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LEADING ARTICLE

Pharmacological Treatment of Depression in Older Patients with Chronic Obstructive Pulmonary Disease: Impact on the Course of the Disease and Health Outcomes

A. M. Yohannes · G. S. Alexopoulos

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Abstract Over 40 % of older chronic obstructive pulmonary disease (COPD) patients suffer from clinically significant depressive symptoms, which may interfere with their daily activities. Untreated depression may increase physical disability, social isolation, hopelessness and healthcare utilization. This review examined the impact of depression on the course of COPD, and the efficacy of antidepressant drug therapy and its implications for clinical practice. The efficacy of antidepressants in published trials in patients with COPD has been inconclusive. Specifically, there has been no clear evidence that antidepressants can induce remission of depression or ameliorate dyspnoea or physiological indices of COPD. Both selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressant (TCA) studies conducted in depressed COPD patients have been significantly limited by methodological weaknesses including small sample size, sample heterogeneity and variability in the scales used to diagnose and monitor the treatment of depression. For this reason, it remains unclear which SSRIs or TCAs should be favoured in the treatment of depressed COPD patients and what are appropriate dosages and duration ranges. Simply offering antidepressant drugs to older depressed COPD patients is unlikely to improve their condition. Promising treatment strategies such as a collaborative treatment approach and cognitive behavioural therapy should be considered for depressed COPD patients, with or without antidepressant drug therapy. Further studies are needed, including large, randomized, controlled trials with long-term follow-up, to examine the efficacy of antidepressants in patients with COPD.

Key Points

One in five older patients with chronic obstructive pulmonary disease (COPD) suffers from major depression.

Untreated depression may increase physical disability, social isolation, hopelessness and healthcare utilization.

The efficacy of antidepressants in published trials in patients with COPD has been inconclusive. Specifically, there has been no clear evidence that antidepressants can induce remission of depression or ameliorate dyspnoea or physiological indices of COPD.

Many older COPD patients with depression have poor adherence to antidepressant therapy, and strategies to enhance adherence, such as a collaborative treatment approach and cognitive behavioural therapy, are worthy of consideration.

A. M. Yohannes (✉)
Department of Health Professions, Research Institute for Health and Social Care, Manchester Metropolitan University, Manchester M13 0JA, UK
e-mail: a.yohannes@mmu.ac.uk

G. S. Alexopoulos
Institute for Geriatric Psychiatry, Weill Cornell Medical College, White Plains, NY, USA

1 Introduction

Chronic obstructive pulmonary disease (COPD) [1] and depression [2] often coexist in old age. Over 40 % of older COPD patients exhibit clinically significant depressive symptoms, which may interfere in their daily activities [3].

More than 20 % of older COPD patients suffer from moderate-to-severe depression, which contributes to spiral deterioration of their condition and necessitates medical intervention [4]. Dyspnoea and exhaustion in COPD, combined with the hopelessness and helplessness of depression, corrode patients' ability to adhere to their rehabilitation and other treatment regimens. As a consequence, depressed COPD patients often continue to smoke and have frequent medical complications, increased mortality, persistent depressive symptoms and signs, disability, decreased social interactions and poor quality of life [1, 3–5]. In addition, studies in COPD patients have observed that suicidal ideation, worthlessness and psychomotor retardation compromise participation in treatment and rehabilitation [2, 4, 5]. The diagnosis of depression in COPD patients is difficult, especially in the elderly, because of the overlap of symptoms and the presence of frailty and comorbidities. Understanding these factors may help clinicians to develop appropriate prevention and treatment strategies, which may reduce the impact of depression and improve the outcomes of COPD.

The National Institute for Clinical Excellence (NICE) guideline for the management of depression in older people recommends the use of antidepressant drug therapy in patients with moderate-to-severe depression and physical illness, including COPD [6]. Furthermore, the NICE guideline further recommends considering collaborative care and instituting high-intensity psychological interventions and combined treatments for patients with persistent depressive symptoms. However, sub-threshold symptoms, or mild depression, should not be treated with antidepressants because the risk to benefit ratio is poor [6]. The guideline also recommends a selective serotonin reuptake inhibitor (SSRI) as the first-line choice of antidepressant treatment, and states that patients should be monitored periodically for changes in their depressive symptoms, using appropriate depression rating scales, e.g. the Patient Health Questionnaire-9 or the Hospital Anxiety Depression Scale [6, 7].

