NHS
South London and Maudsley
NHS Foundation Trust

Use of psychotropics in chronic obstructive pulmonary disorder

Contents

1 Introduction

1.1 Treatment of COPD

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterised by persistent respiratory symptoms. These include breathlessness, chronic cough or sputum production, and frequent chest infections. Airflow limitation is progressive and not fully reversible. The aim of treatment is to reduce symptom burden, minimise the risk and severity of exacerbations, and reduce mortality. It must always include smoking cessation support. Drug treatment should include short-acting beta-2 agonists (SABAs – salbutamol, terbutaline) or short-acting muscarinic antagonists (SAMAs - ipratropium), long-acting beta-2 agonists (LABAs – salmeterol, formoterol) and/or long-acting muscarinic antagonists (LAMAs - tiotropium). Particular patients may require inhaled corticosteroids (ICS – beclomethasone, budesonide, fluticasone furoate), methylxanthines (theophylline), mucolytics, prophylactic antibiotics (azithromycin), oral phosphodiesterase-4 inhibitors (roflumilast) or oral corticosteriods[1].

1.2 Mental illness in COPD

Depression and anxiety are common comorbidities in patients with COPD. Reported prevalence varies widely (depression, 8 - 80%; anxiety, 6 – 74%[2]) and there is a link to severity of illness – patients with severe COPD are twice as likely to develop depression compared to patients with mild illness, and depression and anxiety worsen COPD outcomes (including hospitalisation rates[3] and mortality[4]). Patients with depression and COPD who take antidepressants are more likely to adhere to their COPD treatment[5,6]. There are few high-quality trials examining the efficacy and safety of pharmacological treatments for depression or anxiety in patients with COPD[7,8], so medication choice is instead informed largely by data derived from the non-COPD population. It is worth noting that some symptoms of COPD are similar to those in anxiety and depression – notably fatigue, altered sleep and weight loss – and this may make decisions about treatment effectiveness more difficult.

Patients with schizophrenia or bipolar disorder are more likely than their counterparts in the general population to suffer with COPD (odds ratios from meta-analyses of 1.573 and 1.551 respectively[9]), and proportions of undiagnosed illness may be high (1 in 4 smokers with serious mental illness (SMI) had undiagnosed COPD in one study[10]). The reason for this association is unlikely to be limited to the higher rates of smoking amongst patients with schizophrenia or bipolar disorder[11]; rather, poor self-care, social deprivation, and the prevalence of other physical comorbidities in people with SMI are considered important[9]. Unfortunately, there is also evidence to suggest inequalities in the quality of care after diagnosis, and for increased mortality following acute exacerbations of COPD for patients with schizophrenia compared to those without[12].

The concerns with treating mental illness in a person with COPD are primarily based on overlapping drug side-effect profiles (e.g. anticholinergic effects, respiratory depression or propensity to cause arrythmias), or direct pharmacokinetic interactions. Most of these are theoretical and there are few absolute contraindications. If psychotropic treatment is warranted but options limited by the current airways prescription, each respiratory therapy should be reviewed by the patient's lung clinician to ensure its on-going need and for consideration of alternatives that may pose less risk.

2 Antidepressants in COPD

As noted above, it is not clear whether antidepressant treatment for patients with depression and COPD is effective – data specifically relating to the COPD population are scarce and fraught with the confounders common to chronic medical illness. Even fewer data are available to compare drugs, or even just drug classes to each other. Small studies and case reports describe the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in patients with depression and COPD[13,14]. TCAs are not usually considered first line treatment for depression in the non-COPD population, and for those with COPD, the potential for additive anticholinergic effects from muscarinic antagonist bronchodilators such as tiotropium and ipratropium will diminish their appeal further (although in practical terms, this is probably only theoretical, see section 5). One large cohort study found a worsening of respiratory-related morbidity and mortality in patients with COPD who were new users of SSRIs and serotonin and noradrenaline reuptake inhibitors (SNRIs)[15]. This appears alarming, but should prompt close monitoring (adverse event rates remained small) rather than contraindicating use. Moreover, as beta-2 agonists can lead to dose-related QT interval prolongation and hypokalaemia, the risk of serious arrhythmia is theoretically increased if patients are also taking other agents that may prolong the QT interval or cause other cardiac arrhythmias. This makes TCAs, citalopram and escitalopram less attractive choices (see section 5).

