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Pharmacologic Treatment of Depression in Older Patients with COPD: Impact on the Course of the Disease and Health Outcomes

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Abstract

Over 40% older chronic obstructive pulmonary disease (COPD) patients suffer from clinically significant depressive symptoms that may interfere in 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 drugs therapy and their implication for clinical practice. The efficacy of antidepressants from the 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 the selective reuptake inhibitors (SSRI) and tricycle antidepressant (TCA) studies conducted in depressed COPD patients have been significantly limited by methodological weaknesses including low sample size, sample heterogeneity, and variability in scales used to diagnose and to monitor the treatment of depression. For this reason, it remains unclear whether which SSRIs or TCAs should be favoured in the treatment of depressed COPD patients and what is an appropriate dosage and duration range. Simply offering antidepressant drugs to older depressed COPD patients is unlikely to improve their conditions. Promising treatment strategies such as cognitive behavioural therapy and collaborative care approach should be considered with or without antidepressants drug therapy for depressed COPD patients. Further studies are needed with large randomised controlled trials to examine the efficacy of antidepressants in patients with COPD with long-term follow-up.

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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 that may interfere in their daily activities [3]. More than 20% of older COPD patients are suffering from moderate-to-severe depression, which contribute to spiral deterioration of their conditions that necessitates medical intervention [4]. Dyspnoea and exhaustion of COPD combined with the hopelessness and helplessness of depression corrode the 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 have observed in COPD patients that suicidal ideation, worthlessness and psychomotor retardation compromise participation to treatment and rehabilitation [2,4,5]. The diagnosis of depression in COPD patients is difficult, especially in the elderly because of the over-lap of symptoms and in the presence of frailty and comorbidities. Understanding these factors may help clinicians to develop appropriate prevention and treatment strategies that 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 antidepressants drug therapy in patients with moderate-to-severe depression and physical illness including COPD [6]. Furthermore, the NICE guidance further recommends adding on high intensity of psychological interventions, combined treatments and collaborative care consideration for patients with persistent depressive symptoms. However, sub-threshold symptoms or mild depression should not be treated with antidepressants because risk to patients benefit ratio is poor [6]. It also recommends a selective serotonin reuptake inhibitors (SSRI) as the first line of choice of antidepressant treatment and patients should be monitored periodically for change in their depressive symptoms using appropriate depression rating scales e.g. Patient Health Questionnaire-9 or 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 antidepressants drug therapy and their implication 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 of COPD is likely multi-dimensional with physiological, psychological, and psychosocial contributors [13, 14]. A recent systematic review [14] of long-term follow-up studies of COPD patients with comorbid depression suggests a bidirectional relationship exists. COPD persistently increased the risk of depression (relative risk, 1.69; 95% CI, 1.45–1.96). In addition, 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 a prospective population based

study in newly diagnosed (n = 38, 010) COPD patients in four to eight years follow-up, the new onset of depression was 88% higher in COPD patients compared to their aged sex-matched controls [15]. The risk of developing depression was the highest within the first year following the diagnosis of COPD and tends to decline over-time. Initially, COPD patients may be overwhelmed and 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 active smokers of COPD patients compared to healthy controls [14, 16]. Furthermore, the association of depression and COPD is likely due to lifetime nicotine dependence [17]. Smoking increases the levels of pro-inflammatory cytokines including interleukine-6 (IL-6), tumour necrosis factor alpha (TNFα) and C-creative protein (CRP) [18]. In addition, a recent study reported that depressed smokers showed higher levels of TNFα, IL-6 and CRP compared to non-depressed smokers [19]. A population-based study [n = 2077], reported an association of elevated depressive symptoms and pulmonary function impairment (forced expiratory volume in one second predicted) in older adults aged > 55 years [20]. This association was partly mediated by pro-inflammatory cytokines (e.g. increased levels of IL-6 and CRP) [20].

Depression worsens the outcomes of COPD. A 2-year prospective study documented that depression at baseline was associated with a higher annual rate of COPD exacerbations compared to patients without depression [21]. Furthermore a one-year prospective study reported baseline depression was associated with persistent smoking, longer hospitalization stay, increased symptom burden, poorer physical and social functioning, and increased mortality [22]. Lou and co-workers [24] in a prospective study (n = 7,787) investigated the impact of current smoking, depression on mortality in patients with COPD. Their findings indicated that patients who were current smokers with depressive symptoms were at four folds increase the risk of death. Moreover older COPD patients [25] are prone to life event stress (i.e. stress directly related with experience of decreased physical energy, anxiety and extreme fear of panic distress due breathing difficulties), which was associated with elevated level of depressive symptoms and impaired quality of life compared to their aged matched controls counterparts.

