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Polypharmacy in Patients With COPD: A Scoping Review

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Abstract

Chronic obstructive pulmonary disease (COPD) is a global health challenge. Increasing numbers of patients with COPD are prescribed multiple medications (both for COPD and non-COPD disorders). This increases the risk of polypharmacy in these patients which can be linked with patient harm. However, the definition of polypharmacy is varied across literature (ranging from use of ≥3 to ≥20 medications).

This review aims to report the prevalence of polypharmacy, report the varying definitions of polypharmacy, and report medication related harms amongst patients with COPD.

We identified 28 studies reporting polypharmacy rates in COPD populations. A total of 13 studies (46.3%) defined polypharmacy as the use of ≥5 medications; however, the remaining studies had different definitions of polypharmacy. The available studies include multiple different countries and settings (primary care, secondary care, and community-based surveys). Polypharmacy and hyper polypharmacy (use of ≥10 medications) rates varied from 3.9% to 81.4% and 6.6% to 74.6% respectively.

Polypharmacy in patients with COPD is common but poorly understood due to difficulty in comparing previous literature with differences in methodologies, patient populations, and definitions of polypharmacy. The multimorbid COPD population is likely at higher risk to the effects of polypharmacy through poor adherence, adverse drug reactions, and drug-drug interactions. Clinicians should be mindful of the patient's age, comorbidities, and drug-drug interactions while prescribing medications in the COPD clinic.

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Abbreviations:

ADRs=adverse drug reactions; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **MLTCs**=multiple long-term conditions; **mMRC**=modified Medical Research Council dyspnea questionnaire; **OR**=odds ratio; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analysis

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Introduction

Chronic obstructive pulmonary disease (COPD) is a global health challenge.[1] The Global initiative for chronic Obstructive Lung Disease (GOLD) report recommends a combination of pharmacological and nonpharmacological therapies to manage COPD.[2] The focus for current pharmacological therapy is based on symptoms and disease severity markers such as pulmonary exacerbations, with more recent guidance also linked with blood eosinophil

levels. Pharmacotherapy includes inhaled bronchodilators and corticosteroids depending on the above-mentioned factors. COPD medications are often administered through various inhaler devices, which have the potential to cause issues with inhaler technique, adherence, and treatment burden.[2] In addition to inhaled regimens, more severe COPD may require additional treatments such as roflumilast and/or prophylactic antibiotics. Therefore, COPD management, even in isolation, can be associated with polypharmacy. Those patients on multiple medications have a high risk of suffering from adverse drug reactions (ADRs).[2]

Polypharmacy has various definitions in literature, depending on the number of medications prescribed. A systematic review of definitions done by Masnoon et al explored various terms used in existing literature. This review included 110 studies, out of which 57 studies (51.8%) defined polypharmacy or major polypharmacy as the use of ≥5 drugs, minor polypharmacy as use of 0 to 4 drugs (8 studies [7.3%])), and moderate polypharmacy as the use of 4 to 5 drugs (1 study [0.9%]). The use of ≥10 drugs was defined as hyper polypharmacy (1 study [0.9%]), excessive polypharmacy (7 studies [6.4%]) or severe polypharmacy (1 study [0.9%]).[3]

Multimorbidity in the general population is associated with polypharmacy and specifically a diagnosis of COPD is associated with an increased risk of polypharmacy.[4] Multimorbidity is defined as the coexistence of 2 or more multiple long-term conditions (MLTCs), without reference to a primary condition, that may overlap, vary in severity, and change in terms of health burden over time.[4,5] COPD is associated with multimorbidity with higher rates of cardiovascular diseases (congestive heart failure, ischemic heart disease, arrhythmias, peripheral vascular disease, hypertension, and atrial fibrillation) as well as bronchiectasis, sleep apnea, anemia, secondary polycythemia, lung cancer, diabetes, osteoporosis, anxiety/depression, and gastroesophageal disease.[2] These may significantly impact the patient's clinical condition and prognosis. These conditions can also mimic the symptoms of COPD, limit lung function, or complicate the management of COPD.[2]

Patients with COPD are therefore more likely to have MLTC, polypharmacy, risks of ADRs, hospital re-admissions, and premature mortality.[2,4,5]

Aim

This review aims to report the prevalence of polypharmacy, the varying definitions of polypharmacy used within COPD populations, factors associated with polypharmacy, and medication-related harms in COPD patients.

Methods

Overview

A scoping review was selected to consolidate knowledge on polypharmacy in COPD populations. We identified that evidence in this topic required investigation, and a scoping review enables key findings to be quickly summarized and disseminated. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines for scoping reviews: (1) identify objectives; (2) identify relevant studies; (3) analyze the literature for relevance; (4) extract key data; and (5) review and report results. A prespecified protocol was used to guide data synthesis. The protocol was registered through the Open Science Framework,[6] ensuring transparency and adherence to the established objectives and methodologies for scoping reviews.

Identifying Objectives

The following main objectives were identified as being key areas of interest: What is the prevalence of polypharmacy in COPD? What are the varying definitions of polypharmacy used within COPD populations?