Treatment of depression in patients with COPD is complex and challenging, and the benefit of antidepressant treatment in these patients has been inadequately addressed. This review examined the impact of depression on the course of COPD, and the efficacy of antidepressant drug therapy and its implications for clinical practice.

2 Impact of Depression on the Course of COPD

The exact pathophysiological mechanisms of depression in patients with COPD remain unclear. It is currently assumed that depression in COPD patients is likely to be multidimensional, with physiological, psychological and psychosocial contributors [8, 9, 10]. A recent systematic review [10] of long-term follow-up studies of COPD patients with comorbid depression suggested that a bidirectional relationship exists. COPD persistently increased the risk of depression (relative risk 1.69, 95 % confidence interval 1.45–1.96). In addition, the presence of depression in COPD patients increased the risk of death by 83 %, especially in men suffering from COPD, suggesting that depression worsens the course of COPD. In 4- to 8-year follow-up of a prospective population-based study in newly diagnosed COPD patients ($n = 38{,}010$), the incidence of new-onset depression was 88 % higher in COPD patients than in age- and sex-matched controls [11]. The risk of developing depression was highest within the first year after diagnosis of COPD and tended to decline over time. Initially, COPD patients may be overwhelmed and find it difficult to cope with their respiratory symptoms, which may lead to loss of hope, social isolation and giving up work and enjoyable activities.

Smoking is a risk factor shared by depression and COPD. The rate of depression is significantly higher in COPD patients who are active smokers than in healthy controls [10, 12]. Furthermore, the association between depression and COPD is likely to be due to lifetime nicotine dependency [13]. Smoking increases the levels of pro-inflammatory cytokines, including interleukin (IL)-6, tumour necrosis factor (TNF)-α and C-creative protein (CRP) [14]. A recent study reported that depressed smokers showed higher levels of TNF-α, IL-6 and CRP than non-depressed smokers [15]. A population-based study ($n = 2077$) reported an association between elevated depressive symptoms and impairment of pulmonary function (measured as the forced expiratory volume in 1 second [FEV1] predicted) in older adults aged >55 years [16]. This association was partly mediated by pro-inflammatory cytokines (e.g. increased levels of IL-6 and CRP) [16].

Depression worsens the outcomes of COPD. A 2-year prospective study documented that patients with depression at baseline had a higher annual rate of COPD exacerbations than those without depression [17]. Furthermore, a 1-year prospective study reported that baseline depression was associated with persistent smoking, longer hospitalization, an increased symptom burden, poorer physical and social functioning, and increased mortality [18]. In a prospective study of 7,787 patients with COPD, Lou et al. [19] investigated the impact of current smoking and depression on mortality. Their findings indicated that current smokers with depressive symptoms had a fourfold increased risk of death. Moreover, in a study of 497 elderly people, Lu et al. [20] found that those with COPD were prone to life event stress (i.e. stress directly related to experience of decreased physical energy, anxiety, extreme fear and panic due to breathing difficulties), which was associated with an elevated level of depressive symptoms and impaired

quality of life, compared with their aged-matched control counterparts.

There is sparse evidence in the literature regarding the use of antidepressants in population-based studies. However, the effectiveness of antidepressants has been evaluated by two studies, using large administrative databases. Qian et al. [21] investigated the effects of a depression diagnosis and antidepressant treatment on 2-year all-cause mortality in Medicare beneficiaries with COPD. Furthermore, they explored whether eligibility for social security disability insurance (SSDI) [signifying the severity of COPD that led to permanent disability in order for them to receive Medicare benefits, e.g. care in a skilled nursing home facility] modified these relationships and their impact on treatment outcomes. A depression diagnosis was given in 21.6 % of the patients, and >80 % of those patients were prescribed antidepressants. Nearly one sixth of the sample were SSDI eligible. The antidepressant treatments used by the patients in this study were tricyclic antidepressants (TCAs), SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs), bupropion, monoamine oxidase inhibitors (MAOIs), trazodone, maprotiline hydrochloride and mirtazapine. The findings of this study indicated that eligibility for SSDI modified the effects of depression and antidepressant treatment on mortality in patients with COPD [21]. Baseline depression increased the risk of death by 13 % in beneficiaries who were not eligible for SSDI. However, caution is required in interpretation of the administrative claims data used in this study, because of possible diagnostic misclassification of patients, channelling bias, lack of a control group and absence of spirometry data. In addition, it is not clear which types of class of antidepressants were unfavourable, and what dosages and durations of antidepressant treatment were used in patients with COPD.