2.1 Breathlessness

There may be a relationship between depression, anxiety and breathlessness, with symptoms of anxiety and depression being linked to the development of dysponea[16], and so treating the concurrent mood disorder may ease respiratory symptoms. In addition to this, some authors have suggested a role for antidepressants specifically in the direct treatment of breathlessness via inhibition of fear responses, altering the patient's perception of, and emotional response to, unpleasant stimuli such as breathlessness[17]. Sertraline was not effective when examined in an RCT for this indication (although it did benefit quality of life)[18]. Mirtazapine appears theoretically promising but as yet unproven beyond case series[17].

2.2 Smoking cessation

Smoking cessation is of vital importance in the management of COPD, and COPD patients who continue to smoke are more likely to suffer depression[19]. The antidepressants bupropion and nortriptyline have both been used in smoking cessation, although they are not considered the most effective options (for COPD patients this is varenicline and combined NRT[20]). Nortriptyline showed benefits to depression and anxiety symptoms in a single small study in patients with COPD[21]. The efficacy of bupropion for the treatment of depression or anxiety in patients with COPD is unproven. Although treating psychiatric symptoms and enabling smoking cessation with one single drug is an attractive prospect, given the importance of stopping smoking in this population it is probably preferable to try the most effective treatment (varenicline) for this indication first, and treat the depression or anxiety separately. If other smoking cessation strategies have failed, then consideration of bupropion earlier in the treatment cascade for depression than it might otherwise be would be reasonable. Note also that bupropion is unlicensed for the treatment of depression in some countries.

If patients are already prescribed bupropion for smoking cessation but depressive symptoms persist, then combining bupropion with other antidepressants is possible. Bupropion was used as an

augmenting agent to citalopram in the STAR*D trial[22], and is usually well tolerated, although is known to lower the seizure threshold in a dose-dependent manner and inhibits CYP2D6. Cautious dosing is recommended.

2.3 Summary – antidepressants

Choose an SSRI (avoid citalopram and escitalopram), or mirtazapine if sleep disturbance or poor appetite are particular problems. Consider bupropion (not first line), especially if other smoking cessation strategies have failed.

3 Anxiolytics in COPD

Antidepressants are generally recommended first line for anxiety, but other anxiolytics or sedatives (benzodiazepines, promethazine, pregabalin) may also be prescribed.

3.1 Benzodiazepines

Prescribers often worry about the risk of benzodiazepines causing respiratory depression, but the reality is that benzodiazepines rarely cause respiratory depression in patients without pre-existing respiratory compromise outside overdose, or use with other potent respiratory depressants (significant alcohol use)[23]. For patients with COPD, the magnitude of risk associated with benzodiazepines is unclear. Benzodiazepines are used in patients with COPD to treat breathlessness, especially in end-stage disease. Some small studies of acute administration of benzodiazepines (single dose or short course) report reduction in pulmonary function in patients with COPD (decreased tidal volume and oxygen saturation, reduced ventilatory drive and respiratory muscle function)[24]. Population data on adverse events of low dose benzodiazepines in patients with COPD are conflicting in their results[25], some finding no increased rates of hospital admissions but small increases in mortality[26], others finding increased rates of admission[27] and respiratory adverse events[28]. Severity of disease, age of the patient (older adults are at increased risk of medication-related adverse events), and concurrent prescriptions (other respiratory depressants such as opioids) may be important, although confounding may also skew results that suggest these as influential factors (benzodiazepines may be more likely to be prescribed in severe, end of life disease). Other risks associated with benzodiazepines include confusion, falls, and pneumonia, and again these may be compounded by other co-prescribed drugs (opioids, for example). Overall, it seems prudent to refrain from benzodiazepine use as far as possible for all patients, especially those who are physically frail or who have multiple comorbidities, and this should probably be extended to patients with COPD. There may be circumstances under which the benefits (both physical and mental) from short-term, 'crisis' use of benzodiazepines may outweigh the risks (acute anxiety, for example).