There is sparse evidence in the literature in the use of antidepressants in population based studies. However, the effectiveness antidepressants have been evaluated by two studies using large administrative databases. Qian and co-workers [26] investigated the effects of depression diagnosis and antidepressant treatment on 2 year all cause of mortality in Medicare beneficiaries in COPD patients. Furthermore, they have explored whether social security disability insurance (SSDI) eligibility (signify the severity of COPD that led to permanent disability in order to receive Medicare benefits e.g. skilled nursing home facility) modifies these relationships and impact on treatment outcomes. A depression diagnosis was given in 21.6% of them. Over 80% of patients were prescribed antidepressants. Nearly one-sixth of the sample were SSDI eligible. The antidepressants treatment included were (TCAs, SSRIs, serotonin norepinephrine reuptake inhibitors, bupropion, monoamine oxidase inhibitors, trazodone, maprotiline hydrochloride and mirtazapine). Their findings indicate that eligible to SSDI modifies the effects of depression and antidepressant treatment on

mortality in patients with COPD [26]. Baseline depression increased the risk of death by 13% in beneficiaries who were not eligible for SSDI. However, caution is required as administrative claims data are prone to patient's diagnostic misclassification, channeling bias, lack of a control group and absence of spirometry data. In addition, which types of class of antidepressants are unfavorable including dosage and duration in the treatment of depression 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 (of the first three months on the medication after the initial diagnosis) in COPD patients compared to patients without COPD [27]. COPD patients received less professional healthcare support and inadequate duration of antidepressants during the acute treatment phase compared to patients with other conditions e.g. coronary heart disease and diabetes. Therefore, further investigation is required for the early antidepressant treatment inadequacy for COPD patients [27].

3. Pharmacological treatment of depression in COPD patients

Antidepressants may have differential effects in depressed COPD patients compared with non-COPD depressed patients: 1) Lack of specific studies on antidepressants efficacy; 2) Executive dysfunction is common in COPD patients, and is associated with poor response to antidepressants and 3) Frailty increases the risk of antidepressants use, and in the absence of convincing evidence of efficacy. The benefit/risk ratio is small. Hence, the optimization of medical management of COPD and selection of antidepressants with regard to minimizing drug interactions is important to depression treatment.

We have critically appraised of the published studies that were commonly used antidepressants drug therapy for depression in patients with COPD. We used the following keywords 'depression', 'COPD' 'SSRIs' and 'TCAs' to extract the relevant articles from the databases of PubMed, Scopus and Psychic Info from inception to March 2014. In addition, we have scrutinized the references of the extracted articles to identify potential 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 to placebo [8]. However, the efficacy of antidepressants in depressed COPD patients has been inadequately investigated from the published trials.

3.1 Selective serotonin reuptake inhibitors (SSRI)

To date, only six studies [29–34] examined the efficacy of SSRIs for the treatment of depression in patients with COPD. Most of these studies were based 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 for 6 weeks, with initial dose of 12.5 mg daily increased to 100 mg during the next two weeks [29]. There was no significant improvement in depressive symptoms and signs or physiological measures of COPD. However, 5 out of 6 COPD patients showed some improvement in their

daily activities. A retrospective study [30] explored the effectiveness of sertraline at a daily dose ranging from 25 to 100 mg in 7 patients with obstructive airways disease for the treatment of comorbid depression. They observed significant improvement in dyspnoea scores in all patients. A few patients had shown some improvement in exercise capacity, depression and anxiety. No improvement was observed in forced expiratory volume in one second (FEV1).

3.1.2 Fluoxetine—An 8-week, randomized, double-blind compared the efficacy of fluoxetine 20 mg daily to that of placebo in 42 elderly inpatients with depression and respiratory diseases [31]. Sixty seven per cent of patients in the fluoxetine group had a response in depression scores (17-item Hamilton Depression Rating Scale (HDRS), and response was defined as a reduction in score 50% and/or a final score of 10 or less on HDRS) compared to 37% in the placebo group [31]. However, there was no statistically significant difference between the two groups in response rates and in lung function scores

In a single blind study, Yohannes et al [32] examined the efficacy of fluoxetine 20 mg daily over 6 months. Fourteen depressed COPD patients commenced the fluoxetine therapy, and (n = 7) completed the study. Five patients withdrew because of adverse side effects, 1 withdrew due to family problems, and 1 died due to unrelated cause. Of those who completed the study, 4 responded to fluoxetine (50% reduction in the Geriatric Mental State scale score). There was no significant improvement in FEV1 and physical activity scores after 6 months of fluoxetine therapy.