Identifying Relevant Studies

Search Strategies and Databases

A systematic literature search of the electronic databases PubMed, Medline, and Embase was conducted using Medical Subject Headings terms and keywords identified from various systematic and scoping reviews relevant to the topic.

The first search was executed in PubMed on January 15, 2024, and the last one on Medline on January 24, 2024. A finalized search strategy was formulated by assessing the number and quality of returns, followed by a literature search executed on January 26, 2024, across 3 databases: PubMed, Medline, and Embase (Supplementary Table S1 in the online supplement).

A secondary search conducted in PubMed on February 6, 2024 (Supplementary Table S2 in the online supplement) targeted systematic reviews examining polypharmacy, enhancing the methodological rigor by identifying and incorporating established methods from existing reviews. Acknowledging that eligible studies might be indexed under more general terms not relating to COPD, another secondary search was performed in PubMed on February 10, 2024, focusing on polypharmacy by incorporating terms identified from other systematic and scoping reviews (Supplementary Table S2 in the online supplement).

Eligibility Criteria

The inclusion criteria for this scoping review were as follows: (1) Studies that clearly defined their COPD population, and (2) Studies that contained data on the prevalence of polypharmacy that was reported explicitly for a COPD cohort.

The exclusion criteria for this scoping review were as follows:

1. Studies in languages other than English;
2. Studies that were aimed at pulmonary diseases other than COPD;
3. Studies that did not mention polypharmacy in patients with COPD;
4. Studies that did not detail the rates of polypharmacy in their study population;
5. Animal and genetic studies;
6. Conference abstracts and nonpeer-reviewed articles.

Analyzing the Literature for Relevance

Duplicate studies were removed using EndNote (IBM Systems; Armonk, New York). Two independent reviewers assessed each abstract and formulated a list of "relevant" and "of uncertain relevance" studies. The full manuscripts that met either of these criteria were subsequently independently reviewed by the 2 reviewers, and eligible studies were identified. When consensus was not met, a third independent reviewer adjudicated.

Data Extraction

A charting form was developed for data extraction. A single reviewer independently extracted the following data from eligible studies: title, author, date of publication, location, study type, methods, study size, total COPD patients in the cohort, care center, study period, definition of polypharmacy used in the study, and reported prevalence of polypharmacy. The care center details were extracted from the eligible studies and as each country used different definitions to identify primary/secondary/specialist centers, it was not possible for the authors to standardize these definitions.

We recorded the polypharmacy rates according to the original sources and also, where possible, within the definitions of polypharmacy as the use of ≥ 5 medications and hyper polypharmacy as the use of ≥ 10 medications as proposed in a systematic review by Masnoon et al.[3]

Results

The initial database search identified 2573 articles, and 28 studies met the inclusion criteria. The number of studies omitted at each stage and the reasons for exclusion are described in Figure 1.[7]

The data was extracted from the 28 eligible articles and has been summarized in Table 1.[4,5,8-33] Some papers did not report values for all characteristics, and this is reflected in the table.

Study Characteristics

Table 1 presents an overview of the characteristics of the 28 included studies, including author details, year of publication, study design, total patients with COPD, type of care center, country of publication, study period, definition of polypharmacy used in the study, and prevalence of polypharmacy.

A total of 3 studies each were carried out in the United States (10.7%), Japan (10.7%), and Turkey (10.7%), followed by 2 studies each in the United Kingdom (7.1%), Spain (7.1%), Australia (7.1%), Canada (7.1%), Greece (7.1%), and Italy (7.1%). One study each was conducted in the Netherlands (3.6%), Brazil (3.6%), Portugal (3.6%), Saudi Arabia (3.6%), Iran (3.6%), and Finland (3.6%). One study (3.6%) was conducted across multiple centers in Europe in Belgium, Finland, Germany, Iceland, Italy, and the Netherlands.

A variety of study designs were reported, including cross-sectional (17, 60.7%), cohort (10, 35.7%), and observational (1, 3.6%). The settings included secondary care (10, 35.7%), primary care (10, 35.7%), specialist clinic (6, 21.4%), and community-based surveys (2, 7.2%).

