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REVIEW ARTICLE

Benefit–Risk Assessment of Psychotropic Drugs in Older Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Depression, anxiety, and other mental health disorders, including bipolar disorder and schizophrenia, occur commonly in older adults with chronic obstructive pulmonary disease (COPD), and they are often inadequately treated. We review the available evidence for benefits and risks of pharmacologic treatments (e.g. selective serotonin reuptake inhibitors [SSRIs], serotonin-noradrenaline reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], antipsychotic drugs, and benzodiazepines) for common mental illnesses in older persons with COPD. Evidence to use both SSRIs/SNRIs and TCAs from randomized controlled trials is uncertain for treating major depression in patients with COPD. However, population-based findings indicate that they are widely used, and this valuable intervention (preferably SSRIs/SNRIs) should not be denied for selected patients after evaluating potential risks and benefits, especially patients presenting with major depression and suicidal ideation, when a collaborative-care approach is being used. Although there is some evidence for the short-term use of benzodiazepines for treating insomnia, breathlessness, and anxiety in patients with COPD, their long-term use should be closely monitored or avoided to reduce the increased rate of major adverse events. Currently, there are only limited data on the use of antipsychotic drugs for managing schizophrenia or bipolar disorder in older patients with COPD. Hence, clinicians should use extra caution when prescribing antipsychotic agents and be vigilant for symptoms of acute respiratory failure and other adverse effects. Psychotropic medications are clearly beneficial for younger, healthy persons with depression and anxiety; however, the risk–benefit calculation is not so clear for treating psychological problems, schizophrenia, and bipolar disorder in older adults with COPD, given older-adult sensitivity to medications and the mixed findings of relatively few controlled trials.

Key Points

When prescribing antidepressants, counsel older patients with chronic obstructive pulmonary disease (COPD) about potential adverse effects and their management plan. After prescribing antidepressants to COPD patients, make contact, at least monthly, to monitor for changes in depression and anxiety symptoms.

Robust and well-controlled prospective randomized controlled trials are needed to show the efficacy of antipsychotics and antidepressants in older patients with COPD, with longer-term follow-up.

There is unclear long-term benefit for the use of benzodiazepines for anxiety and dyspnea in older patients with COPD. In older patients with COPD, respiratory and neurocognitive adverse effects have been demonstrated with benzodiazepine use.

Employing a psychiatric collaborative-care approach for treating depression, anxiety, schizophrenia, and bipolar disorder in patients with COPD is a worthy endeavor.

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and impaired quality of life in old age [1]. Comorbid depression is common in patients with COPD. Untreated depression is associated with reduced social interaction and work-related activities, elevated symptoms of social isolation and guilt, and increased healthcare utilization [1, 2]. Untreated depression and anxiety are associated with 30- and 90-day hospital readmission in patients with COPD [3, 4]. The increased rate of healthcare utilization is likely related to poor compliance with COPD medical treatment and/or self-management (e.g., poor inhaler techniques or lack of regular exercise or inability to cope with the impact of the disease due to the severity of depression), and, in turn, results in acute exacerbations and disease progression. Uncontrolled dyspnea and inability to cope at home due to fear of death and anxiety may exacerbate emergency care and rehospitalization [5, 6].

The causes of mental disorders in older adults with chronic diseases are multifactorial. Studies report tobacco smoking, low socioeconomic status, behavioral and affective symptoms, genetic factors, cognitive impairment, and neurotransmitter imbalance (depletion) as potential risk factors for developing mental illness [7–9]. A recent systematic review [8] highlighted tobacco smoking as one of the main factors associated with mental illness, with both accounting for over 200,000 premature deaths in the US per annum. Cigarette smoking is the major cause of COPD but current smoking or a previous history of smoking status is also related to increased depressive and anxiety disorders [2, 10]. Population-based studies repeatedly underscore that the prevalence rate of cigarette smoking is increased three- to fivefold in patients with psychiatric disorders, such as schizophrenia, bipolar disorder, posttraumatic stress disorder and alcohol/illicit drug use disorders, compared with the general population without these disorders [11, 12].

