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ORIGINAL RESEARCH

Cumulative Dispensing of Oral Corticosteroids Over 12 Months in People with COPD

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Purpose: Oral corticosteroids (OCS) are recommended for the treatment of exacerbations in people with COPD; however, high cumulative lifetime doses (≥1000mg prednisolone-equivalent) are associated with adverse health effects. This issue is well defined in asthma but is less well understood in COPD. The aim of this study was to examine cumulative OCS dispensed to people with COPD over 12 months.

Patients and Methods: This was a secondary analysis of data from two randomised controlled trials involving people with COPD followed up for 12 months following pulmonary rehabilitation. Clinical and administrative (respiratory-related hospital admissions and emergency presentations, dispensed OCS and COPD maintenance medications) data were examined to determine cumulative OCS dose relative to the 1000mg threshold and the relationship with clinical features.

Results: Of 232 participants (126 females, age mean 68 ± SD 9 years, FEV_1 53 ± 22% predicted), 48% (n = 112) were dispensed OCS at least once over 12 months. Sixty-two participants (26%) were dispensed ≥1000mg. Participants with a high cumulative dose were more likely to have had a respiratory admission (OR 4.1, 95% CI 2.3 to 8.7) and greater breathlessness (modified Medical Research Council scale ≥2, OR 2.5, 95% CI 1.3 to 5.0); no relationship with disease severity or maintenance medications was demonstrated.

Conclusion: One in four people with COPD were dispensed unsafe lifetime cumulative OCS doses over a period of only 12 months. Further work is needed to determine the magnitude of this issue in COPD and strategies to address exposure to high doses of OCS.

Keywords: exacerbations, systemic corticosteroids, prescriptions, side effects

Introduction

Affecting more than 8% of Australians and 14% of New Zealanders aged 45 years and over,[1,2] chronic obstructive pulmonary disease (COPD) is driving an escalating global burden of disease.[3] COPD has an enormous impact on individuals and society, with the majority of Australia's COPD expenditure attributable to hospital costs (62%) and federal government-subsidised medications through the Pharmaceutical Benefits Scheme (PBS, 28%).[4] Australia and New Zealand are amongst countries with the highest rates of hospital admissions in the world.[5] COPD is the leading cause of potentially preventable admissions in Australia[6] and the rate of COPD-related hospitalisations continues to rise (8% increase from 2014/15 to 2017/18).[7]

Avoiding exacerbations is one of the most important outcomes for people with COPD[8] due to the impact on health-related quality of life, association with accelerated disease progression and increased risk of hospital admission and death.[9] The development and frequency of exacerbations is heterogenous, however, it is estimated that 30–50% of people experience ≥1 exacerbation per year[10] but as many as half may go unreported.[11] The factors most strongly associated with exacerbation risk include exacerbation history, comorbidities, disease severity and bronchodilator reversibility,[12] with even a single exacerbation of moderate severity increasing the risk of future events.[13] Current recommendations for

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the treatment of exacerbations of COPD are for oral corticosteroids (OCS) 30–50mg prednisolone-equivalent per day for 5 days (up to 14 days).[14]

Despite the clinical indications for OCS, use is widely acknowledged to be associated with a range of adverse effects in the general population including osteoporosis, diabetes, cataracts, weight gain, sleep apnoea, renal impairment, pneumonia, myocardial infarction, heart failure, stroke, dyslipidaemia and depression.[15] There is evidence for an increased incidence of adverse events including sepsis, venous thromboembolism and fractures resulting even from short term use (<30 days).[16] In people with asthma, an intermittent pattern of OCS use is frequently observed and the risk of adverse health events increases when cumulative OCS exposure exceeds 1000mg prednisolone-equivalent.[17–20] Such evidence has led to calls for OCS stewardship in the management of asthma.[21] COPD guidelines are clear about the lack of suitability for OCS as a long-term therapy,[14,22–25] but short-term/intermittent use has received less attention despite long-documented associations with adverse effects.[26–30] Recent work has begun to clearly illustrate the dose-dependent nature of the relationship between high cumulative doses of OCS (exceeding 1000mg prednisolone-equivalent) and adverse health effects in people with COPD.[31–33]

In the context of current recommendations alongside evolving concerns regarding risk associated with OCS use in people with COPD, we sought to understand the scale of high cumulative dose dispensing, particularly in relation to the identified risk threshold of 1000mg prednisolone-equivalent.

