trials include treatments with selective serotonin reuptake inhibitors (SSRI) or tricyclic antidepressants (TCA); CBT was applied using various components. Across both treatment types, the majority of studies included patients with a wide range of psychiatric conditions and especially comorbid symptoms of anxiety were often not controlled. Furthermore, greatly varying instruments and methods for assessing depressive symptoms, small sample sizes and rather heterogeneous results were observed. This makes the comparison of treatment options rather difficult and prevents definite conclusions. However, some important implications valuable for further research were obtained. Some limited data suggested that SSRI might show fewer side effects than TCA. A few antidepressants as well as beneficial effects in other outcomes were observed after antidepressant medical treatment. More clearly, CBT showed some potential in terms of improvements in depressive symptoms, and also in other outcome measures. Patient compliance seems more promising for CBT than for antidepressant medical treatment. Overall, the reviewed studies suggest some promising effects for both treatment types and

*Abbreviations:* 6MWD, 6-min walking test distance; CBT, cognitive-behavioral therapy; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in the first second; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitors; QoL, quality of life.

* Corresponding author. Tel.: +4940428386292; fax: +494051491557.
*E-mail address:* anja.fritzsche@uni-hamburg.de (A. Fritzsche).

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effect sizes in studies with significant antidepressant effects were reasonable. However, future randomized controlled trials comparing antidepressant medical and cognitive-behavioral therapy will be essential to assess distinct and most favorable treatment effects. Because recent data is often limited, sound diagnostic criteria of depression and adequate sample sizes are necessary to draw firm conclusions on the effects of these antidepressant treatment options in patients with COPD and comorbid depression.


**Contents**



## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory lung disease with several systemic manifestations and includes the subtypes of chronic bronchitis and/or lung emphysema. It is characterized by progressive and only partially reversible obstruction of the airways, airflow limitation, chronic cough, increased sputum production and dyspnea. COPD is associated with severe disability and dysfunction in everyday life, reduced quality of life and high socio-economic costs.[1–3] About 210 million people worldwide are estimated to suffer from COPD. COPD is the fourth leading cause of death worldwide which accounts for 5% of all human deaths[4] and is projected to rank third by the year 2020.[5]

Comorbid depressive symptoms and depressive disorders are highly prevalent in COPD patients.[6] even when exclusively focusing on the risk of a first episode of depression after COPD diagnosis.[7,8] Recent reviews reported prevalence rates between 8% and 80%.[9–11] A pooled metaanalysis of 13 studies ($N = 900$) demonstrated a prevalence rate of 40%.[12] Comorbid depression in COPD is associated with negative course of disease including increases in mortality, symptom burden and hospitalizations as well as decreases in functional status, quality of life (QoL) and activities.[13–19] Accordingly, recent consensus statements and guidelines on optimal care for COPD patients emphasized the need of depression assessment and adequate treatment of persisting depressive symptoms in COPD patients.[10,11,20,21]

Despite the high prevalence and considerable negative impact of depression in COPD, there is a paucity of evidence regarding its effective management. This fact is already reflected in the poor detection rates of depression in COPD patients, but specifically underlined by the inadequate management that many patients receive.[11,22,23] For example, a previous study demonstrated that in less than 44% of COPD patients clinically relevant depression was correctly diagnosed and that only 31% of these patients received any treatment for these psychological comorbidities.[24]

The present review provides an overview on studies examining the effects of two commonly used treatment options in patients with COPD: antidepressant medical treatment and cognitive-behavioral therapy (CBT). Respective studies were evaluated primarily with respect to effects on depression, and also on other outcome measures important for the course of disease.

Antidepressant medication aims at regulation of neurotransmitter systems in the brain that have been associated with depression. In studies with COPD patients, older tricyclic antidepressants (TCA) and newer selective serotonin reuptake inhibitors (SSRI) have been tested. TCA have successfully been applied for decades and their antidepressant effect is caused by inhibiting the reuptake of the neurotransmitters serotonin, noradrenalin and dopamine from the synaptic cleft. This increase in available neurotransmitters enhances synaptic signal transmission and is supposed to adjust the deficiency of second messengers that underlie depression mechanisms. Today, SSRI are the most commonly prescribed antidepressant drugs.[25,26] They act on serotonin transporters and enhance the concentration of serotonin in the synaptic cleft by inhibiting the reuptake into the presynapse. In contrast to TCA, they are more selective because they do not impact on other monoamine transporters. Furthermore, when compared to TCA, SSRI are associated with less unwanted side effects such as sedation, dizziness and anticholinergic symptoms, which leads to enhanced patient compliance.[27,28]