Older adults with COPD have multiple comorbidities that require polypharmacy, which increases unpredictable drug interactions and major risk of adverse events [13]. In this context, our review provides a state-of-the art summary of current findings in the treatment of psychiatric disorders and interactable dyspnea in patients with COPD, using antidepressant drug therapy, antipsychotic agents, and benzodiazepines. It also highlights the challenges, provides tips for clinical guidance in managing adverse events, and suggests potential future directions for research.

2 Methods: Searching the Literature

We conducted three separate searches to extract relevant articles for this review, and critically appraised the published studies. First, we explored commonly used antidepressant drug therapy for depression in patients with COPD using the keywords *depression*, *COPD*, *SSRIs* and tricyclic antidepressants (*TCAs*) AND *adverse events*. Next, we searched for antipsychotic medications primarily used for those with serious mental illnesses, including bipolar disorder and schizophrenia, using the keywords, *COPD*, *typical antipsychotics*, *atypical antipsychotics*, *bipolar disorder* and *schizophrenia* AND *adverse events*. Third, we searched for articles about benzodiazepine use in the treatment of COPD using the keywords *COPD*, *benzodiazepines*, *insomnia*, *intolerable dyspnea* AND *adverse events*. We searched the PubMed, Scopus and PsychInfo databases from inception to July 2021 and limited our search of the literature to articles published in the English language. In addition, we scrutinized the references of extracted articles to identify other potentially relevant articles. For this review, we included articles that were published as observational, randomized controlled trials (RCTs) and population-based studies; however, we excluded articles published as conference abstracts. The definitive reference list was compiled on the basis of article originality and relevance to the wide-ranging scope of this review in the management of older COPD patients with mental health problems.

3 Depression in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Depression is common in patients with COPD. Major depression is characterized by five or more symptoms continuously present in the past 2 weeks (e.g., anhedonia, lack of interest in pleasurable activities, difficulties with concentration, sleep disturbances, changes in appetite, excessive fatigue, and suicidal ideation) [14].

A recent systematic review of long-term follow-up studies of patients with COPD [15] with comorbid depression established that a bidirectional association occurs: COPD incessantly heightens the risk of depression, and, equally, depression augments the risk of untimely (premature) death in patients with COPD, implying that depression exacerbates the course or trajectory of COPD [16].

The overall prevalence of depression (defined as clinically relevant and warranting medical intervention) in adult patients with COPD is about 40% [10]. This prevalence rate varies, depending on the severity of respiratory impairment, the location of the data collection (e.g., inpatient or outpatient setting), and the type of depression outcome measures used in the study (e.g., screening or clinical diagnostic tools) [2, 10].

Clinical guidelines for managing depression in older adults with physical illnesses, including COPD, advocate the benefits of selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and

TCAs in treating major depression [17]. However, the general consensus is that SSRIs/SNRIs are more favorable as first-line treatment for depression, owing to a relatively better safety record and fewer adverse effects than TCAs [17].

The therapeutic mechanism of action of SSRIs has its foundation in increasing scarcity (deficiency) of serotonin, widely studied as one of the possible risk factors for psychiatric illness, including depression. The SSRIs and multiple-receptor antidepressants venlafaxine, bupropion and mirtazapine, for example, were rationally designed to "target one or more specific brain receptor sites without, in most cases, activating unwanted sites such as histamine and acetylcholine" [18].

In brief, the serotonin transporter gene (SERT) protein is contained on the presynaptic membrane of serotonergic neurons, where it controls the intensity and duration of serotonergic signaling through reuptake of the neurotransmitter into the synapse [18, 19]. SSRIs inhibit the SERT at the presynaptic axon terminal. By inhibiting SERT, an augmented quantity of serotonin (5-hydroxytryptamine [5-HT]) remains in the synaptic cleft and can stimulate postsynaptic receptors for a more prolonged period [18, 19].