The primary aim of this study was to examine the proportion of people with COPD who were dispensed a cumulative OCS dose ≥1000mg over 12 months. The secondary aims were to examine: the pattern, frequency and timing of dispensed OCS; the association of participant features with cumulative OCS dose ≥1000mg; and the proportion of participants with relevant comorbidities dispensed cumulative OCS dose ≥1000mg.

Materials and Methods

Study Design

This is a secondary analysis of data from the 12-month follow-up period of two randomized controlled equivalence trials, comparing remote models of rehabilitation delivery (home-based rehabilitation, HomeBase[34] [NCT01423227] n = 144; telerehabilitation, REAcH[35] [ACTRN12616000360415] n = 88) with traditional center-based pulmonary rehabilitation. All participants provided written informed consent.

Study Population

Both source studies included individuals who had stable COPD and were referred to 8-week pulmonary rehabilitation programs at public hospitals located in Victoria, Australia. In order to meet the criteria for inclusion, individuals were required to be ≥40 years of age, have a primary diagnosis of COPD and a smoking history of ≥10 pack years.[34,35] In these analyses, individuals who did not provide consent for access to Health Services Australia PBS data were omitted.

Data Collection

Participants were assessed at baseline, the end of pulmonary rehabilitation (8 weeks) and for 12 months after program completion. Demographic details (including age and sex) were collected at baseline. Disease severity was determined by FEV_1 (% predicted), measured with spirometry.[22] Breathlessness was quantified by participant using the modified Medical Research Council (mMRC) dyspnea scale in which higher scores indicate greater breathlessness.[36] Scores of 2 or more have been identified as indicating greater symptom burden.[22] A documented diagnosis of cardiovascular disease, comorbid osteopenia/osteoporosis or type II diabetes mellitus (T2DM) as per medical records was also recorded.

At end rehabilitation, program completion was determined for each participant according to attendance at least 70% of planned pulmonary rehabilitation sessions.[37]

For the 12-month follow-up period, medical records were reviewed for respiratory-related hospital admissions and emergency department presentations. The PBS database provided dispensing data for all community pharmacies and private hospitals in Australia, and for public hospital outpatient and discharge dispensing.[38] PBS data regarding dispensed medications were reviewed to identify dispensed OCS as well as long-acting muscarinic antagonist

(LAMA), long-acting beta-agonist (LABA) and inhaled corticosteroid (ICS) (in isolation or combination) including the date of prescription by treating health professional, dispensed dose and date dispensed by pharmacy.

Cumulative doses of dispensed OCS were recorded for each month (month 1 to month 12), and a cumulative 12-month dose was determined for each participant. Each month was progressively classified according to whether the 1000mg threshold was reached. Participants were then classified as: no OCS dispensed; "low" cumulative dose <1000mg OCS dispensed; or "high" cumulative dose ≥1000mg OCS dispensed over 12 months.

The frequency of dispensed OCS was assessed and classified for each participant as: no OCS dispensed; single occasion OCS was dispensed; "infrequent" >1 occasion OCS dispensed with all occasions ≥90 days apart; or "frequent" >1 occasion OCS dispensed with <90 days between occasions.[20]

The timing of dispensed OCS relative to prescription was classified according to: within 1 day of prescription or 2 or more days since prescription.

The number of days of treatment that dispensed doses of: LAMA, LABA or LAMA/LABA, and ICS (in isolation or combination) would provide were counted, with participants receiving no dispensed medications identified. In the absence of an accepted definition, participants were classified as being dispensed an "adequate" dose if dispensed medications would provide ≥300/352 days of treatment, to reflect ongoing COPD medical management according to recommendations.[14]

Statistical Analysis

The primary outcome was the cumulative OCS dose dispensed per participant over 12 months.