3.1.3 Paroxetine—A small, double blind, randomised controlled trial [33], examined the efficacy of paroxetine 20 mg daily over 12 weeks in end-stage of COPD patients with comorbid depression. Twenty-three COPD patients were randomised. Of these, 15 (8 paroxetine and 7 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 did not reach statistical significance. However, almost one third of the patients discontinued treatment due to adverse side effects. Another study [34] compared the efficacy of paroxetine (20 mg daily) against 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 on 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 (TCA)

To date four randomised double-blind studies have investigated the efficacy of TCA's in patients with COPD [35–38].

3.2.1 Despiramine—An 8-week, placebo controlled study [35] examined the efficacy of despiramine in 13 depressed but stable (no hospital admission in 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 in physiological parameters.

3.2.2 Doxepin—There has been only one randomized placebo controlled study of doxepin in 12 depressed COPD outpatients [36]. In this 6-week study, doxepin was started at a dose of 25mg 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 was no significant improvement in depression, anxiety, exercise capacity, and physiological parameters of COPD.

3.2.3 Nortriptyline—A double-blind, placebo controlled trial examined [37] the efficacy of nortriptyline of 12 weeks in COPD patients with major depression, confirmed by psychiatrists using the Structured Clinical Interview for DSM-III. 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 compared to the placebo group. However, there was no improvement in physiological measures of in either group.

3.2.4 Protriptyline—Strom et al [38] examined the efficacy of Protriptyline, 10 mg/d for 12 weeks, in a double blind randomised trial. Twenty six depressed COPD patients with chronic hypoxemia started the trial but only five completed. Twelve patients in the Protriptyline and six patients in the placebo group discontinued treatment due to adverse events. The most common reason for discontinuing protriptyline were anticholinergic side effects i.e. dryness in the mouth. There was no improvement in arterial blood gas tensions, spirometry values, dyspnoea and quality of life scores in either group.

3.3 Potential drugs-drug interactions

The most commonly used agents in COPD are beta-2 adrenergic agonists and anticholinergic agents. Beta-2 adrenergic agonists such as albuterol, indacaterol, and salmeterol can cause dose-related prolongation of the QT interval and potassium loss. Theoretically, co-administration with some serotonin reuptake inhibitors (e.g. escitalopram, citalopram, fluoxetine) and tricyclic antidepressants (e.g. nortriptyline, doxepin) that can prolong the QT interval may result in additive effects and 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. Tricyclic antidepressants (TCAs) can potentiate the cardiovascular adverse effects of beta-2 adrenergic agonists such as hypertension, palpitation, and chest pain. In addition, the anticholinergic action of tricyclics may be added to that of anticholinergic bronchodilators used in COPD (e.g. tiotropium, iptratropium) and 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 beta-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' are reluctant to accept antidepressants drug therapy readily. This is partly due to misconception about depression, lack of adequate support and explanation about depression to patients of the reasons for and the efficacy of treatment by the healthcare professionals [5] and withdrawal of therapy due side-effects see Table 2. It is also possible that those who experience depression, continuous physical discomfort, have compromised lifestyle, and are exposed to chronic psychosocial adversity, further contributes to resignation [9].

Non-compliance to treatment of depression in patients with COPD is multi-faceted. Sirey and co-workers [39] have summarised potential treatment barriers may include: 1. The treatment and rehabilitation of COPD patients is complex and requires active participation of COPD patients. 2. Depressed, disabled COPD patients lack the motivation and energy required to adhering to exercise and other prescribed activities; 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 care of depressed medically ill patients is poor adherence and/or acceptance of antidepressants drug therapy. Patient barriers include lack of knowledge about depression, fear of side effects and concerns about stigmatization of depression may account in part for the poor acceptance of antidepressant drug treatment [32,39]. In addition, patients may blame themselves for their disease, further erodes their motivation and self-esteem to seek treatment related for their depression [5]. Lack of time of educating COPD patients about their depression and limited counselling skills and knowledge about mood disorders by physicians' have been cited as potential barriers to provide adequate treatment for this vulnerable patient group [5, 40].