In a similar vein, TCAs interact with a number of other receptor sites, including histamine, acetylcholine and epinephrine, to achieve their effects. They block the reuptake of serotonin and norepinephrine in presynaptic terminals, which leads to increased concentration of these neurotransmitters in the synaptic cleft. They have substantial adverse effects, including dry mouth, constipation, and atropine-like effects, e.g., orthostatic hypotension, which may increase the risk of falls [18, 19].

Monoamine oxidase inhibitors inhibit the enzyme monoamine oxidase, responsible for the breakdown of synaptic norepinephrine, serotonin, and dopamine neurotransmitters. This medication class has the worst known adverse effect profile among antidepressants, including the possibility of weight gain, sexual dysfunction, and dangerous hypertensive episodes with consumption of tyramine-containing foods. However, a recent systematic review and meta-analysis largely supports the re-evaluation of the use of monoamine oxidase inhibitors as antidepressant agents in the treatment algorithm of depression [20].

3.1 Antidepressant Use for Major Depression in Patients with COPD

There is evidence to suggest that antidepressants can also be used to treat both depression and anxiety (also see Sect. 3.3) in patients with COPD. Antidepressants are beneficial to relieve symptoms of suicidal thoughts and moderate-to-severe depression and often help to improve lack of interest in pleasurable activities and excessive exhaustion, which can lead to a resumption of normal daily activities.

3.1.1 Population-Based Studies of the Use of Antidepressants

A recent large prescription data-based study from The Netherlands reported that COPD patients are five times more likely to have a higher prescription of antidepressant drug or anxiolytic therapy than in matched control groups with or without chronic diseases in a 6-year retrospective study [21]. In addition, the findings highlight that depression and anxiety are more common in patients with COPD than in patients with other chronic diseases (e.g., cardiovascular disease and rheumatoid arthritis). In the same vein, a retrospective population-based cohort study of older people with COPD aged $\geq$ 66 years explored the efficacy of SSRIs or SNRIs in treating major depression [22]. They compared the use of SSRIs or SNRIs among 118,611 community-dwelling individuals and 13,107 long-term care home residents with COPD. The findings indicate that new users of SSRIs, compared with non-users, experienced a higher risk of hospitalization, emergency care visits and COPD- or pneumonia-related mortality and all-cause mortality [22]. Furthermore, respiratory-related mortality was significantly higher among long-term care home residents newly starting SSRI/SNRI drugs than among controls.

In contrast, a recent longitudinal study that examined the efficacy of maintenance therapy of antidepressants following remission of major depression in patients with COPD used hospital-based administrative data (n = 25,458). Regular use of antidepressants was associated with a 15% increase in the rate of adherence to inhaler use compared with non-use of antidepressants [23]. However, caution is required in interpreting these findings, as the sample was predominantly women and Caucasian. Its generalizability to the wider population is questionable. Furthermore, the administrative nature of the data and lack of a formal diagnosis of depression make it difficult to interpret for clinical practice.

3.1.2 Observational Studies and Randomized Controlled Trials (RCTs) Examining the Use of Antidepressants

No recent RCTs have examined the efficacy of SSRIs/SNRIs or TCAs in treating depression in patients with COPD; however, two systematic reviews [24, 25] highlighted the following. First, the efficacy of antidepressant therapy, both the SSRIs/SNRIs or TCAs, was uncertain due to small sample sizes, adverse effects, and high dropout from both observational studies and/or RCTs. Second, there is no clear evidence in terms of antidepressants improving remission of depression or change in severity of dyspnea in patients with

COPD. Third, the observational studies and RCTs that have been conducted had significant methodological weaknesses, including heterogeneity and inconsistency of the screening and diagnostic tools employed in the treatment and monitoring of depression in patients with COPD. Fourth, two trials have shown that SSRIs were beneficial in improving exercise tolerance compared with placebo [25], although these two studies had very low-quality evidence, e.g., the sample sizes were relatively small. Fifth, there is insufficient evidence to make definitive statements about the efficacy or safety of antidepressants for COPD-related comorbid depression. Finally, both systematic reviews have recommended robust prospective RCTs with better methodological qualities and larger sample sizes with long-term follow-up, including outcomes such as adverse events, hospital utilization, and cost effectiveness [24, 25].