Participant characteristics were summarised using descriptive statistics, which involved mean and standard deviation (normal distribution) or median and interquartile range for non-parametric continuous data. Between-group differences in continuous non-parametric data were assessed using the Kruskal–Wallis test. Frequency and proportion were used to describe categorical data and the chi-squared test was used to test for between-group differences. A logistic regression model was developed to quantify the effect of participant characteristics associated with high cumulative OCS doses (relative to no/low doses); the variables (identified a priori) were: disease severity (FEV_1% predicted); breathlessness (score ≥2 on mMRC scale, yes/no); any respiratory admission (yes/no); and adequate ICS dose dispensed (yes/no). Cumulative OCS dose (no OCS, low, high) was also assessed in participants with a documented diagnosis of common comorbidities including cardiovascular disease, osteopenia/osteoporosis and T2DM. Statistical analysis was undertaken using IBM Statistical Product and Service Solutions (SPSS version 28, IBM Corporation, Somers, USA). A p-value less than 0.05 was considered significant.

Results

Participant Characteristics

From the combined 338 participants in both source studies, 232 (126 females) participants were included in these secondary analyses (HomeBase n = 122/144, REAcH n = 88/172, Figure 1). A total of 84 participants were omitted from the REAcH study: seven participants who had previously participated in the HomeBase study; 68 participants who did not have a primary diagnosis of COPD; and 26 participants who did not provide consent to PBS data collection. Participants had moderate disease severity (mean FEV_1 53% predicted) and most were affected by breathlessness in daily activities at baseline (Table 1).

Cumulative OCS Exposure

Over the 12-month follow-up period, a total of 405 OCS scripts were dispensed on 376 days (range dispensed on single day 100mg to 3750mg). 52% of participants (n = 120) were not dispensed any OCS, 22% (n = 50) were dispensed a low cumulative dose and 26% (n = 62) were dispensed a high cumulative dose (Table 1). Of the 376 days on which OCS were dispensed, 161 (43%) were within 0–1 day of an oral antibiotic being dispensed. Participants who were subsequently dispensed a high cumulative dose ≥1000mg were more affected by breathlessness at baseline. Of participants dispensed a high cumulative dose, a higher proportion had a respiratory admission during 12-month follow-