Depressive symptomatology in general and psychomotor retardation and diminished interests in particular, interact with executive dysfunction and contribute to disability in depressed elderly patients [41]. Given, 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, preservation, inertia) interfering with active treatment participation required by COPD [42,43]. Brain anoxia and hypercapnia of COPD often lead to other cognitive problems, which constitutes an additional reason to strengthen the importance of personalised intervention for COPD patients.

Personalized intervention for COPD and depression (PID-C) was developed in response to concerns about treatment adherence on depressed COPD patients. PID-C is a personalised behavioural management intervention. It is administered by the care mangers who work closely with patients to identify treatment barriers and help them work on their rehabilitation program and encourages them to receive their prescribed antidepressants [44]. Physicians

are involved in monitoring their patients' treatment and progress. One hundred thirty eight with major depression and severe COPD were randomised to PID-C or to treatment as usual (TAU) [44]. Diagnosis of major depression was determined by the structural criteria interview depression using the Diagnostic Structured Manual (DSM-IV) [45] and severity of depression was quantified with the Hamilton Rating Scale for Depression [HRSD, 46]. The intervention group received treatment by the care managers for 26 weeks. PID-C was superior to TAU in inducing improving remission of depression (HRSD < 7) and in reducing dyspnoea related disability. These benefits were maintained for six months after the end of the intervention. The interrelationship of the course of depression and dyspnea-related disability in the elderly emphasises the need to target adherence using PID-C to enhance usage of antidepressants and COPD rehabilitation [47].

5. Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) is defined as therapy that focuses on the clients' patterns of thoughts and behaviour that induce a depressed mood [48]. CBT can be performed either in a group or an individual patient setting, and requires multiple sessions to recognize and modify thoughts and behaviours in order to reduce symptoms of depression. Two randomized controlled CBT trials [49, 50] were conducted in COPD patients to treat depression as a group therapy with the duration of seven and eight weeks, respectively. These trials were effective to ameliorate depressive symptoms in patients with COPD. These improvements were maintained in both studies in 8 months and 12 months follow-up [49, 50]. The findings are very encouraging and CBT should be used as part of medical treatment with or without antidepressants drug therapy for depressed COPD patients. However, group CBT may not be appropriate for COPD patients with severe hypoxemia and patients with long term oxygen therapy. These conditions may deter some COPD patients from participating in the group CBT activities.

Simply offering antidepressant drugs to older depressed COPD patients is unlikely to improve their conditions [32]. Therefore, treatment strategies such as PID-C and collaborate care approach should be considered with care managers to supporting and educating depressed COPD patients who are suffering from chronic physical illness about the impact of depression and dyspnoea related disability in their daily activities.

Vigorous inpatient rehabilitation led to improvement of major depression in COPD patients independently of antidepressant drugs [51]. This provides some evidence the importance of pulmonary rehabilitation, through behavioural activation, to improve depression treatment in patients with COPD.

A recent data from the general practitioners in England revealed that the preferred method of treating depressed COPD patients was to provide both the antidepressants drug therapy and psychological therapy, simultaneously [7]. This requires further testing in clinical trials.

6. Discussion

The two population based studies that examined the effectiveness of antidepressant drug therapy in patients with COPD lacks specificity in terms of which types of class of

antidepressants are unfavourable including dosage and duration of treatment. In addition, there are no randomized controlled trials of antidepressants that have been conducted in primary care setting with sufficient sample size and length of follow-up to assess benefits and adverse outcomes in older people with COPD.

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

Among TCAs studies, only one study of nortriptyline [37] that showed clinically significant improvement in depression, anxiety, and quality of life scores compared to placebo. The rest of the studies had significant methodological limitations to the point that their findings are inconclusive. In addition, significant proportion of patients withdrew from their studies due to 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 people with major depression of COPD. Furthermore, the treatment of antidepressant is often inadequate and many depressed COPD patients do not adhere with antidepressant medication.

There is evidence to suggest the bi-directional relationship between depression and COPD [14]. However, none of the 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 on which family of antidepressants or which antidepressant is most efficacious in depression of COPD patients. There are a number of factors that reduce adherence to antidepressant drug therapy including lack of social support, hopelessness and executive dysfunction. Shultz and Malone [52] in their recent review provide helpful practical tips below in prescribing antidepressants in older patients with medical illness. We suggest that in the absence of knowledge specifically related to depressed COPD, their following recommendation are relevant.

