

Review
COPD and Schizophrenia

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Abstract

The prevalence of COPD is higher in people with schizophrenia than in the general population even after adjusting for smoking, but schizophrenia has not generally been considered in discussions of COPD multimorbidity. People with schizophrenia die prematurely and COPD is an important but neglected cause of this mortality. People with schizophrenia have a higher prevalence of ever smoking tobacco than the general population. The link between COPD and schizophrenia may be partially explained by higher rates of smoking, but may also be syndemic, with shared genetic, socioeconomic and environmental risk factors and common pathophysiological mechanisms.

People with a mental illness tend to receive medical care intermittently, there is often a lack of continuity of care and primary and preventive services are infrequently used. Physical symptoms may be viewed as "psychosomatic" leading to under-diagnosis. People with schizophrenia are less likely to receive adequate general medical care, including investigation and treatment, in line with guidelines. Antipsychotic drugs are associated with adverse effects that may be problematic in people with COPD.

The management and outcomes for people with schizophrenia and COPD could be improved by reducing stigma, developing Integrated services, undertaking physical health checks that include asking about respiratory symptoms and arranging spirometry when indicated, care coordination that includes addressing physical health issues, vaccination, support with smoking cessation, exercise and pulmonary rehabilitation.

Introduction

Most patients with chronic obstructive pulmonary disease (COPD) have other clinically relevant chronic disease and this has led to the concept multimorbidity (1). Schizophrenia has not generally been considered in discussions of COPD multimorbidity, but patients with schizophrenia have a higher incidence of COPD than the general population and their diagnosis and management present particular challenges.

Schizophrenia affects many aspects of patients' lives including the ability to sustain employment and live independently, even when in remission (2). Patients with comorbid COPD describe additional disability and isolation arising from the interaction of schizophrenia and respiratory symptoms (3). Adults with schizophrenia die decades earlier than the general population (4) and the mortality gap has widened over time (5). COPD is an important cause of this mortality (5). This review will discuss comorbid schizophrenia and COPD and how management challenges can be addressed.

Epidemiology of schizophrenia and COPD

The median age of onset of schizophrenia is 25 years but in approximately 1 in 5 cases the age of onset is over 40 and more than 25% of patients are now aged over 65 as a result of late onset and ageing with early onset disease, (6). Population studies show that the prevalence of COPD in people with schizophrenia is significantly higher than in the general population (Table 1), including when adjusted for smoking (10). The prevalence of COPD in 269,387 people with schizophrenia admitted to hospital in the US for reasons other than mental illness was 26.6%, compared to 15.6% in patients admitted who did not have schizophrenia (13). A study of admissions in the UK found COPD in 8.1% of people with schizophrenia and in 3.1% of people without a diagnosis of schizophrenia (Odds Ratio (OR) 2.7 (95% CI, 2.2-3.4))

(14). The higher prevalence is reflected in a higher annual incidence of COPD in people with schizophrenia compared to the general population in data from Taiwan (2.21% v 1.43%, relative risk 1.83, 95% confidence interval (CI), 1.62–2.07)) (7).

There were high rates of respiratory symptoms, including wheezing (38%) and dyspnoea (44%) in an Australian study of patients admitted to a mental health unit, half of whom had psychosis. 18% had results consistent with COPD on spirometry, and 60% of these patients did not have a known diagnosis (15). In the Swedish national cohort study, the risk of death from COPD was significantly higher in both men and women with schizophrenia than in those did not have schizophrenia even after adjusting for smoking (adjusted HRs 5.50 (95%CI, 4.09-7.42) and 2.78 (95%CI, 1.87-4.13)) (9).

Some, but not all, other physical health conditions are also more common in people with schizophrenia than in the general population. The prevalence of diabetes and cerebrovascular disease are significantly higher in people with schizophrenia (8-11) (adjusted OR (95%CI) in UK: 1.66 (1.59-1.74), 1.16 (1.06-1.27), respectively)(10). The prevalence of heart failure and cancer are higher in people with schizophrenia in unadjusted analyses, but not in the adjusted analysis (10). Ischaemic heart disease. and hypertension are not more common in people with schizophrenia (8-11).