A study using administrative and pharmacy data from the Veterans Affairs Medical Centers ($n = 778$) compared the use of acute antidepressant treatment (the first 3 months on the medication after the initial diagnosis) in patients with and without COPD [22]. COPD patients received less professional healthcare support and an inadequate duration of antidepressant therapy during the acute treatment phase, compared with patients who had other conditions (e.g. coronary heart disease and diabetes). Therefore, there is a need for further investigation into early antidepressant treatment inadequacy in COPD patients [22].

3 Pharmacological Treatment of Depression in COPD Patients

Antidepressants may have differential effects in depressed patients with and without COPD. There is a lack of specific studies of antidepressant efficacy in patients with COPD. Executive dysfunction is common in COPD patients and is associated with a poor response to antidepressants. Frailty increases the risk of antidepressant use, and there is a lack of convincing evidence of its efficacy. The benefit to risk ratio is small. Hence, optimization of the medical management of COPD and selection of antidepressants with a view to minimizing drug interactions are important in the treatment of depression.

We critically appraised the published studies of commonly used antidepressant drug therapy for depression in patients with COPD. We used the keywords 'depression', 'COPD', 'SSRIs' and 'TCAs' to extract the relevant articles from the databases of PubMed, Scopus and PsychInfo from inception to March 2014. In addition, we scrutinized the references of the extracted articles to identify other potentially relevant articles.

Evidence suggests that antidepressant drug therapies are effective in the treatment of moderate to severe depression in older patients with chronic physical illness, as compared with placebo [23]. However, the efficacy of antidepressants in depressed COPD patients has not been adequately investigated in the published trials.

3.1 Selective Serotonin Reuptake Inhibitors

To date, only six studies [24–29] have examined the efficacy of SSRIs for the treatment of depression in patients with COPD. Most of these studies were based on a small number of subjects and did not use controlled designs (Table 1). What follows is a summary of their findings.

3.1.1 Sertraline

A pilot study ($n = 6$) examined the efficacy of sertraline therapy for 6 weeks, with an initial dose of 12.5 mg daily, increasing to 100 mg during the next 2 weeks [24]. There was no significant improvement in depressive symptoms and signs, or in physiological measures of COPD. However, five of the six COPD patients showed some improvement in their daily activities. A retrospective study [25] explored the effectiveness of sertraline at a daily dose ranging from 25 to 100 mg for the treatment of comorbid depression in seven patients with obstructive airway disease. A significant improvement in dyspnoea scores was observed in all patients. A few patients showed some improvement in exercise capacity, depression and anxiety. No improvement in FEV1 was observed.

3.1.2 Fluoxetine

An 8-week, randomized, double-blind study compared the efficacy of fluoxetine 20 mg daily with that of placebo in

Table 1 Trials of antidepressants for treatment of depression in patients with chronic obstructive pulmonary disease

References	Design	Duration (weeks)	Treatment and dose per day	Sample size (*n*)	Outcome measures[a]
Papp et al. [24]	Pilot study, descriptive	6	Sertraline 12.5 mg/day, increased to 100 mg during the first 2 weeks	6	N/A
Smoller et al. [25]	Case reports	N/A	Sertraline 25–100 mg/day	7	N/A
Evans et al. [26]	Randomized, double-blind, placebo-controlled trial	8	Fluoxetine 20 mg/day versus placebo	42	HDRS ELDRS GMS
Yohannes et al. [27]	Single-blind, open study	24	Fluoxetine 20 mg/day	14	GMS MADRS **MRADL** **BPQ**
Lacasse et al. [28]	Randomized, double-blind, placebo-controlled trial	12	Paroxetine 20 mg/day versus placebo	23	GDS SF-36 **CRQ**
Eiser et al. [29]	Randomized, double-blind, placebo-controlled trial	6	Paroxetine 20 mg/day	28	MADRS HADS BDI SGRQ **6MWD**
Gordon et al. [30]	Randomized, double-blind, crossover trial	8	Desipramine 25 mg/day versus placebo	13	BDI ZSDS
Light et al. [31]	Randomized, double-blind, crossover trial	6	Doxepin 25 mg/day versus placebo	12	BDI 12MWD SSAI
Borson et al. [32]	Randomized, double-blind, placebo-controlled trial	12	Nortriptyline versus placebo, initiated at a dose of 0.25 mg/kg of body weight and increased weekly up to 1 mg/kg of body weight	30	CGI HDRS PRAS 12MWD **PFSI** **SIP**
Strom et al. [33]	Randomized, double-blind, placebo-controlled trial	12	Protriptyline 10 mg/day versus placebo	26	HADS MACL **SIP**