Study Population

The number of patients with COPD in the 28 articles ranged from 14 to 117,005.
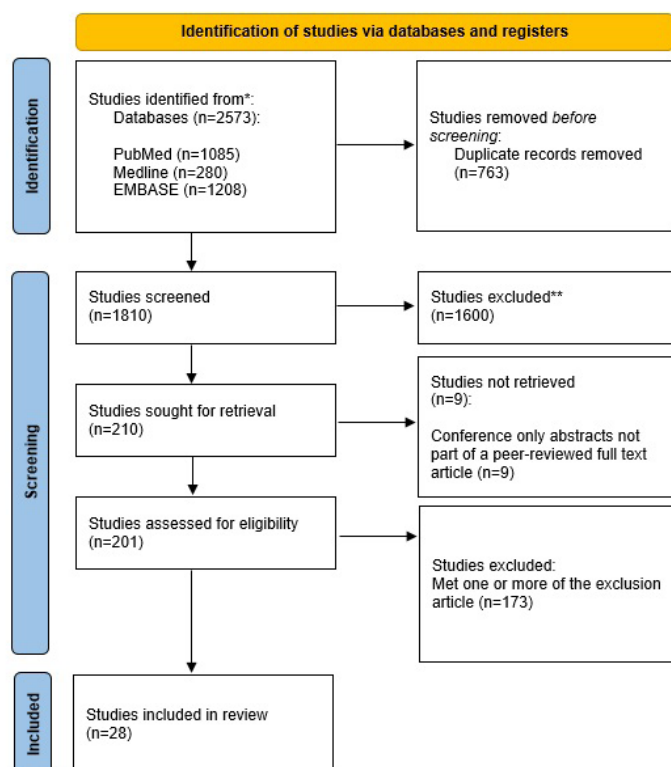
Collectively, the studies had a total population of 909,079 patients, out of which 270,977 (29.8%) patients had COPD. Out of 28 studies, 11 studies (39.3%)[5,10,11,14-16,18,21,23,26,28] consisted of only patients with COPD, while the rest of the 17 studies[4,8,9,12,15,17,19,20,22,24,25,27,29-33] had mixed COPD and non-COPD cohorts. However, in all 28 studies, the polypharmacy rates for patients with COPD were extractable.

Definition of Polypharmacy

The majority of the studies (17, 60.7%) used a single threshold to define polypharmacy, whereas, the remaining 11 studies classified polypharmacy into varying subgroups.

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis Flow Diagram for Study Inclusion

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases

Identification of studies via databases and registers

Identification

Studies identified from*:
Databases (n=2573):

PubMed (n=1085)
Medline (n=280)
EMBASE (n=1208)

Studies removed *before screening*:
Duplicate records removed (n=763)

Screening

Studies screened (n=1810)

Studies excluded** (n=1600)

Studies sought for retrieval (n=210)

Studies not retrieved (n=9):

Conference only abstracts not part of a peer-reviewed full text article (n=9)

Studies assessed for eligibility (n=201)

Studies excluded:
Met one or more of the exclusion article (n=173)

Included

Studies included in review (n=28)

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

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PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analysis

The most common single threshold was ≥5 medications (13, 46.3%), followed by ≥3 medications (2, 7.1%), ≥6 medications (1, 3.6%), and ≥10 medications (1, 3.6%).

The most common subgroup classification seen was the use of 5–9 and ≥10 medications (4 studies, 14.3%). Three studies (10.8%) classified patients into 2 groups: those using ≥5 and ≥10 medications. One study (3.6%) classified patients who used ≥10, ≥15, and ≥20 medications; 1 study (3.6%) defined polypharmacy as ≥4 and ≥8 medications, followed by use of ≥4 and ≥10 medications (3.6%), and the remaining study (3.6%) classified polypharmacy as the use of ≥6 and ≥10 medications (Table 1).

Polypharmacy and hyper polypharmacy rates were varied across literature. Polypharmacy rates in studies that used a single threshold of ≥5 medications ranged from 9.5% to 91.4%. Studies that classified polypharmacy in subgroups of 5–9 and ≥10 medications had polypharmacy rates

ranging from 3.9% to 12.1% and 6.6% to 21.7% respectively. Similarly, polypharmacy rates in subgroups of ≥5 and ≥10 medications ranged from 13% to 78.5% and 11.7% to 23%, respectively.

Factors Associated With Polypharmacy

The most common factors associated with polypharmacy were older age, increasing number of comorbidities, and smoking status.[10]

Age

Twelve studies reported that polypharmacy increased with age, typically reporting the significance of the increase was in ages 65 and over.[4,8,10,13,14,16,18,23,24,30-32] Certain studies showed a statistically significant association,[8,13,14,16,23,27,31,32] however, many other studies[4,10,18,24,30] did not report