Smoking

People with schizophrenia have a higher prevalence of ever smoking tobacco than the general population (OR = 3.1, 95% CI 2.4–3.8) (16), even after controlling for confounding variables (OR = 3.5, 95%CI, 2.3–5.3) (17). On average 62% smoke (16), and rates have not fallen significantly over time (18). Heavy smoking is more frequent in smokers with schizophrenia

than in the general population (ORs 1.9 to 6.4) and cessation rates are lower (OR 0.19, 95% CI, 0.14–0.24) (16). The proportion of people with schizophrenia who start smoking before the onset of their illness is also high (average 77% (range 49–90%)) (16) and studies of first psychotic episodes suggest that most people with schizophrenia start to smoke before the onset of their illness (19). Many do not want to be advised to stop smoking as they think it helps their symptoms (3). There is also a high prevalence of cannabis use (20). Smoking cannabis causes bronchitis and affects lung function but there is conflicting evidence that it leads to COPD, partly because most cannabis users smoke it mixed with tobacco (21).

Physical activity

People with schizophrenia are more sedentary and spend significantly less time undertaking moderate or vigorous physical activity (22). This is problematic if they also have COPD as low levels of physical activity are associated with worse breathlessness and quality of life, and an increased risk of hospitalisation and death (23). Pulmonary rehabilitation is one of the most effective interventions for people with COPD (24) and exercise training in people with schizophrenia leads to significant improvements in mental health (25).

However, significant psychiatric impairment or disruptive behaviour may interfere with an individual's ability to participate in a pulmonary rehabilitation programme.

The link between COPD & schizophrenia

Multimorbidity becomes more common as people age, but in both COPD and schizophrenia comorbidities develop earlier in life than in the general population (1, 10). Because of the typical ages of onset, most people already have schizophrenia when the symptoms of COPD emerge. The link between COPD and schizophrenia may partly be explained by higher rates

of smoking, but may also be syndemic, with shared genetic, socioeconomic and environmental risk factors and common pathophysiological mechanisms (1, 26, 27).

Twin and family studies suggest that heritable factors explain approximately 80% of the risk of schizophrenia (26) and there is some evidence that smoking behaviour and schizophrenia may share a common genetic basis. For example, in a discordant twin study, unaffected co-twins had higher smoking rates and poorer quit rates than controls (28), and one of the genetic loci robustly associated with schizophrenia (29) is in a gene cluster encoding neuronal nicotinic acetylcholine receptors, which is associated with smoking in the general population (30).

Although people with schizophrenia are more likely to smoke than the general population, including before they develop their illness (19, 31), but even after adjusting for smoking COPD remains more prevalent (10). There is evidence that inflammatory pathways involving the same cytokines that have been implicated in the pathogenesis of COPD are also activated in people with schizophrenia (32, 33). For example, elevated levels of interleukin-6 and tumour necrosis factor- α (TNF- α), have been found both in the blood and CSF of people with schizophrenia (34, 35) and the grey-matter loss seen in schizophrenia correlates with elevated levels of TNF- α (26). The association between COPD and schizophrenia does not appear to be due to shared early life events. Some studies have shown that early life events such as prematurity and low birth-weight, which are associated with an increased risk of developing COPD, are also associated with later development of schizophrenia, but other studies have not confirmed this (36) and maternal smoking does not appear to be a risk factor (37).

Illness behaviour

People with schizophrenia often receive medical care intermittently and there is a lack of continuity due to itinerancy (38). Use of medical services reduces after schizophrenia develops, primary and preventive services are infrequently used, and patients are less likely to consult for medical problems (38, 39). This may reflect poor insight, denial of physical illness, unwillingness to see unfamiliar clinicians, difficulties navigating processes to access care and not having transportation (3, 40). People with schizophrenia are also easily overwhelmed by having to deal with physical health conditions as well as their mental illness and frequently prioritise mental health issues (41).

Impaired ability to verbalise symptoms or concerns may contribute to under-diagnosis of medical conditions, as may clinicians focusing on the psychiatric symptoms or viewing physical symptoms as "psychosomatic". Consultations may be difficult for people with schizophrenia as they struggle to understand medical terminology and they are less likely to receive adequate medical care in line with guidelines (42-44). In a UK study, less than a quarter of patients had had all recommended components of physical health assessed (44). There appear to be differences in the medication for COPD prescribed to people with schizophrenia, possibly because of perceived difficulties in using inhaled therapy correctly, and they are less likely to receive smoking cessation advice (12).

Physical symptoms such as breathlessness and fatigue lead to additional burdens on patients and their carers, and can worsen anxiety and panic, and ability to cope. Non-adherence to antipsychotic medication is a common in people with schizophrenia (45) and, as will all long-term conditions, some non-adherence is unintentional and due to factors such as forgetfulness, but some is specifically related to concerns about antipsychotic and other

medication, such as negative attitudes towards medications and concern about side effects (46). Intentional and unintentional non-adherence to COPD therapies and incorrect use of inhaler devices is also common in people with COPD (47) and poor adherence correlates with an increased risk of exacerbations (48).