6MWD Six-Minute Walking Distance, *12MWD* Twelve-Minute Walking Distance, *BDI* Beck Depression Inventory, *BPQ* Breathing Problems Questionnaire, *CGI* Clinical Global Impression, *CRQ* Chronic Respiratory Questionnaire, *ELDRS* Evans Liverpool Depression Rating Scale, *GDS* Geriatric Depression Scale, *GMS* Geriatric Mental State, *HADS* Hospital Anxiety Depression Scale, *HDRS* Hamilton Depression Rating Scale, *MACL* Mood Adjective Checklist, *MADRS* Montgomery–Åsberg Depression Rating Scale, *MRADL* Manchester Respiratory Activities of Daily Living Questionnaire, *N/A* not available, *PFSI* Pulmonary Function Status Instrument, *PRAS* Patient Rated Anxiety Scale, *SF-36* Short Form 36 (general health-related quality of life), *SGRQ* St. George's Respiratory Questionnaire, *SIP* Sickness Impact Profile, *SSAI* Spielberger's State–Trait Anxiety Inventory, *ZSDS* Zung Self-Rating Depression Scale

[a] The outcomes in bold text represent respiratory measures

42 elderly inpatients with depression and respiratory diseases [26]. Sixty-seven percent of patients in the fluoxetine group had a response in depression scores (the 17-item Hamilton Depression Rating Scale [HDRS], and response was defined as a reduction in the score of 50 % and/or a final score of 10 or less), compared with 37 % in the placebo group [26]. However, there was no statistically significant difference between the two groups in response rates and lung function scores.

In a single-blind study, Yohannes et al. [27] examined the efficacy of fluoxetine 20 mg daily over 6 months. Fourteen depressed COPD patients commenced fluoxetine therapy, and ($n = 7$) completed the study. Five patients withdrew because of adverse side effects, one withdrew because of family problems, and one died from an unrelated cause. Of those who completed the study, four responded to fluoxetine (a 50 % reduction in the Geriatric Mental State Scale score). There was no significant improvement in forced expiratory volume in one second FEV1 and physical activity scores after 6 months of fluoxetine therapy.

3.1.3 Paroxetine

A small, double-blind, randomized, controlled trial [28] examined the efficacy of paroxetine 20 mg daily over 12 weeks in end-stage COPD patients with comorbid depression. Twenty-three COPD patients were randomized. Of these, 15 (eight receiving paroxetine and seven receiving placebo) completed the study. A clinically significant difference was observed in quality of life, especially in mastery and emotional function, using the Chronic Disease Respiratory Questionnaire, favouring paroxetine. There was some improvement in dyspnoea and fatigue scores in the paroxetine group, but this did not reach statistical significance. However, almost one third of the patients discontinued treatment because of adverse side effects. Another study [29] compared the efficacy of paroxetine (20 mg daily) with that of placebo over 6 weeks in 28 patients with COPD. There was no statistically significant difference between the two groups in exercise capacity, lung function and quality of life. Paroxetine was unblinded after 6 weeks, and both groups continued to receive paroxetine 20 mg daily. There was a statistically significant improvement in depression scores, walking distance and quality of life 3 months later.

3.2 Tricyclic Antidepressants

To date, four randomized, double-blind studies have investigated the efficacy of TCAs in patients with COPD [30–33].