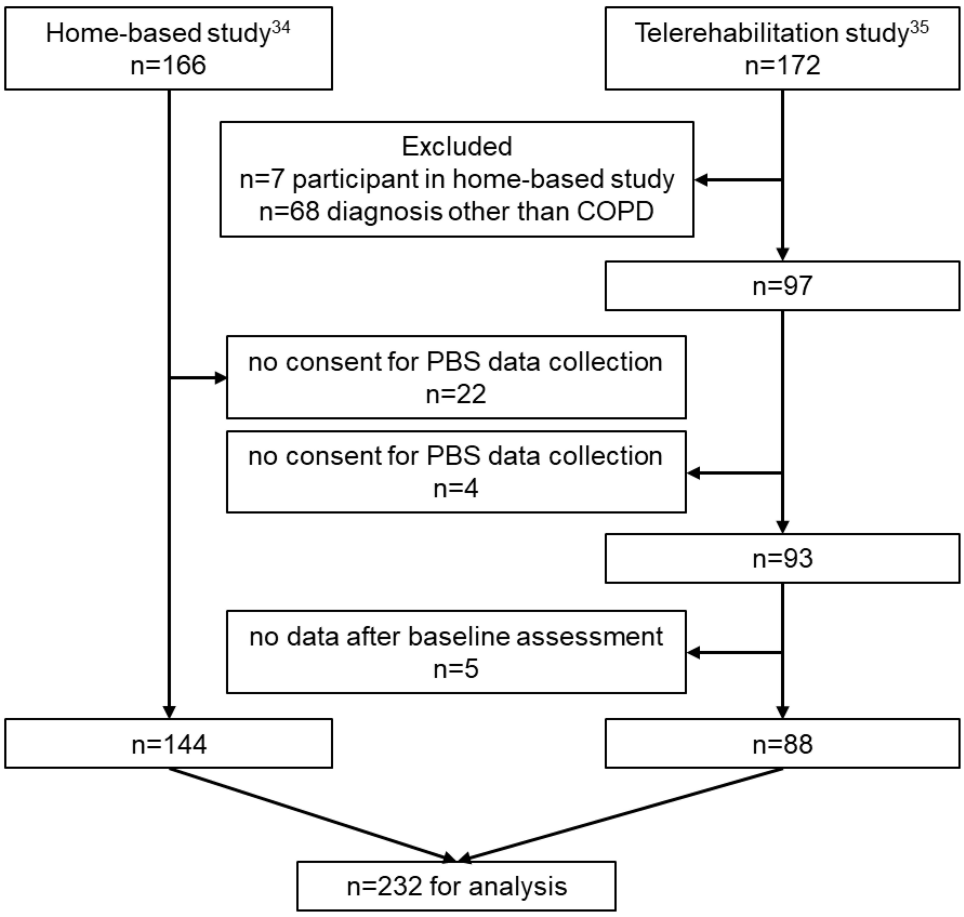

Figure 1 Flow chart of study participants.

up (47% compared to other groups 13% to 23%, $p < 0.001$); 81% were dispensed adequate LAMA/LABA (compared to other groups 60–80%, $p = 0.003$) and 42% were dispensed adequate ICS (compared to other groups 23% to 28%, $p = 0.015$) (Table 1).

Of the 62 participants dispensed a high cumulative dose, 50% (n = 31) were dispensed more than 2500mg (up to 12,000mg) over 12 months (Figure 2); 11% (n = 7) were dispensed ≥1000mg within the first month and 63% (n = 39) were dispensed ≥1000mg within the first six months of the 12-month study period (Figure 3).

For participants who were dispensed OCS more than once, the majority (56/65, 86%) were dispensed OCS again within 90 days (Table 2). These participants displayed similar proportions of adequate LAMA/LABA and ICS. Overall, 44% of OCS scripts (180/405) were dispensed within 0–1 day of prescription and were a higher dose (median 750mg, IQR 300 to 750) compared to scripts filled ≥2 days after prescription (median 300mg, IQR 300 to 750; $p = 0.001$).

Associations of OCS Use with Participant Characteristics

A logistic regression model was developed to quantify the effect of participant features. Disease severity and adequate ICS dose did not contribute to the model. Results demonstrated that participants with any respiratory admission over the 12-month study period were 4.5 times more likely to receive a high cumulative OCS dose compared to participants without respiratory admission (OR 4.1, 95% CI 2.3 to 8.7). Participants with greater breathlessness at baseline were 2.5 times more likely to receive a high cumulative OCS dose compared to participants who scored 0 or 1 on the mMRC scale (OR 2.5, 95% CI 1.3 to 5.0) (Table 3).

Fewer participants who completed pulmonary rehabilitation had any OCS dispensed (81/181,45%) compared to participants who did not complete pulmonary rehabilitation (3/51, 61%, $p = 0.043$). Fewer OCS scripts were dispensed to

Table 1 Participant Demographic and Clinical Features According to Cumulative Oral Corticosteroid Dose Over 12 Months

	All n=232	Categories According to Cumulative OCS Dose		
		No OCS n=120	"Low" <1000mg n=50	"High" ≥1000mg n=62
Baseline				
Age, years mean (SD)	68 (9)	69 (9)	68 (9)	69 (8)
FEV_1, % predicted mean (SD)	53 (22)	58 (23)	48 (16)	48 (22)
Female	126 (54%)	63 (53%)	25 (50%)	38 (61%)
Current smoker	42 (18%)	19 (16%)	12 (24%)	11 (18%)
mMRC score ≥2	138 (60%)	61 (50%)	29 (58%)	48 (77%)
Post pulmonary rehabilitation				
Program completion	181 (78%)	100 (83%)	36 (72%)	45 (73%)
12-month follow-up				
Any respiratory admission[a]	54 (23%)	15 (13%)	10 (20%)	29 (47%)
Adequate LAMA/LABA[b]	162 (70%)	72 (60%)	40 (80%)	50 (81%)
Adequate ICS[c]	66 (28%)	28 (23%)	12 (24%)	26 (42%)
Comorbid conditions				
Cardiovascular disease	170 (73%)	87 (51%)	37 (22%)	46 (27%)
Osteoporosis	35 (15%)	16 (46%)	5 (14%)	14 (40%)
T2DM	25 (11%)	11 (44%)	5 (20%)	9 (36%)

Notes: Data are n (%) unless indicated. Between group differences for categories according to OCS dose: [a]p<0.001; [b]p=0.003; [c]p=0.023.