3.1.3 Adverse Events with Antidepressants

The two recent systematic reviews [24, 25] highlighted the following antidepressant treatment- related adverse events in patients with COPD. First, SSRIs and SNRIs were associated with sexual dysfunction, drowsiness, insomnia, dizziness, nausea, tremors, and constipation. Second, TCAs were associated with constipation, dry mouth, urinary retention, sedation, weight gain, and confusion. Furthermore, these adverse events were accompanied by the disease-related worsened respiratory symptoms of dyspnea, acute exacerbations and pulmonary hypertension, and poorer quality of life [24, 25].

3.1.4 The Risk–Benefit Ratio of Antidepressants for Patients with COPD

The evidence to date from a few small sample-size RCTs examining the efficacy of antidepressants (SSRIs/SNRIs, TCAs) was inconclusive in terms of ameliorating depression in patients with COPD [24, 25]. However, administrative and retrospective drug prescription database studies and population-based studies indicate that antidepressants have been widely used in routine clinical practice for treating depression in patients with COPD [21, 22]. A retrospective study by Pelgrim et al. [21] found that the rate of 'chronic use' of antidepressants and anxiolytics is relatively high in COPD patients compared with patients with other chronic diseases. Hence, chronic use of antidepressants indicates the chronic nature of elevated depression and anxiety in patients with COPD. The use of SSRIs/SNRIs was associated with an increased rate of hospitalization, respiratory-related morbidity, and premature death in older people with COPD compared with non-users [22]. Thus, clear evidence is required from prospective RCTs before making judicious recommendations regarding antidepressant drug therapy. Furthermore, these studies do not provide adequate explanation about the efficacy of these antidepressant drugs, neither using well-validated scales to quantify the severity of depression nor specifying the type of antidepressants used and their effectiveness in terms of quality of life during the follow-up period. The jury is still out to determine the future management of depression in this patient group. However, in the meantime, population-based studies indicate they are widely used and individual COPD patients should not be denied this valuable intervention (antidepressant drug therapy, preferably SSRIs/SNRIs) in selective patients, especially those presenting with major depression and suicidal ideation, using a collaborative-care approach [26]. Furthermore, after prescription of antidepressant drug therapy for patients with COPD, patients should be reviewed regularly for the first few months to monitor the efficacy of treatment, as well as the potential drug adverse effects, and when they occur, to ensure they are treated promptly. Thereafter, it is important to evaluate the patients periodically to titrate their medications when appropriate to a low level of therapeutic doses, depending on the patient's symptoms.

3.2 Antipsychotic Drug Use in Patients with COPD

Antipsychotic medications are primarily indicated for those with serious mental illnesses, including bipolar disorder and schizophrenia. They can also be used alone or as an augmentation to antidepressants in COPD patients with treatment-resistant depression. Although the combined prevalence of bipolar disorder and schizophrenia is 3%, the prevalence of smoking is higher in these individuals than in the general population—as high as 62% in schizophrenia and 37% in bipolar disorder [8, 27]. Those with serious mental illness also smoke more cigarettes than those with other mental illnesses and those without mental illness [27]. Tragically, smoking rates are even higher in those with serious mental illness who live below the poverty line [28]. The potential risk factors to develop comorbid schizophrenia in COPD might be related to the persistence of cigarette smoking, poor living conditions, increased physical disability, and impaired quality of life [27, 28]. In a recent systematic review and meta-analysis of eight studies, the pooled analysis showed a greater likelihood of suffering from comorbid COPD than the general population, both for persons with schizophrenia (odds ratio [OR] 1.573, 95% confidence interval [CI] 1.439–1.720) and bipolar individuals (OR 1.551, 95% CI 1.452–1.658) [29]. This suggests that COPD is more common in individuals with major mental illness than in the general population.