3.2.1 Desipramine

An 8-week, placebo-controlled study [30] examined the efficacy of desipramine in 13 depressed but stable patients (with no hospital admission within the previous 6 weeks due to acute exacerbation of COPD). Despiramine was initiated at a dose of 25 mg daily and increased weekly to a target dose of 100 mg. Six patients completed the trial. Both groups had similarly improved depression scores, and there was no significant difference in physiological parameters.

3.2.2 Doxepin

There has been only one randomized, placebo-controlled study of doxepin, which was performed in 12 depressed COPD outpatients [31]. In this 6-week study, doxepin was started at a dose of 25 mg daily and increased as tolerated, with a maximum dose of 105 mg daily. Three patients withdrew from the study because of adverse side effects. There were no significant improvements in depression, anxiety, exercise capacity and physiological parameters of COPD.

3.2.3 Nortriptyline

A double-blind, placebo-controlled trial [32] examined the efficacy of nortriptyline therapy for 12 weeks in COPD patients with major depression, confirmed by psychiatrists using the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) structured clinical interview for depression. Nortriptyline was started at 0.25 mg/kg of body weight and increased weekly up to 1 mg/kg. Thirty COPD patients completed the study. The nortriptyline group showed greater improvements in depression, anxiety, respiratory symptoms and daily activities than the placebo group. However, there was no improvement in physiological measures in either group.

3.2.4 Protriptyline

Strom et al. [33] examined the efficacy of protriptyline 10 mg/day for 12 weeks in a double-blind, randomized trial. Twenty-six depressed COPD patients with chronic hypoxemia started the trial, but only five completed it. Twelve patients in the protriptyline group and six patients in the placebo group discontinued treatment because of adverse events. The most common reason for discontinuing protriptyline were anticholinergic side effects, such as dry mouth. There was no improvement in arterial blood gas tension, spirometry values, dyspnoea or quality-of-life scores in either group.

3.3 Potential Drug–Drug Interactions

The most commonly used agents in COPD are β_2-adrenergic agonists and anticholinergic agents. β_2-Adrenergic agonists such as albuterol, indacaterol, and salmeterol can cause dose-related prolongation of the QT interval and potassium loss. Theoretically, coadministration with some SSRIs (e.g. escitalopram, citalopram or fluoxetine) and TCAs (e.g. nortriptyline or doxepin) that can prolong the QT interval may result in additive effects and an increased risk of ventricular arrhythmias, including torsade de pointes and sudden death. The risk of ventricular arrhythmia related to QT prolongation is unpredictable but may be increased by congenital long-QT syndrome, cardiac disease, hypokalaemia and hypomagnesaemia. TCAs can potentiate the cardiovascular adverse effects of β_2-adrenergic agonists, such as hypertension, palpitations and chest pain. In addition, the anticholinergic action of TCAs may be added to that of anticholinergic bronchodilators used in COPD (e.g. tiotropium, ipratropium) and may lead to dry mouth, tachycardia, urinary retention, constipation, mydriasis, blurred vision, heat intolerance, confusion, fever and exacerbation of glaucoma. None of the above interactions constitute absolute contraindications to combining antidepressants with β_2-adrenergic agonists and anticholinergic bronchodilators. However, awareness of potential drug interactions, judicious follow-up and appropriate interventions can increase the safety of antidepressant drug therapy in COPD patients.

4 Barriers to Treatment Adherence

COPD patients can be reluctant to accept antidepressant drug therapy readily. This is partly due to misconceptions about depression, lack of adequate support, lack of adequate explanation by healthcare professionals regarding the reasons for and efficacy of treatment [5], and withdrawal of therapy due to side-effects (see Table 2). It is also possible that the experience of depression and continuous physical discomfort, a compromised lifestyle and chronic psychosocial adversity further contribute to resignation on the part of patients [34].

Non-compliance with treatment for depression in patients with COPD is multifaceted. Sirey et al. [35] summarized potential treatment barriers, which may include the following: (1) the treatment and rehabilitation of COPD patients is complex and requires patients' active participation; (2) depressed and disabled COPD patients lack the motivation and energy required to adhere to exercise and other prescribed activities; and (3) impairment in intellectual function afflicts about half of depressed COPD patients and interferes with planning, initiating and sequencing behaviour, thus further complicating treatment adherence. Furthermore, a barrier to the care of depressed medically ill patients is poor adherence to and/or acceptance of antidepressant drug therapy. Patient barriers include lack of knowledge about depression, fear of side effects and concerns about stigmatization of depression, which may in part account for the poor acceptance of antidepressant drug treatment [27, 35]. In addition, patients may blame themselves for their disease, further eroding their self-esteem and motivation to seek treatment for their depression [5]. Lack of time spent in educating COPD patients about their depression and limited counselling skills and knowledge about mood disorders on the part of physicians have been cited as potential barriers to adequate treatment of this vulnerable patient group [5, 36].