Abbreviations: FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LAMA/LABA, long-acting muscarinic antagonist or long-acting beta-agonist; mMRC, modified Medical Research Council dyspnea scale; OCS, oral corticosteroid; T2DM, type II diabetes mellitus.

participants who had completed pulmonary rehabilitation (median 0 [IQR 0 to 2]) compared to participants who did not complete pulmonary rehabilitation (1 [0 to 4], p = 0.020). Of the participants with relevant comorbidities, 40% of participants with osteoporosis (n = 14/35), 36% of participants with T2DM (n = 9/25) and 27% of participants with cardiovascular disease were dispensed a high cumulative dose over 12 months (Table 1).

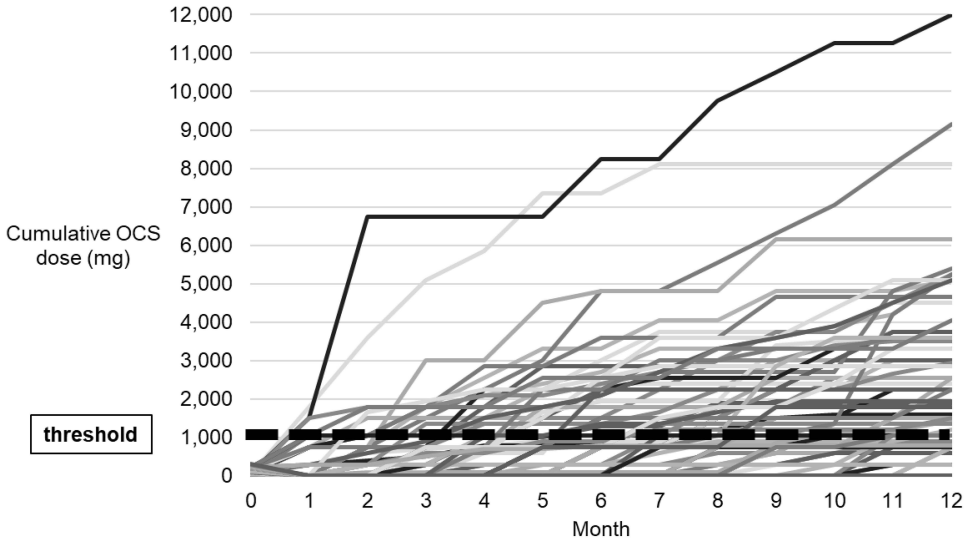

Figure 2 Cumulative dose by month per participant.

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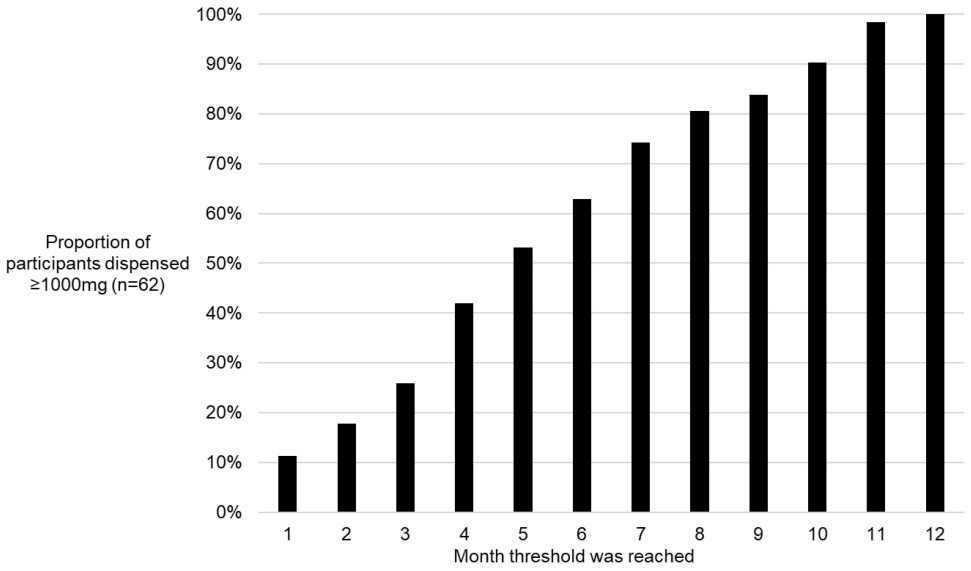

Figure 3 Month threshold was reached for participants dispensed oral corticosteroids ≥1000mg.