Clinicians with more stigmatizing attitudes about mental illness are likely to be more pessimistic about the patients with schizophrenia's adherence to treatment (49). Contrary to expectations, studies show that adherence to medication for somatic conditions, such as diabetes, is better on average in people with schizophrenia than general population (50). However some only take treatment on an irregular basis when their symptoms worsen and others are reluctant to take treatment at all (41). In the only study that has examined the impact of schizophrenia on adherence to inhaled therapies for COPD, there was a numerically higher proportion of people with schizophrenia among patients non-adherent to inhaled therapy compared to adherent patients, but the difference was not statistically significant (51).

Web-based systems, wearable devices, video conferencing and mobile phone technology have the potential to improve medication adherence, healthcare delivery and quality (52). Text messaging, or short messaging service (SMS) have been investigated as tools to improve adherence to antipsychotics in people with schizophrenia. Messages may contain medication reminders, encouragement and reinforcement, or information about coping strategies. Some systems allow recipients to customize the content and timing of messages, and some allow or prompt participants to send a response including details of symptoms. Digital interventions have been shown to improve medication adherence and clinical outcomes in patients with schizophrenia (53) and are capable of improving inhaler adherence

in people with COPD (54). However, some people with schizophrenia are reluctant to use digital services to help manage their physical health, in part because of concerns that web-based communication might prompt psychotic symptoms (41).

Adverse Effects of Antipsychotic Medication

Antipsychotic drugs are the cornerstone of pharmacological treatment of schizophrenia (2). Over the last 30 years there has been a switch from chlorpromazine and other first-generation drugs to second-generation agents (55). Olanzapine, quetiapine, risperidone and aripiprazole now account for over 80% of all antipsychotic prescriptions for schizophrenia in the UK & USA (56, 57). Long-acting injectable preparations of second-generation antipsychotic are also now available. Second-generation drugs have fewer neurologic adverse effects than first-generation agents, but are associated with sedation, postural hypotension, cardio-toxic effects such as arrhythmias, myocarditis, cardiomyopathy & coronary heart disease, weight gain and type 2 diabetes mellitus (Table 2) (58). The sedating, weight gain and cardiac adverse effects may be problematic in people with COPD, but antipsychotics also have specific respiratory adverse effects.

In a 5 year follow-up case controlled study of 21,492 people with schizophrenia in Sweden, including those with and without COPD, the respiratory mortality rate increased with increasing antipsychotic exposure and was highest in the high exposure group (HR 18.5, 95%CI, 13.9–24.6) (59). Wang et al. found that after adjusting for other risk factors the use of antipsychotics in people with COPD was associated with an increased risk of acute respiratory failure (OR 1.66, 95%CI 1.34–2.05, $p < 0.001$) (60). Perez-Vilar et al. also found the adjusted risk for respiratory failure in people with COPD with antipsychotic use in the previous 14 days was 1.13 (OR 1.13, 95% CI 1.06–1.20) and this risk was increased with

older age (61). However, in both of these studies the number of patients who were being treated with antipsychotics for schizophrenia was small. The risk of pneumonia is significantly increased by the use of second-generation antipsychotics in people with schizophrenia (Risk Ratio 1.69, 95%CI 1.43–2.01) (62) but there are differences in the risk of individual drugs (Table 2). It is well known that inhaled corticosteroids (ICS) also increase the risk of pneumonia in people with COPD and the increased risk of pneumonia in people treated with antipsychotics reinforces the need to use ICS in line with the GOLD recommendations (i.e based on previous exacerbation history and blood eosinophil count) as this will maximise the benefits of exacerbation reduction and consequent risk of respiratory failure, whilst minimising the risk of pneumonia (24). Although antipsychotics block the M3 muscarinic receptor and might therefore be expected to act as bronchodilators in COPD, there are no data exploring this effect.

Vaccination

Vaccination rates in people with schizophrenia are low (63). Although they may be more concerned about adverse effects of vaccines than the general population, they have similar general attitudes towards vaccination and willingness to be vaccinated. The biggest barriers to vaccination appear to be lack of awareness and knowledges, cost and practical e.g. lack of transport (64, 65).

Implications for Management

Effective management of people with schizophrenia and COPD can be challenging. The view of schizophrenia is usually negative and physicians dislike treating patients (66). Stigmatisation is common in both clinical and community settings and leads to discrimination in the provision of services for physical illness (67). Clinicians frequently underestimate

patients' abilities and motivations, leading to therapeutic nihilism, and fewer patients being investigated or offered effective therapy. Addressing these attitudes and reducing stigmatization is an essential step to improve outcomes (Figure 1).

