Drugs Ther Perspect (2015) 31:52–56
DOI 10.1007/s40267-014-0167-8

DISEASE MANAGEMENT

Consider behavioural strategies in addition to antidepressants in clinically depressed patients with chronic obstructive pulmonary disease

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Published online: 14 October 2014

Abstract Depression is common in older patients with chronic obstructive pulmonary disease. However, evidence clearly establishing the effectiveness of specific antidepressants in inducing remission of depression and/or improving dyspnoea and physiological measures in this patient population is lacking. Although adherence to pharmacological and rehabilitative treatment is often poor and treatment barriers are multifactorial, collaborative care strategies targeting treatment adherence and behavioural therapy appear to improve depression and dyspnoea-related disability.

Treating co-morbid depression and COPD is complex

Clinically significant depressive symptoms are present in >40 % of older patients with chronic obstructive pulmonary disease (COPD) [1]. Depression, combined with the dyspnoea and exhaustion of COPD, reduces patient participation and adherence to treatment and rehabilitation resulting in frequent medical complications, smoking continuation, disability, persistent depression, social isolation and increased mortality [2]. Diagnosis of depression in older patients with COPD is challenging because of symptom overlap, frailty and co-morbidities, and treatment is complex, particularly as the benefit of antidepressant medication in this patient population has been inadequately addressed [3].

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This article summarizes the effect of depression on disease course and antidepressant efficacy in patients with COPD, as reviewed by Yohannes and Alexopoulos [3].

Strong link between depression and COPD

The relationship between depression and COPD is complex and multidimensional, including physiological, psychological and psychosocial influences [3]. A recent systematic review of longitudinal studies involving 28,759 adults identified a bidirectional association between COPD and co-morbid depression [4]. Depression adversely affected COPD disease course and outcomes, conferring an increased risk of exacerbation and possibly death [relative risk (RR) 1.83; 95 % CI 1.00–3.36]; moreover, patients with COPD had an increased the risk of developing depression than those without COPD (RR 1.69; 1.45–1.96) [4].

Other studies have also reported adverse COPD outcomes in patients with depression [5–7]. Patients with COPD with co-morbid depression had higher annual COPD exacerbation rates than those without depression, and co-morbid depression was independently associated with increased COPD symptom burden, prolonged hospitalization, poor functional status, persistent smoking and poor survival rates [5, 6]. Furthermore, elderly patients with COPD were prone to life-event stress with associated elevated levels of depressive symptoms and impaired health-related quality of life relative to age-matched controls [7].

COPD can be overwhelming initially as patients struggle to cope with respiratory symptoms, which results in an increased risk of depressive symptoms [3]. In addition to the recent systematic review [4], support for a relationship between COPD and risk of depression was shown in a large study of insurance claim data [8]. Relative to the general

population, patients with newly-diagnosed COPD had a nearly two-fold higher risk of depression, with the risk being highest in the first year after COPD diagnosis [8].

Smokers risk both depression and COPD

Smokers are at increased risk of both depression and COPD, with the association between both these outcomes likely due to lifetime nicotine dependency [3]. In a large prospective study in patients with COPD, the interaction between current smoking and depressive symptoms increased the risk of death by fourfold [9].

Pro-inflammatory cytokine levels, which are increased in smokers and more so in depressed smokers, appear to partly mediate an association between elevated depressive symptoms and impairment of lung function, according to a large population-based study in older adults [10].

Antidepressants indicated for depressed elderly with physical illness …

The National Institute for Clinical Excellence (NICE) guidelines recommend the use of antidepressants to treat moderate-to-severe depression in older patients with chronic physical illness, including COPD [11]. Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment choice [11]. In those patients with persistent depressive symptoms, consideration of collaborative care and instituting high-intensity psychological interventions and combined treatments is recommended [11]. Antidepressants are not recommended to treat patients with mild depression or sub-threshold depressive symptoms [11].

… but evidence for their efficacy in COPD is inconclusive

Although antidepressants have been recommended for treatment of older patients with chronic physical illness, the efficacy of antidepressants in published trials in patients with COPD has been inconclusive, with no clear evidence that antidepressants can induce remission of depression, or improve dyspnoea or physiological measures of COPD [3]. No randomized controlled trials of sufficient sample size and length of follow-up have been conducted in the primary-care setting in patients with COPD [3].