Discussion

One in four people with COPD who had undertaken pulmonary rehabilitation were dispensed potentially unsafe cumulative lifetime doses of OCS within 12 months. Of additional concern, just over half of these participants reached the 1000mg threshold within 6 months. As might be expected, a greater proportion of participants with high cumulative OCS doses had a respiratory admission within the 12-month study period. However, as PBS data does not incorporate medications delivered in a public hospital inpatient setting, the true cumulative dose for these participants is likely higher

Table 2 Participant Demographic and Clinical Features According to Time Between Dispensed Oral Corticosteroid Occasions Over 12 Months

Participant Features	No OCS n=120	Categories According to Time Between Dispensed OCS Occasions		
		Single OCS n=47	Infrequent ≥90 days n=9	Frequent <90 days n=56
Baseline				
Age, years mean (SD)	69 (9)	68 (9)	67 (8)	68 (9)
FEV_1, % predicted mean (SD)	58 (23)	49 (17)	38 (12)	49 (22)
Female	63 (53%)	23 (49%)	4 (44%)	36 (64%)
Current smoker	42 (18%)	12 (26%)	2 (22%)	9 (16%)
mMRC score ≥2	61 (51%)	28 (60%)	7 (78%)	42 (75%)
Post pulmonary rehabilitation				
Program completion	100 (83%)	36 (77%)	7 (78%)	38 (68%)
12-month follow-up				
Any respiratory hospital admission[a]	15 (13%)	10 (21%)	2 (22%)	27 (48%)
Adequate LAMA/LABA[b]	72 (60%)	38 (81%)	6 (67%)	46 (82%)
Adequate ICS	28 (23%)	13 (28%)	2 (22%)	23 (41%)

Notes: Data are n (%) unless indicated. Between group differences for categories according to OCS dose: [a]p<0.001; [b]p=0.006.

Abbreviations: FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LAMA/LABA, long-acting muscarinic antagonist or long-acting beta-agonist; mMRC, modified Medical Research Council dyspnea scale; OCS, oral corticosteroid.

Table 3 Logistic Regression for a Participant to Be Dispensed Oral Corticosteroids ≥1000mg Over 12 Months

	Odds Ratio	95% CI	p
Constant	0.1		<0.001
Any respiratory admission (yes/no)	4.5	2.3 to 8.7	<0.001
Score ≥2 on mMRC scale (yes/no)	2.5	1.3 to 5.0	0.010

Abbreviation: mMRC, modified Medical Research Council dyspnea scale.

than demonstrated in these analyses. The only commonly assessed clinical feature associated with high cumulative OCS doses was breathlessness at baseline, highlighting the importance of patient-reported outcomes and their ability to provide a "flag" for concern at time of OCS prescription in clinical practice, along with a history of respiratory admission.

In participants who were dispensed OCS more than once, the majority were dispensed OCS again within 90 days. Participants with high cumulative and more frequent doses demonstrated the highest proportion receiving adequate maintenance therapy. Given participants had moderate disease severity and were affected by breathlessness in daily activities, they might be expected to be managed with both LAMA/LABA and ICS, however, this was not universal.

Written action plans are also recommended as part of COPD management.[14] Developed in conjunction with a health professional, people with COPD are encouraged to self-monitor their symptoms; in the event, they identify an escalation in symptoms, they are recommended to use a previously prescribed "rescue pack" of OCS. It is unclear to what extent activation of action plans contributed to the high cumulative doses of OCS. Over half of OCS doses were dispensed two or more days after prescription and were of a lower dose, which may reflect action plan-based care, but data regarding written action plans were not collected in this study. Our findings that 48% of participants were dispensed OCS are slightly higher than previous studies demonstrating OCS use in 33% of people with COPD from a UK primary care dataset[32] and 44% of people with COPD using maintenance therapy.[39] Recent US Medicare data for patients newly diagnosed with COPD showed that 36% received OCS in the 48 months following diagnosis, 38% of OCS episodes lasted longer than the recommended 5–7 days and 90% of episodes had up to 19 days of OCS therapy supplied.[31] It has been previously noted that treatment with OCS may be of longer duration and higher dose than recommended in clinical guidelines, despite recommendations and evidence for lack of efficacy as well as increased risk of adverse outcomes.[40–42]