Depressive symptomatology in general, and psychomotor retardation and diminished interests in particular, interact with executive dysfunction and contribute to disability in depressed elderly patients [37]. These findings suggest that treatment with antidepressant drugs may be insufficient for COPD patients suffering from major depression. Executive dysfunction has been associated with poor response to antidepressants, confers disability and has behavioural consequences (e.g. reduced initiative, poor planning, perseveration and inertia) interfering with the active treatment participation that is required in COPD [38, 39]. Brain anoxia and hypercapnia in COPD often lead to other cognitive problems, which constitute an additional reason to strengthen the importance of personalized intervention for COPD patients.

Table 2 Commonly reported side-effects in trials of antidepressant therapy in patients with chronic obstructive pulmonary disease

Intolerable drowsiness
Blurred vision
Nausea and vomiting
Dry mouth
Fatigue
Sedation
Somnolence
Tremor
Increased sweating
Insomnia
Dizziness
Confusion or agitation
Orthostatic hypotension
Constipation
Worsening anxiety
Hyponatraemia
Sexual dysfunction
Headache
Suicidal ideation

Personalized intervention for COPD and depression (PID-C) was developed in response to concerns about treatment adherence on the part of depressed COPD patients. PID-C is a personalized behavioural management intervention. It is administered by care managers, who work closely with patients to identify treatment barriers, help them work on their rehabilitation programme and encourage them to take their prescribed antidepressants [40]. Physicians are involved in monitoring their patients' treatment and progress. One hundred and thirty-eight patients with major depression and severe COPD were randomized to receive either PID-C or treatment as usual (TAU) [40]. The diagnosis of major depression was determined by the DSM-IV [41] structured clinical interview for depression, and the severity of depression was quantified by the Hamilton Rating Scale for Depression (HRSD) [42]. The intervention group received treatment by the care managers for 26 weeks. PID-C was superior to TAU in inducing remission of depression (HRSD score <7) and in reducing dyspnoea-related disability. These benefits were maintained for 6 months after the end of the intervention. The interrelationship of the course of depression and dyspnoea-related disability in the elderly emphasizes the need to target adherence using PID-C to enhance usage of antidepressants and COPD rehabilitation [43].

5 Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) is defined as therapy that focuses on the clients' patterns of thought and behaviour that induce a depressed mood [44]. CBT can be performed either in a group setting or in an individual patient setting, and it requires multiple sessions to recognize and modify thoughts and behaviours in order to reduce symptoms of depression. Two randomized, controlled CBT trials [45, 46] were conducted in COPD patients to treat depression in group therapy settings, with durations of 7 and 8 weeks, respectively. These trials were effective in ameliorating depressive symptoms in patients with COPD. These improvements were maintained in both studies at 8 and 12 months of follow-up [45, 46]. These findings are very encouraging, and CBT should be used as part of medical treatment with or without antidepressant drug therapy for depressed COPD patients. However, group CBT may not be appropriate for COPD patients with severe hypoxaemia and patients receiving long-term oxygen therapy, as these conditions may deter some COPD patients from participating in group CBT activities.

Simply offering antidepressant drugs to older depressed COPD patients is unlikely to improve their condition [27]. Therefore, treatment strategies such as PID-C and the collaborative care approach should be considered, with care managers supporting and educating depressed COPD patients suffering from chronic physical illness about the impacts of depression and dyspnoea-related disability on their daily activities.

Vigorous inpatient rehabilitation has led to improvement of major depression in COPD patients independently of antidepressant drugs [47]. This provides some evidence of the importance of pulmonary rehabilitation, through behavioural activation, to improve depression treatment in patients with COPD.

Recent data from general practitioners in England have revealed that the preferred method of treating depressed COPD patients is to provide both antidepressant drug therapy and psychological therapy simultaneously [7]. This requires further testing in clinical trials.