Table 1. Characteristics of Eligible Studies

Sr. No.	Author	Year	Study Type	Study Total	Total COPD Patients in the Cohort	Care Center	Country	Study Period	Polypharmacy Definition (medications per day)	Prevalence of Polypharmacy
1.	Franssen F. et al.[5]	2011	Cross-Sectional	1859	1859	Specialist Clinic	Netherlands	2005–2009	≥5	22%
2.	Mizokami F. et al.[8]	2012	Cross-Sectional	1768	150	Secondary Care	Japan	2009	≥5	53%
3.	Calderón-Larrañaga A. et al.[9]	2013	Cross-Sectional	79,089	1351	Primary Care	Spain	2008	≥3	37.93%
4.	Diez-Manglano J. et al.[10]	2014	Cross-Sectional	398	398	Specialist Center	Spain	2007–2008	≥5, ≥10	78.5%, 11.7%
5.	Notebloom B. et al.[11]	2014	Cross-Sectional	70	70	Specialist Center	Australia	2010	≥4, ≥8	57%, 29%
6.	Runganga M. et al.[12]	2014	Cohort	347	44	Secondary Care	Australia	2009–2010	5-9, ≥10	9.7%, 20.1%
7.	Vrettos I. et al.[13]	2017	Cohort	310	30	Secondary Care	Greece	2015–2016	≥5	13.9%
8.	Savaria F. et al.[14]	2017	Cohort	113,435	113,435	Primary Care	Canada	2003–2014	≥5	81.4%
9.	Detoni K. et al.[15]	2017	Cross-Sectional	83	83	Primary Care	Brazil	2014–2016	5-9, ≥10	48.2%, 21.7%
10.	Vetrano D. et al.[16]	2017	Cohort	22505	22505	Primary Care	Italy	2002–2012	≥5	59.5%
11.	Hanlon P. et al.[4]	2018	Cross-Sectional	502,640	8317	Primary Care	United Kingdom	2006–2010	≥5, ≥10	51.8%, 15.3%
12.	Giovannini S. et al.[17]	2018	Cross-Sectional	1873	220	Community-based survey	Belgium, Finland, Germany, Iceland, Italy, & the Netherlands	2014–2016	5-9, ≥10	12.1%, 15.5%
13.	Sirois C. et al.[18]	2019	Cohort	117,005	117,005	Primary Care	Canada	2000–2015	≥10, ≥15, ≥20	74.6%, 45.4%, 22.4%
14.	Urzal J. et al.[19]	2019	Cohort	483	67	Secondary Care	Portugal	2017	≥5	16.3%
15.	Kaplan C. et al.[20]	2019	Cohort	835	177	Secondary Care	Turkey	2016	≥6, ≥10	11%, 7%
16.	Proietti M. et al.[21]	2019	Observational	6046	1302	Specialist Clinic	Italy	2008–2016	≥5	73.3%
17.	Balkhi B. et al.[22]	2021	Cross-Sectional	17237	14	Secondary Care	Saudi Arabia	2016	≥5	78.6%
18.	Ierodiakonou D. et al.[23]	2021	Cross-Sectional	245	245	Primary Care	Greece	2019	≥ 5	55.23%
19.	Brinker L. M. et al.[24]	2021	Cohort	231	62	Specialist Clinic	United States	2016–2019	≥10	33%
20.	Yamaoka M. et al.[25]	2021	Cohort	2603	58	Secondary Care	Japan	2014–2017	≥6	4.6%
21.	Moradkhani B. et al.[26]	2021	Cross-Sectional	100	100	Specialist Clinic	Iran	2019–2020	≥5	58%
22.	Witt J. et al.[27]	2022	Cross-Sectional	3005	322	Community-based survey	United States	2005–2006	≥4, ≥10	80.6%, 37.5%
23.	Prosser T. R. et al.[28]	2023	Cross-Sectional	709	709	Primary Care	United States	2016–2017	≥3	27.9%
24.	Veizi BGY. et al.[29]	2023	Cross-Sectional	235	32	Secondary Care	Turkey	2016–2019	≥5	81.3%
25.	Faquetti M. L. et al.[30]	2023	Cohort	34,169	2291	Primary Care	United Kingdom	2016–2019	≥5	10.3%
26.	Kanai M. et al.[31]	2024	Cross-Sectional	884	43	Secondary Care	Japan	2014–2019	5-9, ≥10	3.9%, 6.6%
27.	Ozkok S. et al.[32]	2021	Cross-Sectional	392	24	Secondary Care	Turkey	2016–2020	≥5	9.5%
28.	Jyrkka J et al.[33]	2009	Cross-Sectional	523	64	Primary Care	Finland	1998	≥5, ≥10	13%, 23%

SR=serial number; COPD=chronic obstructive pulmonary disease

the statistical association. Most studies showed a strong link with polypharmacy and age, with one study showing a higher rate of polypharmacy in older patients (86.8% among patients aged ≥75 years),[14] while 2 studies showed no links between age and polypharmacy.[5,19] Surprisingly, a cross-sectional study across multiple European countries in home care patients showed an inverse association of hyper polypharmacy with age (odds ratio [OR] 0.69, 95% confidence interval [CI] 0.56–0.83).[17]

Gender

Gender had a significant role to play with polypharmacy status. A total of 4 studies showed a higher prevalence of polypharmacy in females,[8,17,32,33] while 2 studies showed a higher prevalence in males.[9,23] One study showed no statistically significant difference between polypharmacy and gender.[5]

Comorbidities

Comorbidities and polypharmacy were common phenomena reported in 13 studies.[4,10,13,14,16-18,23,24,30-33] The most common diseases included diabetes mellitus,[4,10,13,14,18,24,30,31] cardiovascular diseases,[4,10,13,14,18,23,24,31] dyslipidemia,[13,24,31] cerebrovascular diseases,[13,14,31] dementia,[13,31] and COPD,[4,10,13,16,23,24,31] which is relevant to our study. A total of 3 studies[4,23,24] also highlighted the increasing risk of polypharmacy in patients with depression-anxiety diagnosis.