3.2 Promethazine

Promethazine is an anticholinergic drug, and so (as for TCAs) may compound the anticholinergic effects of concomitant inhaled bronchodilators (but the risk is probably very small, see section 5). Like all antihistamines, it may also thicken bronchial secretions, making them more difficult to clear, so carries a manufacturer's warning cautioning against their use in patients with bronchitis or

bronchiectasis. In practice this is unlikely to be problematic, and indeed small studies suggest promethazine might improve exercise tolerance and reduce breathlessness in patients with severe chronic airway obstruction[29] or COPD[30] without altering lung function, possibly by reducing the feeling of breathlessness.

3.3 Pregabalin

Recently concerns have been raised about the effect of pregabalin on the central nervous system, as a small number of cases of respiratory depression have been reported worldwide[31]. This appears to occur independently of other concurrent risk factors (opioid prescriptions, comorbidity)[32]. As a result, pregabalin should be used with caution for patients with respiratory disease. If possible, it should be avoided in patients with COPD and reserved for when other options are unsuitable. Patients who are also prescribed other CNS depressants, those who are older than 65 years, and those with renal impairment (which results in increased plasma concentrations of pregabalin) should receive lower doses.

3.4 Summary - anxiolytics

Aim to use antidepressants first line in the treatment of anxiety. Promethazine may be used (not recommended specifically for the treatment of anxiety or depression, but may be a useful sedative agent). Avoid benzodiazepines and pregabalin if possible. Antipsychotics may be used but see comments below.

4 Antipsychotics in COPD

4.1 Acute respiratory failure

Patients with COPD, as with all respiratory illnesses, are at heightened risk of developing acute, chronic, or acute-on-chronic respiratory failure[33]. Acute respiratory failure (ARF) occurring in patients with severe COPD may worsen pre-existing chronic respiratory failure, with the increased airway obstruction during the acute event putting an additional mechanical load on the already compromised system[33]. Avoiding any insults that may risk causing ARF, especially in a patient with COPD, is therefore wise.

A handful of case reports describe ARF in patients with COPD within the first two weeks of starting antipsychotics (typical, atypical, oral and parenteral)[34], and these seem to be corroborated by an observational case-crossover study which found a 1.66-fold dose-dependent increased risk of ARF associated with antipsychotics[35]. Note that this finding has not yet been replicated in a trial, other than one nested case-control study from the same group showing a similarly increased risk in non-COPD patients[36].

It is suggested that the serotonergic, histaminergic and dopaminergic effects of antipsychotics may impair respiratory muscle activity or cause central respiratory depression. Quetiapine in particular appears to have attracted several case reports describing respiratory failure after normal therapeutic doses used in delirium[37,38] and sleep apnoea[39]. These cases should not be taken to suggest that

quetiapine is more likely to cause ARF than other antipsychotics; there is no obvious reason for quetiapine to be particularly problematic (respiratory depression is reported in overdose[40], but this is also true for other antipsychotics). It is the antipsychotic of choice in many critical care units for treatment of symptoms in delirium, and so confounding by indication may be an explanation. Transient rises in plasma concentrations caused by reduced metabolism of quetiapine (e.g. due to hepatitis) may explain some of the findings in the case reports[37], and it is possible that there is additive toxicity in respiratory depression when it is combined with methadone or other opiates[41].

A further possible mechanism for antipsychotics causing ARF is that of acute laryngeal dystonia (an extrapyramidal side effect) precipitating acute respiratory distress, and this has been described in the literature[42], including one fatality[43]. Finally, neuroleptic malignant syndrome may also cause acute respiratory failure[44,45].