6 Discussion

The two population-based studies that have examined the effectiveness of antidepressant drug therapy in patients with COPD lacked specificity in terms of which types of antidepressants were found to be unfavourable, and what dosages and durations of antidepressant treatment were used. In addition, no randomized, controlled trials of antidepressants have been conducted in primary care settings with sufficient sample sizes and a sufficient length of follow-up to allow assessment of benefits and adverse outcomes in older people with COPD.

SSRI studies conducted in depressed COPD patients have been significantly limited by methodological weaknesses, including small sample sizes, sample heterogeneity and variability in the scales used to diagnose and monitor the treatment of depression. For this reason, it remains unclear which SSRI should be favoured in the treatment of depressed COPD patients and what is an appropriate dosage and duration range.

Among the TCA studies, only one study of nortriptyline [32] showed clinically significant improvements in depression, anxiety and quality-of-life scores, compared with placebo. The rest of the studies had significant methodological limitations, to the point that their findings were inconclusive. In addition, significant proportions of the patients withdrew from those studies because of adverse events, as reported in Table 2. Therefore, the potential risks and benefits of various classes of antidepressants require careful consideration when SSRIs and TCAs are prescribed in older COPD people with major depression. Furthermore, antidepressant treatment is often inadequate, and many depressed COPD patients do not adhere to their antidepressant medication.

There is evidence to suggest that there is a bidirectional relationship between depression and COPD [10]. However,

no studies have reported the benefits of antidepressants in improving lung function in depressed patients with COPD. Further study is needed.

6.1 Implications for Clinical Practice

This review found no clear evidence as to which family of antidepressants or which antidepressant is most efficacious in treating depression in COPD patients. There are a number of factors that reduce adherence to antidepressant drug therapy, including lack of social support, hopelessness and executive dysfunction. In their recent review, Shultz and Malone [48] provided helpful and practical tips for prescribing antidepressants in older patients with medical illness. We suggest that in the absence of knowledge specifically related to depression in COPD, their recommendations (listed below) are relevant:

- When prescribing an antidepressant, 'start low and go slow', but try not to reach a therapeutic dose in patients with adequate tolerance.
- Prior to commencing antidepressant drug treatment, COPD patients should have their diagnosis of depression explained to them and be informed of potential side effects. It is important for clinicians to emphasize that most side effects are transient, and to make themselves available in case side effects do develop. Normally, side effects resolve within a few weeks. Clinicians can help patients with interventions to help them cope with side effects until they resolve [48].
- Scheduling follow-up visits at least every 4 weeks, especially in the early stages, is paramount in order to monitor patients' adherence to treatment and progress. When side effects occur, it is important to thoroughly evaluate patients' adherence and clinical state before switching to another drug or discontinuing antidepressants altogether.
- Depressed COPD patients who are poorly tolerating or failing to respond to antidepressants should be referred to a psychiatrist for detailed assessment.
- Personalized intervention for depression and COPD in collaboration with care managers is worthy of consideration, especially in patients who are poorly adherent to rehabilitation and antidepressant treatment. By targeting treatment adherence, this approach has been shown to improve both depression and dyspnoea-related disability in patients with major depression and severe COPD.
- Older COPD patients with moderate-to-severe depression are most likely to suffer from comorbidities, and optimization of medical conditions and selection of antidepressants (SSRIs) with a view to minimizing drug interactions is worthy of consideration.
- It is important to use validated outcome measures to monitor patients' conditions and determine the effectiveness of antidepressant drug therapy in patients with COPD on a regular basis.

7 Conclusion

To date, the efficacy of specific antidepressants in improving depression, dyspnoea and physiological measures of COPD is unknown. Poor adherence to COPD rehabilitation and to antidepressant drug therapy further undermines good care. In addition to knowledge-derived, much-needed, methodologically sound drug trials, the clinical care of depressed COPD patients can be improved by collaborative care models and problem-solving therapy to address barriers to patient adherence to rehabilitation and antidepressant prescriptions.

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Conflicts of interest Dr. Alexopoulos is a stockholder in Johnson and Johnson and has served as a consultant to Lilly and on speakers' bureaux for Astra Zeneca, Forest, Merck, Avanir and Lundbeck. Dr. Yohannes declares no conflicts of interest relevant to the content of this article.

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