In a large population-based study of persons aged 18 years and older ($n = 766,427$), the prevalence of COPD in patients with bipolar disorder was higher than in the general population (5.68% vs. 2.68%; OR 2.03, 95% CI 1.65–2.29)

[30]. Two Taiwanese studies [30, 31] further reported that the presence of comorbid bipolar disorder in COPD patients was associated with lower socioeconomic status, longer hospitalizations, more outpatient visits, older age, and male sex, with elevated symptoms of comorbid hypertension and use of second-generation antidepressants (e.g., SSRIs and SNRIs).

3.2.1 Types of Antipsychotic Drugs

A number of antipsychotic drugs have been approved by the US FDA and are available for treating bipolar disorder and schizophrenia. The antipsychotic drugs are beneficial in treating hallucinations and delusions, reducing the risk of suicide in patients with schizophrenia and bipolar disorder.

Broadly, the antipsychotic drugs are classified into two categories: (1) typical antipsychotics and (2) atypical antipsychotics. The distinction between typical and atypical is based on their adeptness to instigate extrapyramidal adverse effects, including tardive dyskinesia, not their relative efficacy for psychopathology, cognition, or effects on prolactin secretion [32].

Typical antipsychotics (first-generation antipsychotics) include chlorpromazine, fluphenazine, molindone, thiothixene trifluoperazine, and haloperidol, and are often associated with a higher incidence of extrapyramidal adverse effects, such as akathisia, acute dystonias, parkinsonism, and tardive dyskinesia [32, 33].

Atypical antipsychotics (second-generation antipsychotics) as the choice of first-line treatment of schizophrenia include clozapine, aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone. These are defined by a low extrapyramidal adverse effect liability, including weight gain, diabetes mellitus, hyperlipidemia, myocarditis, tardive dyskinesia, and sexual defects [34]. Clozapine has been shown to reduce the risk of suicide in patients with schizophrenia [32, 33].

Briefly, the two classes of antipsychotic drugs differ in their mechanism of action. The typical antipsychotics work by inhibiting dopaminergic neurotransmission. In addition, they have noradrenergic, cholinergic, and histaminergic blocking action. Similarly, the atypical antipsychotic drugs using serotonergic mechanisms act exclusively as blockers of dopamine-2 (D2) receptors [32, 33]. The reader is referred to two recent reviews for other mechanisms of action and more detailed explanation about antipsychotic drugs that include noradrenergic mechanisms and histaminergic mechanisms [32, 33].

3.2.2 Population-Based Studies and Antipsychotics in COPD Patients

In their population-based study, Wang et al. [35] found that antipsychotic agents were associated with an approximately twofold dose-dependent increased risk of acute respiratory failure in patients with COPD. A Danish nationwide population-based study ($n = 72,692$) by Jorgensen and co-workers showed that COPD patients with schizophrenia were at higher risk of 30-day mortality and less likely to receive optimal medical treatment, such as long-acting muscarinic antagonists or long-acting β2-agonists [36]. In addition, the authors highlighted a significantly amplified risk of mortality of COPD patients with schizophrenia following hospital admission for an acute exacerbation compared with patients without schizophrenia. Furthermore, in a large retrospective study ($n = 923$) in older COPD patients with a mean age of 75 years, antipsychotic therapy was associated with a higher risk of bloodstream infections (e.g., presence of viable bacterial or fungal microorganisms) during the first year of follow-up [37].

3.2.3 The Risk–Benefit Ratio of Antipsychotic Drugs for Patients with COPD

To date, no or very little data exist from published studies that employed randomized controlled designs to examine the efficacy of antipsychotic drugs in treating either schizophrenia or bipolar disorder in patients with COPD; we relied on published observational, retrospective, and population-based studies. Thus, there are insufficient data to support the potential benefits of antipsychotic drugs in managing schizophrenia or bipolar disorder in patients with COPD. Hence, clinicians should use extra caution when prescribing antipsychotic agents and be vigilant for symptoms of acute respiratory failure and other symptoms. It is advisable, where appropriate, to employ a psychiatric collaborative-care approach, e.g., a case manager (care liaison) to monitor the patient's condition, encourage individuals to comply with the treatment plan, and, when adverse effects occur, to treat promptly [26]. Healthcare professionals should weigh the risks and benefits when prescribing antipsychotic agents and, where appropriate, start with the lowest doses and 'go slow' for patients with COPD [24]. Prospective RCTs are needed to ascertain the efficacy of antipsychotic drugs for this patient group.