Smoking Status

COPD patients with polypharmacy were more frequently ex-smokers as compared to nonsmokers (75.4% versus 68.4%; $p=0.0005$).[10] The average pack years between those with and without polypharmacy was significantly different (58 versus 40 years, $p=0.004$).[23]

Medication Adherence

Polypharmacy was linked to poor medication adherence only in COPD patients aged ≥65 years (OR 1.34, 95% CI 1.13–1.59).[16] Poor adherence with polypharmacy ($p<0.001$) was also seen in an observational study done by Moradkhani et al.[26] A regression model was run in this study which showed the odds of patients with polypharmacy having high medication adherence was 81% less than those without polypharmacy, while controlling for other covariates ($p=0.008$).[26]

COPD patients were more likely to have polypharmacy (73.3% to 55.6%, *p* value <0.001), and the combination of COPD and polypharmacy led to poor medication adherence.[32] Vetrano et al reiterated in their study how complex regimens lead to poor adherence.[16]

Health Status and Frailty

In addition to poor functional health status, polypharmacy patients were less likely to be living independently (*p*=0.017).[27] This may correlate with studies suggesting higher rates of frailty in these group as the Charlson Comorbidity Index, which predicts the 10-year mortality in comorbid patients, was used by Díez-Manglano et al[10] to determine that polypharmacy was associated with a worse Charlson score (*p*=0.004).

Polypharmacy was significantly associated with failure to improve activities of daily living in a mixed cohort of COPD and non-COPD patients (OR 2.22. 95% CI 0.48–10.16).[12]

Two studies[25,32] reported that polypharmacy patients were at a higher risk of pain, falls, dyspnea, and flare-ups. When asked, polypharmacy patients self-report poor health status as well.[33]

Hospital Admissions

Díez-Manglano et al reported an increase in medications even after hospital admission for COPD acute exacerbation, with the mean number increasing from 5 to 6.6 at discharge.[10]

The IBenC study by Giovannini et al[17] in home care patients (including those with COPD), showed that recent hospitalization in the past 90 days was statistically associated with increased probability of hyper polypharmacy (*P*-value 0.012).

Severity of COPD

Franssen et al reported increasing use of respiratory drugs with advancement in GOLD stages and a worsening modified Medical Research Council (mMRC) dyspnea score.[5] An observational study done by Díez-Manglano et al showed polypharmacy was associated with severe dyspnea using the mMRC scale (3.7 versus 3.5, *p*=0.02), however, patients with polypharmacy showed no differences in their GOLD staging as compared to nonpolypharmacy patients.[10]

Multimorbidity

A cross-sectional study in Greece found the majority of the patients with polypharmacy were suffering from multimorbidity as compared to those without polypharmacy (98% versus 51%, *p*<0.001).[23]

Clinical Outcomes of Polypharmacy

Most extracted studies provided little information on how polypharmacy was linked to ADRs, hospitalization, and mortality in a COPD-specific population. A cross-sectional UK biobank study in 8317 patients with self-reported COPD reported higher risk of ADRs, such as bleeding (OR 4.61, 95% CI 3.35 to 6.19), CNS depression (OR 3.75, 95% CI 3.31 to 4.25), constipation (OR 3.42, 95% CI 3.10 to 3.77), urinary retention (OR 3.38, 95% CI 2.94 to 3.87), falls (OR 2.27, 95% CI 2.13 to 2.42), and renal injury (OR 2.22, 95% CI 1.86 to 2.62).[4]

Similarly, a cross-sectional study from Greece showed that COPD patients with polypharmacy were at a higher cumulative risk of falls, constipations, and cardiovascular events. In addition, 15 pairs of major drug-to-drug interactions were recorded in 11.5% cases, however, the details of these were not mentioned.[23]

Additionally, Witt et al reported, in a cross-sectional study of 3005 U.S. community-dwelling older adults, high-risk medications increased ADRs, and this risk furthered with polypharmacy. These high-risk medications included antihistaminic, anticholinergic, benzodiazepines, antipsychotics, anxiolytics/sedatives, tricyclic antidepressants, muscle relaxants, anti-arrhythmic, COX-2 inhibitors, and narcotics.[27]

Detoni et al conducted a retrospective review of medication management services delivered to COPD patients and identified the drug therapy problems in these patients. The most common drug therapy problem in COPD patients was ADR (25.8%), followed by unnecessary drug therapy (20.8%), and nonadherence to prescribed medications (18.8%). The most common ADR identified was oral candidiasis associated with the use of inhalers, however, the frequency of the ADRs were not described.[15]

Discussion

Despite the increasing prevalence of COPD worldwide, polypharmacy in COPD is poorly understood and described in literature. Our literature search identified 28 studies that reported the prevalence of polypharmacy in patients with COPD, however, there was no set definition for polypharmacy across these papers. Most studies defined polypharmacy with a threshold of ≥5 medications,[5,8,13,14,16,19,21-23,26,29,30,32] but other studies defined polypharmacy as the use of ≥3 medications,[9,28] ≥6 medications,[25] and ≥10 medications.[24] A further subcategory was defined in 7 papers wherein hyper polypharmacy was studied along with polypharmacy.[4,10,12,15,17,31,33] These varied definitions create inconsistencies across studies and limit the conclusions that can be drawn from these studies. Allowing for this, the studies suggest varied polypharmacy rates ranging

from 9.5% to 91.4% in studies with a single definition of polypharmacy (≥ medications). Similarly, studies with polypharmacy subgroups of 5–9 and ≥10 medications had polypharmacy rates ranging from 3.9% to 12.1% and 6.6% to 21.7%, respectively. This large range likely reflects both the different patient populations and settings as well as the varying definitions.