CBT is an evidence-based psychological intervention and includes a wide range of established behavioral and cognitive techniques for different mental disorders.[29] Recommended

elements of CBT for depression include behavioral activation, enhancing competency through skill-building exercises and establishing a more adaptive cognitive style.[30] Cognitive components target automatic thoughts and their influence on feelings,[31] awareness of cognitive biases associated with physical limitations,[32] problem-solving techniques, sleep-management skills[33] and techniques such as thought stopping and self-instructional training to reduce maladaptive thoughts.[34] Behavioral components can involve enhancement of activities, but also non-specific relaxation or stress management techniques. CBT has been demonstrated to be effective in reducing depressive symptoms in all age groups and is therefore recommended as antidepressant therapy for all age groups including elderly patients,[35] which form the majority of COPD patients. The general elements of CBT (behavioral activation, enhancing competency through skill-building exercises and establishing cognitive changes) are similar when treating patients with vs. without COPD. However, because some symptoms of COPD and depression overlap (e.g., fatigue, sleep problems, reduced activity levels), it is necessary to carefully differentiate between psychological and physiological origin of these symptoms in COPD patients and to select appropriate interventions accordingly. Moreover, CBT in COPD patients should include specific educational elements about COPD, for example targeting the vicious circle of dyspnea or depression-related activity avoidance-deconditioning-more dyspnea and more depressive symptoms and respective interventions to increase the physical activity level. In addition, specific goals for the symptom management of the chronic lung disease[31] and respective specific coping skills (e.g., breathing trainings, symptom management in the public, cognitive interpretations of physical symptoms) should be considered in antidepressant CBT treatments in COPD.[34]

## Method

A literature search was conducted for studies examining the impact of antidepressant medical treatment and cognitive-behavioral therapy on depressive symptoms using the OVID (PsycINFO, PSYNDEX, PsycCRITIQUES, MEDLINE and EMBASE) and PubMed databases. Essential keywords were *COPD, cognitive-behavioral therapy, CBT, depression, psychotherapy,* and *antidepressant*. Furthermore, additional literature was selected from articles' reference lists. For significant antidepressant treatment effects in single studies, Cohen's $d$ was calculated as a measure of effect size with $d = 0.2$ denoting a small effect, $d = 0.5$ denoting a medium effect and $d = 0.8$ denoting a large effect.[36]

## Results

### Antidepressant medical treatment

#### Effects of tricyclic antidepressant treatment (TCA)

An overview of studies examining the effects of TCA is provided in Table 1. From the identified five studies, only one randomized, double-blind placebo-controlled trial was able to show improvements over placebo after 12 weeks of nortriptyline regarding depressive symptoms, anxiety, respiratory symptoms, physical comfort and functioning.[37] This was also the only study with depression being diagnosed according to DSM-III criteria and with an acceptable sample size and drop-out rate. The effect size for the difference in reduction of depressive symptoms between placebo and nortriptyline was $d = -1.07$. A second study suggested at least some improvements in depressive symptoms after eight weeks of desipramine, but similar effects were found after eight weeks of placebo treatment.[38] In a double-blind crossover trial regarding hospitalized veterans, doxepin hydrochloride did not lead to significant improvements in exercise capacity or depression scores.[39] A small uncontrolled study reported faster recovery in 10 patients of all COPD stages after an imipramine–diazepam combination without providing details on measurement instruments.[40] Overall, the majority of studies were of considerably small sample size with half of the studies including less than 14 patients. All these studies demonstrated high drop-out rates. For example, only 5 out of 26 patients completed the trial in one of these studies.[41] Reasons for the high number of drop-outs were mostly strong side effects. In addition, only two studies used DSM criteria to diagnose depression and a great variety of measurement instruments for depression was employed across studies. Moreover, comorbid symptoms of anxiety were reported in at least two studies and were not controlled for in other studies, which might have interacted with antidepressant treatment.

#### Effects of selective serotonin reuptake inhibitor treatment (SSRI)

An overview of the studies is shown in Table 2. From the identified six studies, three used a randomized double-blind placebo-controlled design, but these studies reported conflicting results. First, an increased response rate was found for well-tolerated fluoxetine over the placebo after five or more weeks of treatment.[42] Second, paroxetine treatment led to large and significant differences in emotion and mastery domains of disease-specific QoL scores and to nonsignificant – but clinically important – differences in dyspnea and fatigue scales that were nonsignificant due to a lack of power in the small sample.[43] Third, after six weeks of blinded paroxetine vs. placebo treatment, no differences between groups could be found.[44] Improvements in depression were correlated with increases in walking distance. However, three months of unblinded treatment revealed significant improvements in depression scores, walking distance and QoL.[44] Effect sizes for depression reduction varied between $d = 1.27$ and $d = 1.98$, depending on the applied instruments.