3.3 Anxiety Disorders and COPD

Anxiety disorder is an umbrella term for a variety of abnormal and pathological fear states, including generalized anxiety disorder, phobia disorders, panic disorders, and posttraumatic stress disorder [38, 39]. These disorders are characterized by various clinical symptoms, such as persistent worry, situational avoidance, and even physical manifestations of dyspnea. Since anxiety may manifest in both psychiatric and somatic disorders, proper diagnosis includes

a comprehensive differential evaluation and clear establishment of a symptom timeline [33]. Anxiety disorders are clinically diagnosed using established *Diagnostic and Statistical Manual, 5th Edition* (DSM-V) diagnostic criteria [14] or International Classification of Diseases (ICD) criteria [40]. However, instruments are expensive and time-consuming to administer in routine clinical practice; thus, screening tools such as the Hospital Anxiety Depression scale [41] and disease-specific tools such as the Anxiety Inventory for Respiratory Disease [42] have been used to measure anxiety in patients with COPD.

Comorbid generalized anxiety disorder is common in patients with COPD. The prevalence of anxiety in COPD patients is estimated to range from 6 to 74% [1, 2]. The exact mechanism of anxiety in COPD remains unclear and appears to be multifactorial, including various behavioral (e.g., lack of physical activity, insomnia, and active smoking), social, and biological factors [24]. Furthermore, the presence of elevated anxiety symptoms in COPD has been reported to be related to a history of tobacco smoking and lifetime nicotine dependence [43]. In a population-based study, factors associated with generalized anxiety disorder in patients with COPD ($n = 746$) were not having a confidant, exposure to parental domestic violence, and lifetime depressive disorders [44].

General pharmacological options for anxiety disorders include various medications aimed at stabilization and alleviation of these symptoms [45]. The summary below provides potential benefits and adverse effects.

- *Reuptake Inhibitors* SSRIs and SNRIs aim to increase levels of serotonin (5-HT) in the synapse. These medications aim to potentially restore the neurochemical imbalance caused by anxiety. Adverse effects may include nausea, diarrhea, insomnia, sexual dysfunction, and serotonin syndrome.
- *TCAs* TCAs also modulate reuptake receptors to increase the availability of synaptic serotonin. However, their action on α-cholinergic, muscarinic, and histaminic receptors generates a less favorable adverse effect profile, including arrhythmias, urinary retention, and postural hypotension.
- *Benzodiazepines* Benzodiazepines inhibit activity at the γ-aminobutyric acid A receptor. Short-term benzodiazepines are commonly used for managing acute episodes of anxiety; however, chronic use is associated with dependence, cognitive impairment, rebound anxiety, and potential for respiratory depression.
- *Azapirones* Azapirones act as agonists to the 5-HT_{1A} receptor to modulate the firing rate of serotonin neurons. Buspirone is a common choice for the treatment of anxiety because of its milder adverse effects and lower risks of withdrawal symptoms. It is commonly used in patients with a history of alcoholism or drug-dependency disorders.
- *Pregabalin* Pregabalin is an effective treatment for generalized anxiety disorder (GAD). It has been approved in Europe by the European Medicines Agency for treating generalized anxiety disorder, but not by the US FDA [46]. Current evidence suggests pregabalin is a well-tolerated and useful treatment in patients with generalized anxiety disorder, either alone or in combination with second line antidepressants such as SSRIs. Pregabalin has been associated with risk of misuse and dependence in patients with a history of opiate or substance abuse [46].

In COPD patients with comorbid anxiety, there is high use of anti-anxiety medications in patients over 75 years of age compared with younger COPD patients. Furthermore, in a 6-year retrospective study, the risk for use of two or more anxiolytic prescription medications was associated with older age group [21]. Although commonly not the primary concern in older patients with multiple comorbidities, anxiety should be properly managed to prevent chronic disease progression, predisposition to suicidal ideation, and hospitalization [2, 47]. Specifically, in COPD patients, proper anxiety management is critical to avoid increased risk of morbidity and to reduce emergency healthcare utilization [2].