Integrated services

Managing multimorbidity can be problematic as health-care training, guidelines and services generally focus on individual diseases. Patients with schizophrenia usually have some contact with primary care services each year and in many countries most mental health care is delivered in primary care. Primary care has the knowledge and experience to diagnose and manage COPD, but many primary care clinicians are not aware of the high rate of physical illness in patients with schizophrenia and seem not to diagnose and manage their medical conditions (68).

Integrated care models for the management of physical-mental multimorbidity are crucial (69-71). Case managers and psychiatric nurses have an important role to play, including motivating patients to engage with screening and monitoring, and liaising with primary care services (69). Educating primary care services about the increased risk of COPD in people with schizophrenia and training community psychiatric nurses to carry out physical health checks can lead to an increase in their uptake and quality, and also improves the lifestyle advice given to people with schizophrenia (72).

Risk Registers

It has been suggested that schizophrenia should be considered a "risk factor" for cardiovascular disease and patients should be put on risk registers and offered more intensive prevention advice and diagnostic screening (73). In the same way, schizophrenia should be

considered a “risk factor” for COPD and patients should be offered risk reduction advice and regular health checks and investigated if they develop respiratory symptoms or have repeated respiratory infections.

Routine health checks

Practice guidelines recommend that people with schizophrenia have their physical health reviewed at least annually (74); however, audits show that assessment and treatment of physical health problems is poor (44). Annual physical health checks are effective and reduce emergency department attendances and emergency admissions (75).

Clinicians often assume that people with schizophrenia will not participate in health checks, but evidence shows that they are willing to engage in health assessment and education activities when invited to do so (76). Minoritized ethnic groups do have worse rates of engagement with health services (77) and have low awareness of physical health checks and this needs addressing using specific strategies e.g. co-developed culturally appropriate resources in different languages and formats explaining why health checks are important and what they involve. Community organisations, such as charities and faith groups can also help raise awareness of the importance physical health checks, what they involve and support people to access them.

World Health Organization (WHO) guidelines recommend screening for cardiovascular disease and diabetes, but they do not mention COPD (78). Underdiagnosis of COPD is common even in people without mental health problems. Patients often do not report symptoms of cough, breathlessness, and decreasing exercise capacity as they assume that the symptoms are just a “smoker's cough” or a result of ageing, obesity, or being unfit. The

situation is likely to be worse in people with schizophrenia given the consulting behaviour as discussed above. Specific questions about respiratory symptoms, functional status, or changes in ability to do activities of daily living should be included in health checks to identify COPD and spirometry arranged if indicated.

Signposting and care-coordination

People with schizophrenia and COPD often have poor independent living and self-management skills, and high levels of homelessness and poverty (41, 70). Ensuring patients with schizophrenia and COPD can afford medication and have suitable accommodation is essential. Signposting sources of information and guidance on self-management, how to respond to worsening symptoms, financial and housing issues is important. Support services for people with COPD are often not used to dealing with people with schizophrenia and this should be addressed to avoid further widening of health inequalities.

Care coordination is a key component of the management of people with schizophrenia and could also improve physical health. Medicines optimisation, vaccinations, smoking cessation, self-management plans and pulmonary rehabilitation all improve outcomes in COPD (24). Facilitating these interventions, as well as timely access to respiratory care when needed, are important roles for care coordination in people with schizophrenia and COPD. Whilst there are no studies of the benefits of care coordination in people with schizophrenia and COPD, it has been shown to lead to significant reductions in cardiovascular risk (79).

Non-pharmacological interventions

WHO guidelines (78) recommend that lifestyle interventions including weight management, cardiovascular disease and cardiovascular risk reduction, and diabetes treatment and prevention should be central strategies for the management of physical health in adults with severe mental illness. The guidelines do not specifically address the importance of these interventions in people with COPD, although they do acknowledge the importance of smoking cessation.

Smoking cessation treatments are effective and well tolerated in people with schizophrenia (80, 81), but they are often not offered to them (82, 83), perhaps because of false beliefs that patients are not interested in treatment (84). It is essential that effective smoking cessation support is offered to all patients with schizophrenia, but this is particularly important in people with schizophrenia and COPD given the benefits on exacerbations and mortality (24).