COPD therapy often involves the use of combination inhalers, e.g., triple inhaled long-acting beta agonist, long-acting anticholinergic, and inhaled corticosteroid in a single inhaler. Consensus is needed on how best to report these in polypharmacy studies as the use of triple therapy can be classified as either the use of 3 different medications or one single inhaler. Drug-drug interactions are defined by the number of active pharmaceuticals taken, but compliance may be different in those with simpler drug regimens as compared to those with "open triple" and "multiple inhalers."

Overall, we found the most common factors associated with polypharmacy were older age, increased comorbidities, and smoking status.[4,5,9,10,14,17,23,27,32,33] Some studies showed polypharmacy associated with increased age with several studies reporting a statistically significant association.[8,13,14,16,23,27,31,32]

However, COPD is commonly associated with MLTC, and both MLTC and COPD prevalence increases with age. The various methodologies used in the extracted literature make it difficult to understand what are independent predictors of polypharmacy. Notably, polypharmacy and comorbidities both contribute to poor adherence to medication in patients with COPD.[13,16,32]

Comorbidities are also common in patients with COPD, with the most common ones being cardiovascular diseases. COPD-heart failure and COPD-coronary artery disease clusters are strongly associated with polypharmacy.[8,10] Apart from cardiovascular diseases and COPD, polypharmacy was also associated with diabetes mellitus and dementia.[13]

These comorbidities are drivers to polypharmacy, increasing the use of potentially inappropriate medications, medication error, poor drug adherence, drug-disease interaction, and drug-drug interactions that can lead to severe ADRs.[9,10,21]

Polypharmacy is a concern not only due to the immediate costs of the medication regimens and the increased risk of nonadherence (which in turn increases the risk of COPD exacerbations), but also due to the concern over ADRs and drug-drug interactions.[15] A major proportion of COPD health care costs relate to hospitalizations. Notably, hospitalized patients with COPD are twice as likely to have polypharmacy regimens than non-COPD hospitalized patients.[24] The available literature, however, is limited in looking at the independent contributions of polypharmacy, frailty, and multimorbidity in driving hospitalizations. Relatively few studies do comment on potential adverse drug reactions in COPD as possible factors associated with admission.[23] Ierodiakonou et al found specific drug-drug interactions, such as liver damage, rhabdomyolysis, and arrhythmia, increased with polypharmacy, suggesting side effects of multiple medications being a cause for increased hospital admission.[23]

Detoni et al investigated the most common types of medication-related problems in a cohort of 83 patients with COPD and non-COPD patients in Brazil and found that ADRs were the most common (25.8%), with unnecessary medication use (defined as duplicate therapy, no medical indication, or where nonmedication therapy was more appropriate), and nonadherence the second and third most common problems respectively (20.8% and 18.8%, respectively).[15] High levels of inappropriate medication use in patients with COPD suggests the need to emphasize and screen for potentially inappropriate medications in these patients to help reduce medication burden, improve adherence, and reduce the risk of hospitalization. One of our stated aims was to report the medication-related harms in COPD, but we found the literature lacking in this detail. Therefore, future prospective studies should consider this in their study design.

Since polypharmacy is associated with a high risk of ADRs, drug-drug interactions, and reduced medication adherence, specialist pharmacy services can be utilized in respiratory clinics to reduce the impact of polypharmacy and provide regular medication review to patients. In addition, COPD is associated with multimorbidity (especially cardiovascular diseases) which is often managed by specialists or primary care physicians, hence, a high degree of care coordination and effective communication between multidisciplinary teams will improve patient outcomes.

A few studies we identified have analyzed polypharmacy in hospitalized elderly patients wherein polypharmacy was more common in those 75 years or older and with multiple comorbidities.[8,17] These patients with polypharmacy are at increased risk of frailty and worse long-term outcomes.[9,12] In terms of smoking status and medication adherence, nonsmokers were more compliant with long-term treatment than smokers and ex-smokers.[16]

Future studies require attempts to avoid unhelpful variation in definitions. It is commonly held that polypharmacy is defined as the use of ≥5 medications and hyper polypharmacy is ≥10 medications. These will usefully be applied in future studies as they are aligned with current thinking. However, future studies should also consider analyses where drug count is also analyzed using continuous statistical approaches beyond the current categorical approach. Future studies would be advised to be methodical in reporting drug regimens as the complexities

of COPD pharmacotherapy with open and closed triple inhalers needs critical thought. Closed triple inhaled therapy represents a reduced treatment burden, for example, and the potential for drug-drug interactions may be different from that where patients are variably complying with open triple therapy. Future studies should state if COPD was diagnosed by spirometry, and ideally, these studies should compare patients who were solely managed by primary care and those who were hospitalized or had received outpatient hospital-based COPD care.