3.4 Efficacy of Benzodiazepines in Elderly Patients with COPD

No recent RCTs have examined the efficacy of benzodiazepines in older patients with COPD, but the few RCTs that did examine the efficacy of benzodiazepines in patients with COPD with symptoms of intolerable dyspnea and insomnia are over a decade old and were relatively small in sample size.

Stege et al. [48] focused on the respiratory efficacy of benzodiazepines in a double-blind crossover trial studying the effects of temazepam ($n = 14$) on gas exchange in patients with severe normocapnic COPD, including dyspnea, sleep quality, and insomnia. They found that 1 week use of temazepam 10 mg did not influence circadian respiratory function or reduce sensation of dyspnea or sleepiness [48]. However, low medication dosage and small sample size were cited as potential limitations to the trial. In addition, a recent Cochrane systematic review [49] examined the benefits of benzodiazepine in ameliorating dyspnea in malignant and non-malignant diseases in older adults. The review included older trials examining the efficacies of diazepam [50], alprazolam [51, 52], and dyspnea-like symptoms in elderly patients with COPD. Benzodiazepines were not beneficial for the relief of breathlessness sensation [49], irrelevant of dosage, modality, administration frequency, or

treatment duration in the relief of breathlessness, suggesting a lack of evidence to support benzodiazepine use in preventing episodic dyspnea. However, the review highlighted unclear bias risk assessment and possible unit-of-analysis error as study limitations. Furthermore, benzodiazepines may be considered as a second- or third-line of treatment for the short-term, when opioids and non-pharmacological measures failed to control breathlessness [49].

Insomnia is also a common condition in elderly persons, including COPD patients, that may lead to neurocognitive effects if uncontrolled [53]. Lu et al. [54] conducted a meta-analysis of 81 patients from five studies examining the efficacy of five types of benzodiazepines (flurazepam, triazolam, nitrazepam, temazepam, flunitrazepam) in insomnia patients with COPD. The findings indicate benzodiazepines improved partial sleep quality, total sleep time, and sleep latency and efficiency time compared with placebo. However, caution is required in interpretation of the data, as the studies vary in terms of dosage and duration of the intervention (e.g., 2 nights to a 2-week period), and quality assessment data were generally low quality or unclear and accompanied by adverse events. We concur with Lu et al. that when making decisions about benzodiazepine use to improve sleep in patients with COPD, one should carefully consider the severity of disease, type of benzodiazepine, dose, route, frequency of delivery, duration of treatment, and psychodynamic aspects of use [54]. They should be used only after consideration and/or trial of cognitive behavioral therapy for insomnia.

3.4.1 Adverse Events of Benzodiazepines in Patients with COPD

Patients taking benzodiazepines have been shown to depress central respiratory drive and chemoreceptor response to hypercapnia, leading to potentially harmful effects when paired with underlying lung pathology [55]. Similarly, elderly patients with COPD have been shown to have increased risk for respiratory failure, serious adverse respiratory outcomes, and hospitalization for pneumonia or COPD [56–58]. Use of two or more types of benzodiazepines or a combination of benzodiazepines and non-benzodiazepines was associated with a twofold increased risk for respiratory failure [56]. Liao et al. [59] also showed that these combinations were associated with increased admissions for acute COPD exacerbation. Furthermore, benzodiazepine use in combination with opioids was also associated with increased respiratory events, with greater effects in higher-complexity COPD patients [60].

Benzodiazepines cause neurocognitive impairment through interaction with the γ-aminobutyric acid type A receptor [61]. Although they have demonstrated a broad effect profile in elderly patients, there are few studies investigating cognitive effects in elderly patients with COPD. Two studies showed brain impairment and reduced motor command with the use of benzodiazepines and other psychotropic medications [62, 63]. Drowsiness was also a reported adverse effect with benzodiazepine use in this population [49, 50].