The data published so far do not confirm causality, and do not clearly show that any single antipsychotic drug or drug class is more or less likely to cause ARF than another. Given the published reports associated specifically with quetiapine, until further research is available other antipsychotics should be used where possible, and quetiapine avoided. It would be prudent to dose antipsychotics extremely cautiously in people with COPD, especially in patients for whom metabolism of drugs may be compromised, given the association of raised plasma concentrations of antipsychotics with respiratory depression. Avoiding antipsychotics entirely in patients already experiencing acute respiratory failure would be wise, if other pharmacotherapeutic options are available and/or if the benefits of antipsychotic treatment are unclear (e.g. In delirum[46]).

4.2 Infection

There is a somewhat complicated relationship between antipsychotics and the incidence of pneumonia. Many studies report an increased risk of pneumonia for patients taking antipsychotics (almost double compared with no use[47]), but not all analyses support these findings. Despite this uncertainty it should probably be assumed that antipsychotics do increase the risk of pneumonia, including for patients with COPD[48]. The mechanism for direct causation is unknown. Sedation, dystonia, dyskinesia, xerostomia, hypersalivation, poor physical health and impairment of immune response (especially for clozapine[49]) have all been suggested[50].

Where possible, use of antipsychotics should be minimised for patients with COPD, assuming that the risk of pneumonia (already heightened for patients with COPD[51,52]) is additive (although whether or not COPD is associated with increased mortality and morbidity from pneumonia has been a controversial topic[53,54]). It will of course be the case that for many patients with chronic psychiatric illness long term antipsychotic treatment is unavoidable. There is insufficient evidence to support choosing (or avoiding) any single drug over another (apart from clozapine, which does appear to be particularly associated with infections[49], but it is also a drug that cannot be readily replaced with another). Use minimally effective doses (some studies suggest a dose-related effect[55]), avoid polypharmacy (combinations of multiple antipsychotics and mood stabilisers may be worse[56,57]) and treat contributary side effects promptly (sedation, xerostomia, hypersalivation).

Be aware that plasma concentrations of clozapine may rise during periods of infection[58], and patients with chest infections who smoke may do so less frequently and/or with less efficiency, which also causes clozapine plasma concentrations to rise. Reduce doses by a third whilst awaiting guidance

from plasma concentration monitoring for patients with severe infections (those that require hospitalisation), and for anyone with signs of clozapine toxicity.

4.3 Summary – antipsychotics

Avoid use of antipsychotics for patients with COPD where possible, and especially where evidence to support benefit is limited (eg. Delirium) and/or other pharmacological treatments can be used (eg. Anxiety). Where use of an antipsychotic is essential, avoid quetiapine if possible. Be aware of the possibility of increased susceptibility to pneumonia for patients taking antipsychotics and minimise risks where possible. Reduce clozapine doses for patients with severe infections.

5 Addictions and substance misuse

5.1 Opiate substitute treatment

Respiratory depression is common in patients with opioid use disorder, and may be undetected in routine practice[59]. The opioid agonists methadone and buprenorphine, just like opiates themselves, are respiratory depressants[59]. For patients with COPD, there may be an additive effect of these factors, increasing the risk of clinically significant severe respiratory depression in the event of any further respiratory assault, e.g. infection. In conjunction with their specialist addictions prescriber, patients taking methadone or buprenorphine should be encouraged to consider a reduction in dose to mitigate the risk of respiratory depression. Note that as a partial agonist, buprenorphine was thought to have less of an effect on respiratory drive than methadone, but recent data suggest this may not be the case[59].

5.2 Benzodiazepines

Individually, opiates and benzodiazepines increase the risk of adverse respiratory events in patients with COPD[28]. In combination, this risk is increased further[28]. Avoid prescribing in patients with opioid use disorders. If unavoidable, minimise doses (see section 5.1).

5.3 Pregabalin

As discussed in section 3.3, pregabalin (and gabapentin) has been associated with respiratory depression. In patients who take opiates there appears to be an increased risk of overdose when heroin and pregabalin are taken together[60], and an increased risk of abuse of pregabalin as it also reportedly enhances the opioid high[61]. Avoid prescribing in patients with opioid use disorders.