Three other studies exclusively reported descriptive results. It could be demonstrated that five of six patients who were treated with sertraline for six weeks showed improvements in daily living activities.[45] Participants with psychiatric conditions felt subjective improvements, but no significant changes in physiological measures were observed. A further study described seven patients with obstructive airways disease (including asthma) that received sertraline in addition to their regular medications.[46] Improvements in dyspnea and some subjective improvements in exercise tolerance were observed, but not in $FEV_1$. All participants tolerated sertraline well. In another study, the acceptability of fluoxetine, however, was found to be very poor in depressed elderly patients with COPD and only four of seven patients responded to it.[47]

**Table 1** Antidepressant medical treatment drug therapy in COPD patients; TCA treatment trials.

| TCA study | Study design | Intervention | Participants | Instruments | Outcome | ES[a] for depression |
|---|---|---|---|---|---|---|
| Gordon et al. (1985) | Randomized double-blind crossover trial | Desipramine for 8 wks and placebo for 8 wks, order was blinded. Initial dose 25 mg/d, increased weekly to maximum tolerated (not exceeding 100 mg). | $N = 13$, stable COPD outpatients stage III. None met DSM-III criteria of depression. $N = 6$ completed trial. Anxiety not assessed. | BDI and Zung self-rating depression scale | Depression scores improved significantly after treatment with placebo and with desipramine. No effect on physiological measures. | $d = 0.85$ for desipramine group, $d = 0.99$ for placebo group |
| Light et al. (1986) | Randomized double-blind crossover trial | Doxepin hydrochloride for 6 wks and placebo 6 wks, order was blinded. Doses received as tolerated. Maximum dose 105 mg/d. | $N = 12$ outpatients with COPD stage III and high levels of depression. $N = 9$ completed trial. Anxiety scores higher than average for hospitalized veterans. | BDI; 12MWD; Spielberger's state-trait anxiety inventory | No significant improvements in exercise capacity or depression and anxiety scores. Increase in 12MWD correlated with improvements in depression or anxiety. | $d = 0.46$ for placebo, $d = 0.37$ for doxepin hydrochloride group |
| Sharma et al. (1988) | Double-blind method | Imipramine—diazepam combination | $N = 10$ consecutive COPD patients (all stages) evaluated for depressive disorders | N.A. | Helped depressed patients recover faster, but diazepam may trigger respiratory failure. | — |
| Borson et al. (1992) | Randomized double-blind placebo-controlled trial | Nortriptyline vs. placebo for 12 wks ¼ of 1 mg/kg of body weight increased weekly until 1 mg/kg of body weight. | $N = 36$ in patients with COPD stage II—III and comorbid depressive disorder (DSM-III criteria). $N = 30$ ($n = 17$ placebo) completed trial. 83% with significant anxiety symptoms | CGI, Hamilton depression rating scale; PRAS; 12MWD; PFSI; SIP; Dyspnea questionnaire | Superior improvements for nortriptyline group in depression. Further improvements in anxiety, respiratory symptoms, physical comfort and day-to-day functioning. No change in physiological measures | $d_{korr} = -1.07$ |
| Ström et al. (1995) | Randomized double-blind placebo-controlled trial | Protriptyline vs. placebo for 12 wks, 10 mg/d. | $N = 26$ ($n = 12$ placebo) stable COPD patients, at least stage II, with mild to moderate hypoxaemia. $N = 5$ completed trial | HADS, MACL; SIP; Dyspnea (self-developed scale) | No improvement in depression or anxiety scores, arterial blood gas tension, spirometry values, dyspnea or QoL scores. High rates of anticholinergic side effects | $d_{korr} = -0.33$ |

**/d** = a day; 12MWD = 12 min walking distance; BDI = Beck Depression Inventory; **CGI** = Clinical Global Improvement Scale; **COPD** = chronic obstructive pulmonary disease; **ES** = effect size; **HADS** = Hospital Anxiety and Depression Scale; **MACL** = Mood Adjective Checklist; **n.a.** = not available; **PFSI** = Pulmonary Functional Status Instrument; **PRAS** = Patient-Rated Anxiety Scale; **QoL** = Quality of life; **SIP** = Sickness Impact Profile (generic health status); **Stage I—IV** = Global Initiative for Obstructive Lung Disease (GOLD) standard for severity of COPD; **TCA** = tricyclic Antidepressant; **wks** = weeks.

[a] Effect sizes are reported when available or calculation possible.