Future work with a clear definition for polypharmacy is needed with more cross-sectional and longitudinal studies of polypharmacy in people living with COPD. Better clarity on the independent predictors of hospitalizations is also needed, and these studies should consider the complex interactions between adherence, MLTC and frailty, polypharmacy, and age. Studies that highlight the patient factors and medication combinations that enhance the risk of adverse medication reactions are needed. Additionally, prospective studies should consider analyses by sex and smoking status. Interventional studies to rationalize medication regimens are also welcomed.

One of the limitations of the study was that the available literature notes a diagnosis of COPD but the studies herein rarely, if ever, documented if this was a spirometry supported COPD diagnosis. In addition, the available literature does not allow us to make recommendations of suitable interventions to minimize treatment burdens or risk of drug-drug interactions.

Conclusion

Polypharmacy in COPD patients is common yet poorly understood due to difficulty in comparing previous literature with differences in methodologies, patient populations, and definitions of polypharmacy. The most common factors associated with polypharmacy were old age, number of comorbidities, and smoking status. There is likely a complex interaction between the multimorbidity present within a COPD population that amplifies the risks of polypharmacy. Polypharmacy is a growing concern due to increasing costs, nonadherence to medications, ADRs, and drug-drug interactions. Clinicians should be mindful of the patient's age, comorbidities, and risks of drug-drug interactions while prescribing medications in the COPD clinic.

References

1. Quaderi SA, Hurst JR. The unmet global burden of COPD. *Glob Health Epidemiol Genom*. 2018;3:e4. https://doi.org/10.1017/gheg.2018.1

2. Agustí A, Celli BR, Criner GJ, et al. Global initiative for chronic Obstructive Lung Disease 2023 report: GOLD executive summary. *Respirology*. 2023;28(4):316-338. https://doi.org/10.1111/resp.14486

3. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? a systematic review of definitions. *BMC Geriatr*. 2017;17:230. https://doi.org/10.1186/s12877-017-0621-2

4. Hanlon P, Nicholl BI, Jani BD, et al. Examining patterns of multimorbidity, polypharmacy and risk of adverse drug reactions in chronic obstructive pulmonary disease: a cross-sectional UK Biobank study. *BMJ Open*. 2018;8(1):e018404. https://doi.org/10.1136/bmjopen-2017-018404

5. Franssen F, Spruit M, Wouters E. Determinants of polypharmacy and compliance with GOLD guidelines in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2011;6:493-501. https://doi.org/10.2147/COPD.S24443

6. Koumides A. Multimorbidity & polypharmacy in COPD (chronic obstructive pulmonary disease) - a scoping review. Open Science Framework website. Published February 2024. Accessed February 2024. https://doi.org/10.17605/OSF.IO/KMD65

7. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467-473. https://doi.org/10.7326/M18-0850

8. Mizokami F, Koide Y, Noro T, Furuta K. Polypharmacy with common diseases in hospitalized elderly patients. *Am J Geriatr Pharmacother*. 2012;10(2):123-128. https://doi.org/10.1016/j.amjopharm.2012.02.003

9. Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, et al. Polypharmacy patterns: unravelling systematic associations between prescribed medications. *PLoS One*. 2013;8(12):e84967. https://doi.org/10.1371/journal.pone.0084967

10. Díez-Manglano J, Barquero-Romero J, Mena PA, et al. Polypharmacy in patients hospitalised for acute exacerbation of COPD. *Eur Respir J*. 2014;44(3):791-794. https://doi.org/10.1183/09031936.00014814

11. Noteboom B, Jenkins S, Maiorana A, Cecins N, Ng C, Hill K. Comorbidities and medication burden in patients with chronic obstructive pulmonary disease attending pulmonary rehabilitation. *J Cardiopulm Rehabil Prev*. 2014;34(1):75-79. https://doi.org/10.1097/HCR.0000000000000036

12. Runganga M, Peel NM, Hubbard RE. Multiple medication use in older patients in post-acute transitional care: a prospective cohort study. *Clin Interv Aging*. 2014;9:1453-1462. https://doi.org/10.2147/CIA.S64105

13. Vrettos I, Voukelatou P, Katsoras A, Theotoka D, Kalliakmanis A. Diseases linked to polypharmacy in elderly patients. *Curr Gerontol Geriatr Res*. 2017;2017(1):4276047. https://doi.org/10.1155/2017/4276047

14. Savaria F, Beauchesne MF, Forget A, Blais L. Polypharmacy, chronic kidney disease, and benign prostatic hyperplasia in patients with chronic obstructive pulmonary disease newly treated with long-acting anticholinergics. *Respir Med*. 2017;132:195-202. https://doi.org/10.1016/j.rmed.2017.10.023

15. Detoni KB, Oliveira IV, Nascimento MMG, Caux TR, Alves MR, Ramalho-de-Oliveira D. Impact of a medication therapy management service on the clinical status of patients with chronic obstructive pulmonary disease. *Int J Clin Pharm*. 2017;39:95-103. https://doi.org/10.1007/s11096-016-0402-6