6 Drug interactions

6.1 Beta-2 agonists

At high doses, particularly as nebulised therapy, SABAs can cause hypokalaemia. This increases the risk of torsade de pointes[62]. Prolongation of the QT interval also increases this risk. At therapeutic doses most antidepressants do not cause QT prolongation, but some caution may be warranted with citalopram and escitalopram. While antipsychotics, particularly (but not limited to) amisulpride, haloperidol, and quetiapine are more clearly a problem, , this is likely plasma concentration-related. Regular ECGs will to confirm the absence of QT prolongation, and these are especially important in patients who may be exposed to large doses of SABAs (as in COPD).

6.2 Muscarinic antagonists

In theory, combining anticholinergic drugs, such as promethazine, clozapine, or clomipramine (not an exhaustive list – use medichec.com to check anticholinergic burden scores for individual drugs), with ipratropium or tiotropium would worsen anticholinergic side-effects, such as dry mouth, blurred vision, constipation, urinary retention, and cognitive impairment. Note especially the risk for patients taking clozapine, who are already at heightened risk of death from gastrointestinal hypomotility. Despite the likelihood of any significant problems occurring in patients taking inhaled anticholinergic bronchodilators likely being low, the person should be assessed for these side-effects prior to initiation of more anticholinergic therapy.

6.3 Theophylline

At very high plasma concentrations, theophylline can cause hypokalaemia, so the same warnings regarding torsade de pointes and QT prolonging drugs outlined in section 5.1 also apply here. The CYP1A2 inhibitor fluvoxamine causes rapid and potentially toxic increases in theophylline plasma concentrations – doses of theophylline must be halved[62]. Theophylline can lower the seizure threshold – many psychotropics are also known to do so (clozapine and bupropion, for example). There are case reports and small studies suggesting that theophylline can counteract the sedation from benzodiazepines. The mechanism for the observation is unclear, it may be that xanthines block adenosine receptors, which regulate neurotransmitter release, leading to a stimulant effect[62]. There are no data examining the consequence of this interaction on the anxiolytic effects of benzodiazepines. Theophylline reduces lithium plasma concentrations by around 20 – 30%, presumably by affecting renal clearance. This is an interaction that can probably be managed with careful monitoring of lithium plasma concentrations. Prior to co-administration, the need for theophylline should be reviewed by the respiratory clinician and plasma concentrations measured.

6.4 Azithromycin

Macrolide antibiotics are known to potentially prolong the QT interval, and it is possible that azithromycin will have the same effect[62]. Be aware of the additive risk if combining with other QT prolonging drugs (antipsychotics, citalopram, escitalopram, lithium) and of the potential for other drugs for COPD to cause hypokalaemia and further add to the risk (see section 5.1 and 5.3).

6.5 Roflumilast

Fluvoxamine increases the plasma concentration of roflumilast by inhibiting the activity of CYP1A2, and the concentration of its active metabolite by inhibiting CYP2C19. This may be beneficial (increased clinical activity of roflumilast), but monitor for increased side effects (nausea, diarrhoea, headache)[62]. Note also that roflumilast has been associated with an increased risk of psychiatric disorders (insomnia, anxiety, depression, suicidal ideation and suicide), and it is not recommended by the manufacturer for patients with a history of depression with suicidal ideation or behaviour[63].

7 Patient information

Asthma and Lung UK, 'Looking after your mental health': https://www.blf.org.uk/support-for-you/looking-after-your-mental-health

Patient information leaflet:
https://www.blf.org.uk/sites/default/files/Looking_after_your_mental_health_v2.pdf

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Contributors

Grainne D'Ancona, Consultant pharmacist, respiratory and sleep medicine (GSTT)

Nicky Kalk, Consultant psychiatrist, addictions (SLaM)

Contact

Siobhan Gee, principal pharmacist for liaison psychiatry: 07773108081; Siobhan.Gee@slam.nhs.uk

Psychiatric Medicines Information: 0203 228 2317;
pharmacy_staff_medicines_information@slam.nhs.uk

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