**Table 2** Antidepressant medical treatment in COPD patients; SSRI treatment trials.

| SSRI study | Study design | Intervention | Participants | Instruments | Outcome | ES[a] for depression |
|---|---|---|---|---|---|---|
| Papp et al. (1995) | Pilot study; descriptive | Sertraline for 6 wks, 12.5 mg/d. Increased to 100 mg during first 2 wks. | $N = 6$ consecutive COPD (severity not reported) outpatients, 3 with comorbid anxiety or depression. | n.a. | Well tolerated, all reported general sense of well being. 5 showed improvements on daily living activity scale. No improvements in physiological parameters, subjective improvement in psychiatric conditions. | – |
| Smoller et al. (1998) | Case reports (6 retro-1 prospectively) | Sertraline (25–100 mg/d) added to regular medication. Varying durations. | $N = 7$ patients with obstructive airways disease (incl. asthma). Psychiatric conditions varied. | Varied across patients | Improvements in dyspnea, regardless of comorbidities, but not in $FEV_1$. Some reported improvements in exercise tolerance, mood, and anxiety. | – |
| Evans et al. (1997) | Randomized double-blind placebo-controlled trial | Fluoxetine vs. placebo for 8 wks, 20 mg/d. | $N = 82$ acute geriatric medical inpatients with depression (ELDRS, GMS). $N = 42$ ($n = 21$ placebo) completed trial. $N = 38$ with respiratory diseases. | HAMD, ELDRS, GMS | No significant difference between groups in response rate. Trend for fluoxetine group to respond better than controls after 8 wks (subjective report). Significantly more recovery from depression after $\geq$5 wks fluoxetine. | – |
| Yohannes et al. (2001) | Single-blinded, open study | Fluoxetine for 6 mths, 20 mg/d. | $N = 57$ COPD patients stage II–III and depression (GMS). $N = 14$ agreed to fluoxetine, $N = 7$ completed. Anxiety not assessed. | GMS and MADRS; MRADL, BPQ | 72% refusal rate. Of the 7 who completed trial, 4 responded to fluoxetine (criteria for major depression). 5 withdrew because of adverse side effects. | – |
| Lacasse et al. (2004) | Randomized double-blind placebo-controlled trial | Paroxetine vs. placebo for 12 wks, 2 patients 10 mg/d, other tolerated 20 mg/d. | $N = 23$ outpatients with COPD (average stage III) and significant depressive symptoms (GDS). $N = 15$ ($n = 7$ placebo) completed trial. Anxiety not assessed. | GDS; SF-36, CRQ | GDS improved significantly after paroxetine but not after placebo. Adjusted between-group mean difference ns. Significant improvements in emotion and mastery domains and clinically important improvement (ns.) in dyspnea and fatigue scale after paroxetine. Respiratory stable. | – |
| Eiser et al. (2005) | Randomized double-blind placebo-controlled trial | Paroxetine vs. placebo for 6 wks, unblinded paroxetine for 3 mths. 20 mg/d. | $N = 28$ stable outpatients with COPD stage II–III and depression (ICD-10 criteria) | HADS, BDI and MADRS. SGRQ; 6MWD | 6 wks of blinded treatment led to ns. between-group differences. After unblinded 3 mths of treatment, depression scores, walking distances and QoL had significantly improved. | HADS-D: $d = 1.33$ BDI: $d = 1.27$ MADRS: $d = 1.98$ |

**/d** = a day; **6MWD** = Six-min walking distance; **BDI** = Beck Depression Inventory; **BPQ** = Breathing Problems Questionnaire; **COPD** = chronic obstructive pulmonary disease; **CRQ** = Chronic Respiratory Questionnaire (COPD disease-specific QoL inventory); **ELDRS** = Evans Liverpool Depression Rating Scale; **$FEV_1$** = Forced expiratory volume in 1 s; **GDS** = Geriatric Depression Scale; **HADS** = Hospital Anxiety and Depression Scale; **GMS** = Geriatric Mental State; **HAMD** = Hamilton Depression Rating Scale; **MADRS** = Montgomery-Asberg Depression Rating Scale; **mths** = months; **MRADL** = Manchester Respiratory Activities of Daily Living Questionnaire; **n.a.** = not available; **ns.** = not significant; **SF-36** = Medical Outcome Survey – Short Form 36 (general health related QoL); **SGRQ** = St. George's Respiratory Questionnaire (perceived health status); **SSRI** = selective serotonin reuptake inhibitor; **Stage I–IV** = Global Initiative for Obstructive Lung Disease (GOLD) standard for severity of COPD; **QoL** = Quality of life; **wks** = weeks.

[a] Effect sizes are reported when available or calculation possible.