Difficult to determine appropriate SSRI

The selection of the appropriate SSRI to use for the treatment of depression in COPD patients remains unclear, as the six published studies investigating the use of SSRIs in this indication (of which only three used a randomized design) have been significantly limited by methodological weaknesses, including small sample sizes, sample heterogeneity and variability in assessment scales (Table 1) [3].

Most studies of tricyclic antidepressants are inconclusive

Most published studies of tricyclic antidepressants (TCAs) to treat depressed COPD patients have methodological limitations preventing conclusive findings and many have a high rate of study withdrawal because of adverse effects (Table 1) [3]. Only four well designed trials assessing the efficacy of TCAs in patients with COPD have been published, with only results from a study of nortriptyline treatment for depression finding clinically significant improvements in outcome parameters of mood, physical symptoms and function, compared with placebo (Table 1) [12–15].

Consider risks and benefits of antidepressant therapy

The risks and benefits of the various classes of antidepressants should be carefully considered when prescribing antidepressants for older patients with COPD and major depression. Adverse events that are commonly reported with the use of antidepressants in patients with COPD are summarized in Table 2.

Moreover, some antidepressants may interact with bronchodilators commonly used for the treatment of COPD. For example, dose-related QT interval prolongation and potassium depletion can occur with β_2-adrenergic agonists such as albuterol, indacaterol and salmeterol. Co-administration of these agents with some SSRIs (escitalopram, citalopram and fluoxetine) and TCAs (nortriptyline and doxepin) that can also prolong the QT interval may result in an additive effect, leading to an increased risk of ventricular arrhythmias and sudden death [3]. TCAs may also potentiate the cardiovascular adverse effects that can occur with β_2-adrenergic agonists [3]. Furthermore, the frequency and severity of the anticholinergic-mediated adverse effects of TCAs (e.g. dry mouth, tachycardia, urinary retention, constipation, mydriasis, blurred vision, heat intolerance, confusion, fever and exacerbation of glaucoma) may be increased in patients who are also receiving anticholinergic bronchodilators (e.g. tiotropium and ipratropium) to treat COPD.

Although the use of antidepressants concomitantly with β_2-adrenergic agonists and anticholinergic bronchodilators is not absolutely contraindicated, healthcare providers should be aware of potential drug interactions [3]. The safety of antidepressant treatment in patients with COPD

Table 1 Summary of randomized, double-blind, placebo-controlled trials of antidepressants in the treatment of depression in patients with chronic obstructive pulmonary disease (COPD)

Treatment	Outcomes and comments
Selective serotonin reuptake inhibitors	
Fluoxetine 20 mg/day for 8 weeks ($n = 42$) [16]	No significant difference between fluoxetine and placebo in response rate (defined as ≥50 % decrease in 17-item Hamilton Depression Rating Scale score and/or final score ≤ 10) [67 vs. 38 %]
	Outcomes in fluoxetine recipients tended to continue to improve over time
Paroxetine 20 mg/day for 12 weeks ($n = 23$) [17]	Relative to placebo, paroxetine significantly improved quality of life (especially the emotional function and mastery domains of the Chronic Respiratory Questionnaire)
	Almost one-third of patients discontinued treatment because of adverse effects
Paroxetine 20 mg/day vs. placebo for 6 weeks, followed by open-label paroxetine for 3 months ($n = 28$) [18]	Placebo-controlled phase: no significant difference between placebo and paroxetine in depression and general quality of life scores, lung function and walking distance
	Open-label phase: significant improvements from baseline in depression and respiratory quality of life scores, and walking distance with paroxetine
Tricyclic antidepressants	
Desipramine 25 mg/day increased weekly to 100 mg/day for 8 weeks [crossover design] ($n = 13$) [13]	Depression scores improved to a similar extent with desipramine and placebo
	No difference between treatments in physiological COPD parameters
	Only 6 patients completed the trial
Doxepin 25 mg/day increased as tolerated to maximum 105 mg/day for 6 weeks [crossover design] ($n = 12$) [14]	No significant improvements in depression or anxiety scores, exercise capacity and physiological COPD parameters with either treatment
	Three pts withdrew because of adverse effects
Nortriptyline 0.25 mg/kg increased weekly to 1 mg/kg for 12 weeks ($n = 30$) [12]	Nortriptyline improved depression relative to placebo, with improvements in anxiety, some respiratory symptoms and daily activities scores
	Physiological measures were generally unaffected
Protriptyline 10 mg/day for 12 weeks ($n = 26$) [15]	No improvements in quality-of-life scores or physiological COPD parameters with either protriptyline or placebo
	Only 5 patients completed the study; 12 protriptyline and 6 placebo recipients discontinued because of adverse effects, commonly anticholinergic in nature