16. Vetrano DL, Bianchini E, Onder G, et al. Poor adherence to chronic obstructive pulmonary disease medications in primary care: role of age, disease burden and polypharmacy. *Geriatr Gerontol Int*. 2017;17(12):2500-2506. https://doi.org/10.1111/ggi.13115

17. Giovannini S, van der Roest HG, Carfì A, et al. Polypharmacy in home care in Europe: cross-sectional data from the IBenC study. *Drugs Aging*. 2018;35:145-152. https://doi.org/10.1007/s40266-018-0521-y

18. Sirois C, Ouali A, Simard M. Polypharmacy among older individuals with COPD: trends between 2000 and 2015 in Quebec, Canada. *COPD*. 2019;16(3-4):234-239. https://doi.org/10.1080/15412555.2019.1646716

19. Urzal J, Pedro AB, de Oliveira IF, et al. Inappropriate Prescribing to elderly patients in an internal medicine ward. *Acta Med Port*. 2019;32(2):141-148. https://doi.org/10.20344/amp.10683

20. Kaplan C, Bilge U, Acar N, Unluoglu I. Determination of polypharmacy and inappropriate drug use in patients aged over 65 years who presented to the emergency department. *Turk Geriatri Derg*. 2019;22(3):287-294. https://doi.org/10.31086/tjgeri.2019.104

21. Proietti M, Agosti P, Chiara Lonati, et al. Hospital care of older patients with COPD: adherence to international guidelines for use of inhaled bronchodilators and corticosteroids. *J Am Med Dir Assoc*. 2019;20(10):1313-1317.e9. https://doi.org/10.1016/j.jamda.2019.01.132

22. Balkhi B, AlQahtani N, Alwhaibi M, et al. Prevalence and factors associated with polypharmacy use among adult patients in Saudi Arabia. *J Patient Saf*. 2021;17(8):e1119-e1124. https://doi.org/10.1097/PTS.0000000000000439

23. Ierodiakonou D, Theodorou E, Sifaki-Pistolla D, et al. Clinical characteristics and outcomes of polypharmacy in chronic obstructive pulmonary disease patients: a cross-sectional study from Crete, Greece. *Clin Respir J*. 2021;15(12):1310-1319. https://doi.org/10.1111/crj.13434

24. Brinker LM, Konerman MC, Navid P, et al. Complex and potentially harmful medication patterns in heart failure with preserved ejection fraction. *Am J Med*. 2021;134(3):374-382. https://doi.org/10.1016/j.amjmed.2020.07.023

25. Yamaoka M, Chono M, Fukumoto M, Watanabe T, Fukaya T, Momosaki R. Impact of number of drugs on rehabilitation outcomes in patients after traumatic brain injury: a retrospective cohort study. *PM R.* 2021;13(5):496-502. https://doi.org/10.1002/pmrj.12460

26. Moradkhani B, Mollazadeh S, Niloofar P, Bashiri A, Oghazian MB. Association between medication adherence and health-related quality of life in patients with chronic obstructive pulmonary disease. *J Pharm Health Care Sci.* 2021;7:40. https://doi.org/10.1186/s40780-021-00222-x

27. Witt LJ, Wroblewski KE, Pinto JM, et al. Beyond the lung: geriatric conditions afflict community-dwelling older adults with self-reported chronic obstructive pulmonary disease. *Front Med.* 2022;9:814606. https://doi.org/10.3389/fmed.2022.814606

28. Prosser TR, Bollmeier SG. Assessment of Medication Regimen Complexity of COPD Regimens in Individuals Visiting Community Pharmacies. *Int J Chron Obstruct Pulmon Dis.* 2023;18:1499-1510. https://doi.org/10.2147/COPD.S406718

29. Yavuz Veizi BG, Tasci I, Naharci MI. Geriatric syndromes in the population older than 90 years: the prevalence and association with chronic diseases. *Australas J Ageing.* 2023;42(3):472-479. https://doi.org/10.1111/ajag.13209

30. Faquetti ML, la Torre AM, Burkard T, Obozinski G, Burden AM. Identification of polypharmacy patterns in new-users of metformin using the Apriori algorithm: a novel framework for investigating concomitant drug utilization through association rule mining. *Pharmacoepidemiol Drug Saf.* 2023;32(3):366-381. https://doi.org/10.1002/pds.5583

31. Kanai M, Minamisawa M, Motoki H, et al. Prognostic impact of hyperpolypharmacy due to noncardiovascular medications in patients after acute decompensated heart failure - insights from the clue of risk stratification in the elderly patients with heart failure (CURE-HF) registry. *Circ J.* 2024;88(1):33-42. https://doi.org/10.1253/circj.CJ-22-0712

32. Ozkok S, Aydin CO, Sacar DE, et al. Associations between polypharmacy and physical performance measures in older adults. *Arch Gerontol Geriatr.* 2022;98:104553. https://doi.org/10.1016/j.archger.2021.104553

33. Jyrkkä J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Patterns of drug use and factors associated with polypharmacy and excessive polypharmacy in elderly persons. *Drugs Aging.* 2009;26:493-503. https://doi.org/10.2165/00002512-200926060-00006