- When prescribing an antidepressants ‘start low and go slow’ but try not 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 to emphasize that most of side effects are transient and make yourself available in case side effects develop. Normally the side-effects resolve within a few weeks. Clinicians can help patients with interventions to help them cope with side effects until they resolve [52].
- Scheduling follow-up visits, at least every 4 weeks, especially at the early stages is paramount in order to monitor the patient’s adherence to treatment and progress. When side effects occur, it is important to conduct a thorough evaluation of

adherence and clinical state before switching to another drug or discontinue antidepressants altogether.

- Depressed COPD patients who are poorly tolerating or fail 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 poorly adhering 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.
- Many older COPD patients with moderate-to-severe depression are most likely to suffer with comorbidities and optimization of medical conditions and selection of antidepressants (SSRIs) with regard to minimizing drug interactions is worthy of consideration.
- It is important to use validated outcome measures to monitor patient's condition and determine the effectiveness of antidepressants drug therapy in patients with COPD in regular basis.

7. Conclusion

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

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Key points

- One in five older COPD patients is suffering from major depression.
- Untreated depression may increase physical disability, social isolation, hopelessness and healthcare utilization.
- The efficacy of antidepressants from the 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 compliance such as collaborative treatment approach and cognitive behavioural therapy are worthy of consideration.

Table 1

Trials of Antidepressants for treatment of depression in patients with COPD

Year	Design	Duration in weeks	Treatment and dose per day	Sample size	Outcome measures*
Papp et al. (1995) [29]	Pilot study, descriptive	6	Sertraline 12.5mg/d. Increased to 100 mg during the first 2 weeks	6	n/a
Smoller et al. (1998) [30]	Case reports	n/a	Sertraline 25 – 100mg/d.	7	n/a
Evans et al. (1997) [31]	Randomized double-blind placebo-controlled trial	8	Fluoxetine 20mg/d versus placebo	42	HDRS ELDRS GMS
Lacasse et al. (2004) [33]	Randomized double-blind placebo-controlled trial	12	Paroxetine 20mg/d versus placebo	23	GDS SF-36 **CRQ**
Yohannes et al. (2001) [32]	Single-blinded, open study	24	Fluoxetine 20mg/d	14	GMS MADRS **MRADL** **BPQ**
Eiser et al. (2005) [34]	Randomized double-blind placebo-controlled trial	6	Paroxetine 20mg/d	28	MADRS HADS BDI SGRQ **6MWD**
Gordon et al. (1985) [35]	Randomized double-blind crossover trial	8	Desipramine 25mg/d versus placebo	13	BDI ZSDS
Light et al. (1986) [36]	Randomized double-blind crossover trial	6	Doxepine 25mg/d versus placebo	12	BDI 12MWD SSAI
Borson et al. (1992) [37]	Randomized double-blind placebo-controlled trial	12	Nortriptyline vs placebo initiated at a dose of 0.25mg/kg of body weight increased weekly until 1mg/kg of body weight	30	CGI HDRS PRAS 12MWD **PFSI** **SIP**
Strom et al. (1995) [38]	Randomized double-blind placebo-controlled trial	12	Protriptyline 10mg/d versus placebo	26	HADS MACL **SIP**

* outcomes in bold represent respiratory measures

n/a = not available
/d = a day
BDI = Beck Depression Inventory
BPQ = Breathing Problems Questionnaire
CGI = Clinical Global Impression

CRQ = Chronic Respiratory Questionnaire
ELDRS= Evans Liverpool Depression Rating Scale
GMS= Geriatric Mental State
GDS = Geriatric Depression Scale
HADS = Hospital Anxiety Depression Scale
HDRS = Hamilton Depression Rating Scale
SF-36 = Short Form 36 (general health related quality of life)
MADRS = Montgomery Asberg Depression Rating Scale
MACL – Mood Adjective Check List
MRADL = Manchester Respiratory Activities of Daily Living Questionnaire
PFSI = Pulmonary Function Status Instrument
PRAS = Patient Rated Anxiety Scale
SGRQ = St.George's Respiratory Questionnaire
SIP – Sickness Impact Profile
SSAI = Spielberger's State-trait Anxiety Inventory
ZSDS = Zung Self-rating Depression Scale
6MWD = Six-minute walking distance
12MWD = Twelve-minute walking distance

Table 2

Commonly reported side-effects in COPD trials with antidepressants

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