Table 2 Common adverse effects experienced with antidepressants in patients with chronic obstructive pulmonary disease, as reviewed by Yohannes and Alexopoulos [3]

Intolerable drowsiness, somnolence, sedation
Blurred vision, dizziness, orthostatic hypotension
Dry mouth, increased sweating, tremor
Fatigue, headache, nausea and vomiting, constipation
Confusion or agitation, worsening anxiety, insomnia, sexual dysfunction
Hyponatraemia
Suicide ideation

can be improved by appropriate follow-up and monitoring and, when required, the modification of pharmacological therapy.

Follow general guidelines for depressant use in older patients

In the absence of specific guidelines for the treatment of depression in patients with COPD, general guidelines for the prescribing antidepressants to older patients with medical illness should be followed [19]. Treatment should start with a low dosage of an appropriate antidepressant, with the dosage being gradually increased based on the efficacy and tolerability of the drug in the individual. Patients should be informed of potential adverse effects and methods of managing such events. The effectiveness of antidepressant therapy should be monitored on a regular basis, with changes to the regimen and/or referral to psychiatrists and care managers being made as required [19].

Treatment adherence can be poor

Depressed patients with COPD may be disinclined to accept antidepressant treatment and can have poor adherence to therapy. Barriers to both pharmacological and physical rehabilitation therapy can include [3]:

- misconceptions about depression and stigmatization concerns;
- lack of adequate knowledge of depression;
- lack of adequate support;
- adverse effects of treatment (inducing fear and/or treatment withdrawal);
- inadequate physician's explanation of necessity for treatment and its efficacy;
- limited physician knowledge of mood disorders and counselling skills;
- behavioural inertia resulting from depression and associated cognitive problems;
- inability to actively participate in complex treatment and rehabilitation;
- lack of motivation and energy required to adhere to exercise and other activities;
- intellectual function impairment interfering with planning, initiating and sequencing behaviour.

The adherence of the patient to their antidepressant treatment should be evaluated before switching to another antidepressant or discontinuing antidepressant therapy altogether; personalized interventions to target treatment adherence should be considered [19].

Concerns about treatment adherence has led to the development of the Personalized Intervention for Depression and COPD (PID-C), a behavioural management intervention administered by care managers, who work closely with patients to identify treatment barriers, help them work on their rehabilitation programme and encourage treatment adherence [20]. In a randomized trial in 138 patients with major depression and severe COPD, PID-C was more beneficial than usual treatment, leading to a higher remission rate and a greater reduction in depressive symptoms and in dyspnoea-related disability over 28 weeks [20]. Benefit continued over the 6 months following the cessation of the intervention.

Behavioural strategies may be beneficial

Antidepressant treatment alone may not improve depressive symptoms in some patients with COPD [3]. Improvement in depression outcomes and physical disability has been seen with the implementation of collaborative care interventions, psychological therapy and pulmonary rehabilitation through physical conditioning and behavioural activation [3].

Group cognitive behavioural therapy (CBT) sessions may be challenging to attend for some patients with COPD; however, encouraging results have been published from two randomized controlled trials of group CBT to treat depression in patients with COPD [21, 22]. Symptoms of depression and anxiety improved in patients from both trials over the 7 and 8 week study durations, with benefit maintained over $\geq$8 months of follow-up.

Disclosure This article was adapted from *Drugs and Aging* 2014;31(7):483–92 [3] by salaried/contracted employees of Adis/Springer, and was not supported by any external funding.

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