**Table 3** Treatment trials using CBT components in COPD patients.

| CBT study | Study design | Intervention | Participants *(controls)* | Instruments | | ES[a] for depression |
|---|---|---|---|---|---|---|
| Adams et al. (2006) | Pilot study, randomized controlled trial | 6 weekly group sessions (90 min) of CBT vs. general health education. | $N = 22$ *(11=general health education)* patients with COPD stage III–IV and moderate levels of anxiety. | BDI; BAI, SGRQ | No between-group differences in BAI or BDI scores. CBT group improved in SGRQ more than education group. | – |
| Cully et al. (2009) | Case reports | ACCESS intervention; 6 individual active treatment sessions (45min), telephone possibility. | $N = 3$ male veterans with cardiopulmonary diagnoses. $N = 2$ COPD patients; stage I and III; not meeting diagnostic criteria of depression or anxiety (MINI); BDI>13. | BDI-II; STAI, CRQ, SF-36, CSQ | Improvements in anxiety and depression as well as functional status were observed and lasted to 3-months follow-up. | – |
| de Godoy & de Godoy (2003) | Randomized controlled trial | 12-week treatment. G1 with physical exercise (24 sessions), education (3 sessions), physiotherapy (24 sessions) plus psychotherapy (12 sessions) vs. G2, same treatment without psychotherapy. | $N = 30$ *(16=G2)* COPD outpatients; more than two thirds at least stage III. Half the patients (53.3% of G1, 46,6% of G2) with at least low levels of anxiety or depression (BDI>11, BAI>9). | BDI; BAI, 6MWD | Both groups increased walking performance, G1 almost twice as much (group differences ns.). G1 improved in depression and anxiety levels, G2 did not. | $d_{korr} = -0.68$ |
| de Godoy et al. (2005) | Randomized controlled trial | 12-week treatment. G1: PRP (physical exercise, individual psychotherapy sessions, group educational sessions, physical therapy); vs. G2: PRP without physical exercise; vs. G3: PRP without psychotherapy. | $N = 49$ ($G1 = 19$; $G2 = 16$, *G3=14)* consecutive patients with COPD stage II–III. Mild to moderate levels of anxiety and depression (BDI). | BDI; BAI, SGRQ, distance walked-weight product | G1 and G2 patients improved in anxiety and depression as well as SGRQ and exercise tolerance. G3 improved in anxiety. | G1: $d = 1.58$ G2: $d = 1.11$ |
| de Godoy et al. (2009) | Long-term evaluation of pulmonary rehabilitation program (PRP) | 12 weeks PRP (24×physical exercise, 24×respiratory rehabilitation, 12×group psychotherapy, 3×education). Pre-, post-PRP and two years later (current). | $N = 30$ outpatients with COPD stage III - IV. 50% with clinically significant depression (BDI); 46,6% with clinically significant anxiety. | BDI; BAI, SGRQ, 6MWD | Post-PRP evaluation revealed improvements in BDI, BAI and SGRQ Activity, Impact and Total scores as well as in 6MWD. After two years no significant changes since post-treatment except for SGRQ Impact score (borderline). | pre to post evaluation: $d = 0.90$. Post to current evaluation: $d = 0$ |

(*continued on next page*)

Table 3 (*continued*)

| CBT study | Study design | Intervention | Participants *(controls)* | Instruments | | ES[a] for depression |
|---|---|---|---|---|---|---|
| Emery et al. (1998) | Randomized controlled trial | EXESM vs. ESM and WL for 10-week period. Small groups. | $N = 79$ (EXESM = 29; ESM = 25; *WL=25)* COPD outpatients stage III. Subclinical depression (CES-D). | CES-D; Bradburn Affect −Balance Scale; STAI, SCL-90-R, MHLC, SIP, cognitive assessments | EXESM and WL groups showed reductions in depressive symptoms and SIP scores. EXESM showed improvements in anxiety and organized verbal processing. All groups increased mental efficiency performance. | EXESM: $d = 0.80$ WL: $d = 0.42$ |
| Heslop et al. (2009) | Non-randomized study | Nurse-led individualized CBT program with average of 4 sessions (range 2−13). | $N = 10$ COPD outpatients, 80% stage III. Doctors evaluated depression and/or anxiety being significant. | HADS-D; HADS-A, $FEV_1$ | Improvements in anxiety and depression scores and less hospital admissions during the 6 months after CBT compared to 6 months before. | $d = 1.53$ |
| Hynninen et al. (2010) | Randomized controlled trial | Group CBT (7 weekly 2h sessions) vs. standard care plus telephone contact every 2 weeks. Masters-level psychology student in charge. | $N = 51$ *(26=standard care)* COPD outpatients, stage II. Prescreened for depression and anxiety (BAI>15 and/or BDI>13). 33% met DSM-IV criteria for mood-disorder, 25.5% for an anxiety disorder; 45.1% for either. | BDI-II; BAI, SGRQ, PSQI, actigraphy, CSQ | CBT group improved in anxious and depressive symptoms, control group did not. Sleep efficiency improved from post-treatment to follow-up, but no subjective improvement reported. | Post-treatment: $d=0.7$ Follow-up: $d = 1.0$ |
| Kunik et al. (2001) | Randomized controlled trial | One 2h session of group CBT vs. one 2h session of COPD education. Both groups received 6 additional weekly calls. | $N = 48$ *(29=COPD education)* COPD in- and outpatients. Recruited regardless of depressive or anxious symptoms. Mild levels of anxiety and depression (GDS). | GDS; BAI, SF-36, 6MWD, CSQ | CBT group was superior to education in reduction of depressive and anxious symptoms. No change in COPD severity or physical functioning. | $d_{korr} = -0.52$ |