3.4.2 Risk–Benefit Ratio for Elderly Patients with COPD

Based on evidence from several observational studies and a few older RCTs, it appears that the benzodiazepines demonstrate unclear benefit and a higher risk profile than clinical alternatives for elderly patients with COPD. Despite concerns regarding benzodiazepine respiratory-related depression in elderly COPD patients, they are widely used [56, 57]. Furthermore, benzodiazepine treatment for < 90 days was associated with increased risk of hospitalization and mortality [64]. In contrast, benzodiazepine treatment for more than 90 days remained unaffected but patients were at increased risk of death by suicide [64]. Interestingly, low-dose benzodiazepines did not increase the risk of hospital admissions or mortality [65]. A recent systematic review suggested that for some types of anxiety and insomnia in patients with COPD, benzodiazepines may have symptomatic benefits in the short-term [66]; however, these benefits need to be weighed carefully against the increased risk rates of COPD exacerbations, respiratory tract infections, and mortality [66]. Conversely, growing evidence suggests that non-pharmacological therapy such as pulmonary rehabilitation, cognitive behavioral therapy, relaxation therapy, exercise therapy, and physical activity [67, 68] are beneficial for the treatment of anxiety, depression. and dyspnea in patients with COPD [68].

4 Limitations of this Review

The majority of the studies were relatively small in sample size and were uncontrolled, thus prospective well-controlled RCTs with a large sample size are required to demonstrate the efficacy of these drugs in patients with COPD.

There is limited published literature examining sex differences in the presence of comorbid psychiatric disorders in patients with COPD. In one relatively small sample-size observational study ($n = 16$ COPD patients), it was reported that women are most likely to exhibit a higher prevalence rate of anxiety and twice as likely to exhibit major depression as men [69]. Furthermore, women are most likely to report worse perceived control of symptoms and greater functional impairment in their daily activities than men. To date, no studies have examined sex differences in terms of the efficacy of antidepressant drugs, benzodiazepines, and antipsychotic medications in RCTs to warrant a sex-specific treatment in patients with COPD.

5 Conclusion

The adverse events that were highlighted were intended as a guide to assist clinicians and make them aware when prescribing antidepressants, antipsychotics, and benzodiazepines to patients with COPD. A well-controlled observational trial showed that less than one-third of COPD patients are likely to receive appropriate treatment for comorbid anxiety and depressive symptoms [9]. The reasons behind patients' reluctance to receive antidepressant drug therapy include fear of stigma and social isolation by family members and caregivers [24, 25]. It is therefore important to devise appropriate treatment strategies to overcome patient-related barriers by using a collaborative care model and offering a choice of treatment to patients as to whether to receive drug therapy or psychological-based therapy such as cognitive behavioral therapy [26, 70]. Future research also needs to consider the pathophysiological mechanisms behind the onset of depression in patients with COPD to enhance current treatment strategies to improve the well-being of this vulnerable patient group.

Evidence from the limited published literature suggests that benzodiazepines should be avoided or closely monitored periodically for long-term use when treating older patients with COPD (with sleeping disorders or persistent dyspnea) because of their toxic adverse effects. If benzodiazepine use is unavoidable, low-dose use may be more beneficial to avoid adverse events.

Healthcare professionals should be vigilant about the presence of comorbid mental health disorders in patients with COPD as these disorders may interfere with the patient's ability to comply with pharmacotherapy (e.g., psychotropic medications) and discontinuation (early droppout) of pulmonary rehbilitation program and impairing quality of life [71] and increasing healthcare utilization and premature mortality. Thus, identifying these problems using screening tools and developing effective interventions that incorporate a collaborative care approach are a worthy endeavor.

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Declarations

Author contributions AMY contributed to the conceptualization of the review objectives and the development of an outline, completed the literature, and wrote the first draft. JWJ contributed to the conceptualization of the review objectives and the development of an outline, completed the literature, and wrote part of the first draft. MEK contributed to the conceptualization of the review objectives and the development of an outline and edited the first draft before submission. AMY, JWJ and MEK reviewed and edited the whole manuscript and approved the final submission.

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Code availability Not applicable.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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