Inactivity and obesity worsen COPD symptoms. Exercise can improve psychiatric symptoms in people with schizophrenia (85) and is a fundamental component of COPD management (24). People with schizophrenia and COPD may find it difficult to participate in the group exercises and education sessions that comprise conventional centre-based face-to-face pulmonary rehabilitation, but they may be able to participate in telerehabilitation (86), particularly with the support of a family member or support worker, and this can achieve similar benefits (24).

Improving vaccination rates in people with schizophrenia and COPD can be achieved with targeted vaccination programmes (65). Education on the importance of immunization should be provided as part of routine psychiatric care, and care-coordinators can help overcome barriers. Vaccination clinics co-located in psychiatric clinics can overcome problems such as

difficulty getting to vaccination centres (65). Mental health services should actively reach out to individuals at risk and ensure that registers up to date regarding vaccination status.

Anti-psychotic monitoring

Clinicians prescribing antipsychotics to older patients with schizophrenia and COPD should be aware that they can induce or aggravate somatic conditions and consider the pros and cons of treatment and dose escalation. Patients prescribed antipsychotics should have their physical health monitored regularly including checking for adverse effects of antipsychotic medications, in line with management guidelines (78, 87).

Conclusions

Schizophrenia and COPD have been neglected comorbidities. Although not common, diagnosing and managing them presents considerable challenges for health services. Being aware of the increased risk of COPD and alert to its diagnosis, ensuring regular physical health checks consider respiratory symptoms, developing integrated care services and avoiding stigma could make a significant difference to outcomes, including survival in this disadvantaged group of patients.

Declarations of Interest

SR has none to declare.

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Author Contribution:

Both authors contributed to the conception of the manuscript, reviewed the literature and were involved in critical revision of the manuscript for important intellectual content and approval of the final version to be published.

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Table 1. The prevalence of COPD in people with schizophrenia in population studies

Study Location	Number of people with schizophrenia	Prevalence of COPD in people with schizophrenia (%)	Prevalence of COPD in general population (%)	Risk (95% CI)
Taiwan (7)	4,417	3.83	2.88	OR 1.66, (1.42-1.94)
Norway (8)	10,112	6.7	4.7	N.S.
Sweden (9)	8,277	6.5	4.7	HR ^a 2.06 (1.80-2.34)
UK (10)	15,028	5.2	3.7	OR ^b 1.27 (1.17-1.37)
Iowa ^c (11)	1,074	10.8	3.6	OR 1.88 (1.51-2.32))
Finland (12)	67	12.2	4.3	OR ^d 4.23 (1.61-11.10).

OR – odds ratio; HR – hazard ratio; CI – confidence interval; N.S. – not stated

^a adjusted for age, marital status, education, employment status, income and substance misuse disorders

^b adjusted for age, sex, ethnicity, region, smoking status, BMI category, alcohol misuse, and drug misuse

^c people aged 18-65 years insured with Wellmark Blue Cross/Blue Shield

^d adjusted for age and sex

Table 2. Adverse Effects of second generation antipsychotic drugs

	Sedation	Weight gain	Impaired glucose tolerance/Type 2 diabetes	Anti-cholinergic	Hypotension	Risk of Acute Respiratory Failure in COPD OR (95% CI) [†]	Risk of Pneumonia in Schizophrenia RR (95% CI) [‡]
Clozapine	+++	+++	+++	+++	+++	NK	3.18** 2.62–3.86
Quetiapine	++	++	++	+	++	1.80 (1.09-3.00)*	1.63** 1.31–2.04
Risperidone	+	++	++	+	++	2.14 (1.11-4.10)*	1.32** 1.12–1.56
Olanzapine	++	+++	+++	+	+	2.89 (0.50-16.67)	1.83** 1.48–2.28
Aripiprazole	–	–	–	–	–	NK	NK

+++ high incidence/severity, ++ moderate, + low, - very low

CI – confidence interval; OR – odds ratio; RR – relative risk; NK - Not known

[†] Data from Wang et al. (60) OR adjusted for admission to ICU, heart failure, pneumonia, asthma, cancer, antiplatelets, ACEIs, non-cardiovascular selective β -blockers, first generation antihistamine, BZDs/non-BZDs, antidopaminergics, opioids, anaesthetics, gastrointestinal antispasmodics anticholinergics, NSAIDs, respiratory-failure-causing drugs, amiodarone, nebulized/inhaled SABAs, nebulized/inhaled SAMAs, methylxanthines, number of type of COPD medications, number of COPD ER visit or hospitalization, and number of steroid or antibiotic use from outpatient visits.

[‡] data from Kuo et al. (62)

* $P < 0.05$.

** $P < 0.001$

Figure 1. Key Management issues for People with Schizophrenia and COPD