| | | | | | | |
|---|---|---|---|---|---|---|
| Kunik et al. (2008) | Randomized controlled trial | 8 sessions of CBT group treatment (1h) vs. COPD education (45min + discussion). | *N* = 108 *(56=COPD education)* COPD patients stage III. BDI>14 and/or BAI>15. 53.2% with DSM-IV diagnosis of depression, 38.1% of anxiety and 62.2% either. | BDI-II; CRQ, SF-36, BAI, 6MWD, service use | Improvements in BDI-II, BAI, CRQ, SF-36 mental health score and emotional composite score and 6MWD. Differences between groups ns., most improvements larger for CBT group. Improvement up to 44 weeks. | COPD education: *d* = −1.05, CBT: *d* = −1.45 |
| Lisansky & Clough (1996) | Pilot study; one group pre- and post | 8 weekly sessions (90min) of cognitive-behavioral self-help educational program, led by nurses. | *N* = 8 participants with stage II - III COPD. | Symptom | Questionnaire; SIP, General-Cognitive Error Questionnaire, COPD-Cognitive-Error Questionnaire | No significant change in depressive symptoms. Decreases in Psychosocial and Total SIP Scores, General-Cognitive Error Questionnaire personalization subscale and COPD-Cognitive Error Questionnaire selective abstraction subscale. *d* = 0.41 |
| Stanley et al. (2005) | Case reports | 8 weekly 1h sessions of group CBT (cognitive approach for anxiety, behavioral activation for depression). | *N* = 5 male veterans with COPD stage II − III and BDI >13 and/or BAI >15. *N* = 3 with Major Depression (DSM-IV criteria). | BDI; BAI, CRQ, SF-36 | *N* = 3 improved in BDI scores evident one year after treatment. Same patients improved in BAI scores. Some improvements in CRQ and SF-36. | − |

**6MWD** = Six-minute walking distance; **ACCESS** = Adjusting to Chronic Conditions using Education, Support, and Skills; **actigraphy** = objective sleep efficiency; **BAI** = Beck Anxiety Inventory; **BDI** = Beck Depression Inventory; **CBT** = cognitive-behavioral therapy; **CES-D** = Center for Epidemiological Studies − Depression Inventory; **COPD** = chronic obstructive pulmonary disease; **CRQ** = Chronic Respiratory Questionnaire (COPD disease-specific QoL inventory); **CSQ** = Client Satisfaction Questionnaire; **ES** = effect size; **ESM** = Education and stress management; **EXESM** = Exercise, education and stress management; **$FEV_1$** = Forced expiratory volume in 1 s; **G1** = Group 1; **G2** = Group 2; **G3** = Group 3; **GDS** = Geriatric Depression Scale; **HADS** = Hospital Anxiety and Depression Scale; **HADS-A**: anxiety scores; **HADS-D**: depression scores; **MHLC** = Multidimensional Health Locus of Control inventory; **MINI** = Mini international Neuropsychiatric Inventory; **ns.** = nonsignificant; **PRP** = Pulmonary Rehabilitation Program; **PSQI** = Pittsburgh Sleep Quality Index (subjective sleep quality);**SCL-90-R** = Hopkins Symptom Checklist; **SF-36** = Medical Outcomes Survey Short Form-36 (general health related QoL); **SGRQ** = St. George's Respiratory Questionnaire (perceived health status); **SIP** = Sickness Impact Profile (generic health status); **Stage I−IV** = Global Initiative for Obstructive Lung Disease (GOLD) standard for severity of COPD; **STAI** = Spielberger Anxiety Inventory Trait Anxiety; **WL** = Waiting List.