International guidelines provide recommendations for use of OCS in management of a COPD exacerbation in an ambulatory setting, based on the findings of a small number of clinical trials;[23] three trials undertaken between 1996 and 2008 included a total of 204 participants with exacerbations who had required a hospital visit,[43] were discharged from the emergency department[29] or managed in ambulatory care.[44] Outcomes were reported between 10 and 90 days and meta-analysis results showed a 160mL improvement in FEV_1 and "trend" towards a reduction in hospital admissions but no improvement in treatment failure or mortality, which led to a conditional recommendation for OCS based on very low-quality evidence.[23] A recent study in ambulatory care did not suggest that OCS are more effective than placebo for the management of exacerbations.[45] Alongside the evolving evidence for adverse effects associated even with short courses[31–33] and escalating use,[46] this is a critical issue.

If people living with COPD received a guideline-based dose of OCS for an exacerbation (40mg daily for 5 days),[14] the lifetime cumulative threshold would be reached with their fifth exacerbation. The maximum dose allowed as per guidelines (50mg for 14 days) would see people exceeding the threshold with their second exacerbation. There are heterogenous estimates for frequency of exacerbations,[47] but with a decreasing age at COPD diagnosis (UK data)[48] and increased risk of future multiple exacerbation events and worsening disease progression associated with each exacerbation,[13] these findings of high cumulative doses of OCS over 12 months are alarming. Work in intermittent OCS use in asthma has showed dose–response relationships for almost all adverse effects starting from cumulative lifetime doses as low as 500mg.[20] A similar pattern of increased risk with increased cumulative dose is emerging in COPD, which may be exacerbated by age along with the number and severity of comorbidities.[31,32] Our results suggest that there is a considerable proportion of people with COPD who are at risk of adverse outcomes associated with current

patterns of OCS use and highlight the need to address patient-level challenges (eg, ensuring patients and healthcare professionals are aware of the risks associated with high cumulative doses) as well as improve system-level processes (eg, ability to flag high-risk individuals). Ongoing emphasis on exacerbation risk minimisation strategies is essential, as is the development of new therapies[46] and therapy optimisation approaches.[49]

There are some limitations to this study. Although the PBS dataset is commonly used in research,[38] data are for dispensed medications (not consumed) and do not include prescription instructions or indication for treatment. There was no accepted definition of "adequate" maintenance therapy available for application in our analyses. Participants in this study may not be representative of the broader population of people with COPD living in the community as they had attended pulmonary rehabilitation and participated in a clinical trial; the impact of these factors on the outcomes of interest in these analyses is not known. Strengths of this study include the use of a comprehensive administrative dataset encompassing all relevant medications without the need to rely on participant recall. Additionally, participants had a confirmed diagnosis of COPD as a requirement for source study enrolment.

Conclusion

A quarter of people with COPD who had undertaken pulmonary rehabilitation were dispensed potentially unsafe cumulative lifetime doses of OCS over 12 months. Future work is required to further elucidate the magnitude and clinical significance of this issue in the management of people with COPD.

Abbreviations

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; OCS, oral corticosteroids; PBS, Pharmaceutical Benefits Scheme; T2DM, type II diabetes mellitus.

Data Sharing Statement

The data that support the findings of this study are available from Professor Anne Holland (anne.holland@monash.edu) upon reasonable request.

Ethics and Consent Statement

These studies were conducted in accordance with the Declaration of Helsinki and were approved by the Alfred Health Human Research Ethics Committee with governance approvals obtained from all sites. These trials were prospectively registered (NCT01423227 at clinicaltrials.gov, ACTRN12616000360415 at anzctr.org.au).

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Disclosure

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the 2024 Thoracic Society of Australia and New Zealand Annual Scientific Meeting (oral presentation, Respirology 2024;29(S1):TO033, https://doi.org/10.1111/resp.14673) and American Thoracic Society International Conference (poster presentation, Am J Respir Crit Care Med 2024;209:A4275, https://doi.org/10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A4275).

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