[a] Effect sizes are reported when available or calculation possible.

Overall, most studies were of small sample size and/or demonstrated high drop-out rates. Similar as in TCA studies, a great variety of measurement instruments for depression was used across the studies — none used DSM criteria — and comorbid symptoms of anxiety were either not controlled for or not excluded. This might have interacted with antidepressant treatment.

**Effects of cognitive-behavioral therapy (CBT)**

An overview of studies examining the effects of CBT is provided in Table 3. Overall, no study exclusively tested COPD patients with comorbid depression only and no trial tested antidepressant treatment independently from effects on anxiety. From the 12 studies identified, six were randomized and controlled trials. One study was a long-term evaluation and the other studies were non-randomized trials, case reports and pilot studies.

Four of the randomized controlled trials showed significantly improved depression scores for the treatment groups, but not for the control groups.[34,48–50] The remaining two trials revealed treatment effects for depressive symptoms.[32,33] These were not observed for stress management (CBT-format) without exercise, however, antidepressant effects were also obtained in the waiting list condition.[32] Furthermore, no superiority compared to an educational intervention was found.[33]

One randomized and well controlled trial with adequate sample size and application of diagnostic DSM criteria reported significant improvements in depressive symptoms after CBT, but not after enhanced standard care.[48] This improvement lasted up to the 8-months follow-up. The objectively measured sleep efficiency had improved at 8-months follow-up, whereas the subjectively reported experience of sleep was rated poor at all times. Other secondary outcomes were not improved through reduction of mental health symptoms.

Kunik et al.[34] have found a single two-hours-session of CBT to reduce depressive symptoms in mild depressed COPD patients. No reduction was observed in the control group receiving COPD education.

In two other randomized controlled trials, only treatments including psychotherapy led to significantly improved depression levels.[49,50] The group receiving additional psychotherapy improved almost twice as much in walking ability as the group without.[49] A long-term evaluation of the same pulmonary rehabilitation program that included psychotherapy showed improvements in anxiety, depression, QoL and 6MWD to last up to 24-months of follow-up.[51]

All remaining studies used small sample sizes. Significant improvements in depression scores and disease specific and generic QoL were observed after CBT with eight sessions[52] and after a similar intervention.[53] In a nurse-led CBT individualized program, depression scores were significantly improved in patients with COPD after an average of four sessions, which was paralleled by reductions in mean hospital admissions.[54]

A cognitive-behavioral self-help educational program revealed significant decreases in the Psychosocial and Total Sickness Impact Profile (SIP) scores.[55] This indicates improvements in generic health status and improvement in the disease's impact on everyday life. A pilot study revealed superior improvement in perceived health status after six group sessions of CBT compared to general health education. However, no group differences in depression or anxiety scores were retrieved.[56]

Across studies that found significant antidepressant effects in favor of CBT, the mean effect size was $d = 0.93$ (range: 0.52–1.58).

## Discussion

Although depression is highly prevalent in COPD and associated with negative course of disease,[13,19,57,58] it often remains undiagnosed and/or untreated in these patients.[18,24,43,59] This review aimed at summarizing the current state of findings from trials that examined the effects of antidepressant medical treatments and CBT in patients with COPD.

Overall, antidepressant medical as well as CBT treatment trials in COPD patients are rare and heterogeneous in their results. Therefore, firm conclusions on the effectiveness of these treatment options are difficult to draw. A variety of reasons for these inconclusive results become obvious in this review. First, many trials have not used sound diagnostics for confirming clinical significant depression based on established DSM criteria as an inclusion criterion for their participants. Rather, questionnaire scores from various instruments were used to confirm a certain level of depressive symptoms. Other trials included patients regardless of depressive symptoms or comorbid other symptoms of psychopathology. Therefore, it can be assumed that included nondepressed participants might have benefited less from some of the evaluated interventions leading to biased outcomes. Second, many trials have treated depression not independently from anxiety, which might have led to confounded results and less optimal treatment of depression in COPD patients, particularly in CBT trials. This is due to the fact, that patients with depression and comorbid anxiety disorder needed more time to recover from depression than those with depression alone[60,61] and have an higher risk for chronicity in depression and treatment resistance.[62,63] Furthermore, CBT treatments of depression and anxiety differ with respect to included therapeutic elements.[64]

Third, COPD education has often been regarded as a control condition, which led to sub-optimally educated treatment groups. Evidence suggests that patient education can be an important base for further treatment in COPD,[65,66] which might have reduced potential treatment effects. Fourth, many trials were considerably limited by their small sample size, often as a result of high drop-out rates, in particular during antidepressant medical trials. Therefore, a lack of significant treatment results might have been caused by limited statistical power. Finally, instruments measuring QoL were often not included in trials, thus, limiting conclusions on possible treatment effects on this important outcome measure in COPD patients.

Bearing all the aforementioned shortcomings in mind, at least some conclusions and suggestions might be derived from the reviewed studies, in particular from the larger randomized controlled trials.

In antidepressant medical trials, compliance with and feasibility of medical treatments has been reported as low and a preference of patients for psychological treatments has been assumed.[47] The main reasons for limited compliance or

refusal of antidepressant medication were fear of side effects, frustration with taking many medications, and/or denial of psychological symptoms.[24,42] Stage and colleagues[67] have hypothesized that doses of antidepressant medications might have to be lower in elderly populations such as patients with COPD which could have contributed to the reported side effects. Diazepam may even trigger respiratory failure.[40] However, some promising results have been obtained. For TCA treatment, Borson et al.[37] found nortriptyline to be superior to placebo with an effect size of $d = 1.07$ for the reduction of depressive symptoms. Interestingly, respiratory symptoms, physical comfort and day-to-day functioning improved as well. For SSRI treatment, Eiser et al.[44] have found paroxetine treatment to be very effective after three months. An important direction for future research could be the possible triad with smoking cessation. Smoking is not only a major cause for the development of COPD, but also closely linked to depression.[68] Because smoking cessation, which is generally regarded to be essential for COPD treatment,[20] was improved in studies using the antidepressants bupropion and nortriptyline,[69] examining the effects of antidepressant medications regarding the interactions between antidepressant effects and smoking behavior in COPD patients appears highly important.

When comparing the two medical treatments, the applicability of TCA for patients with COPD seems to be more difficult due to more side effects, whereas SSRI seem to be more promising with regard to their effects on symptoms of depression.[70,71] However, future randomized controlled trials are clearly warranted to proof these observations.

The identified CBT trials have shown some promising potential in terms of reducing depressive symptoms in patients with COPD as well as improving subjective and objective markers of the course of disease. However, a depression specific CBT approach that either excludes comorbid anxiety or that specifically targets comorbid symptoms of depression and anxiety has yet to be evaluated in patients with COPD. The observed broadness of inclusion criteria, employed components and duration of CBT makes the comparison of the reviewed treatment trials difficult. Some trials have revealed antidepressant effects of CBT when compared to control conditions.[34,48,50] Others showed improvements of CBT groups in walking or exercise ability.[33,49,50] Yet other studies have found comparable effects in CBT treatment groups and control groups[32,33] and, thus, no superiority of CBT in terms of antidepressant effects. However, compliance and satisfaction with CBT treatments in patients with COPD seem to be promising[34,48–50,52] and the need for behavioral approaches is emphasized.[72] Nevertheless, similar to the medical treatment option, future randomized controlled trials are clearly warranted to draw definite conclusions on the antidepressant effects of CBT in patients with COPD.

When comparing the two treatment options – antidepressant medical treatment and CBT – some aspects seem to be important. COPD education could be an effective first step before the specific effects of antidepressant treatments are to be tested or compared in patients with COPD.[66,67] COPD education might enhance perceived self-efficacy, thus, increasing the motivation to engage in any form of treatment.[66] For example, patient-perceived mastery over COPD has been suggested to be negatively related to mental health engagement.[73] Whereas compliance to CBT seems to be good in elderly patients,[35] antidepressant medical treatment might be less accepted as discussed above.[47] Therefore, some authors conclude CBT to be the treatment of choice,[74] but a direct comparison of CBT and antidepressant medical treatment in COPD patients is currently lacking.

Moreover, further research is needed to test the effects of both treatment options with regard to the severity of depression. For example, Mikkelsen et al.[16] state that mild depression might be treated with CBT whereas cases of major depression should be treated pharmacologically. Additionally, most of the reviewed studies did not examine physical and psychological outcome measures together. Because some studies demonstrated improvements in both outcome domains,[44,75] future studies should include both, physical and psychological outcome measures.

## Conclusion

The high prevalence of depression in patients with COPD and its negative impact on the course of disease make the treatment of comorbid depression an important issue for the disease management. Antidepressant medical treatments and CBT are two treatment options with some promising potential. However, the current data base for these treatments is considerably limited, both by the small number of studies and several methodological shortcomings, leading to heterogeneous results. Further studies with larger sample sizes and improved diagnostics are clearly needed for firm conclusions about the effects of these treatments on psychological and physical well being in patients with COPD.

## Author contributions

All authors participated in developing the study design and in writing the manuscript.

## Conflict of interest statement

None declared.

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