

Title:

Characterization of patients with chronic obstructive pulmonary disease (COPD) treated with single-inhaler triple therapy (SITT) or multiple-inhaler triple therapy (MITT) in Australia, using MedicineInsight and Pharmaceutical Benefits Scheme (PBS) data.

Rationale and background:

This study aimed to provide evidence of real-world use of Trelegy Ellipta (once-daily single inhaler, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 mcg) in Australia post-PBS listing, and compare this with new users of multiple-inhaler triple therapy (MITT) in Australia post-approval of Trelegy.

The findings from this study will be used to inform the Drug Utilization Sub-Committee (DUSC) post-PBS listing review for Trelegy Ellipta. The results of the study have contributed to our understanding of how the medicine is used and whether PBS restrictions have been adhered to.

Research question:

The primary objective of this study was to describe the sociodemographic and clinical characteristics of patients aged 35 years and over with evidence of a diagnosis of COPD (with or without asthma) who initiate SITT (i.e. Trelegy Ellipta) or MITT, in the Australian general practice setting on or after 1 June 2018.

The secondary objective was to describe the sociodemographic and clinical characteristics of patients who initiate SITT or MITT in the 3-month period 1 June–31 August 2018, and compare them with patients who initiate SITT or MITT in the period 1 June–31 August 2019.

Study design:

This was a retrospective cohort study, providing descriptive analyses of data from patients who initiated COPD triple therapy on or after 1 June 2018. The full study period covered the period from 1 June 2016 to 31 October 2019, inclusive.

Study population:

The study population comprised patients aged 35 years and over, who were initiated on SITT or MITT on or after 1 June 2018. As there are differences in the way asthma and COPD are managed, patients with COPD only and patients with COPD plus asthma were analysed separately. For the analysis of acute exacerbations of COPD prior to initiation of triple therapy, only patients from the main study population who had at least 24 months of records (follow-up) at the practice prior to the index date were included in this analysis.

Data sources:

MedicineInsight is a large-scale, national primary care data program in Australia that extracts longitudinal patient information from the clinical software used in general practice. With data from 2.7 million patients and almost 14 million clinical encounters in the 2017–18 financial year, MedicineInsight supports public health and health services research, as well as contributing evidence for the development of health systems policy and practice. MedicineInsight provides anonymised information on patient clinical history, including pathology tests, prescriptions, vaccines, and diagnoses.

The 10% PBS sample provides information on medicines dispensed for a random sample of 10% of the Australian PBS dataset. However, as it is primarily an administrative dataset, the PBS does not incorporate patient clinical history or diagnoses.

Key findings

Initiation of SITT or MITT between 1 July 2018 and 31 October 2019

- Of the MedicineInsight general study population 3,819 (46%) patients were initiated on SITT and 4,404 (54%) patients were initiated on MITT (but not SITT) on or after 1 June 2018. Of the PBS 10% sample 4,958 (57%) patients were initiated on SITT and 3,781 (43%) patients were initiated on MITT (but not SITT) on or after 1 June 2018.
- While MedicineInsight covers approximately 12% of Australian patients, the absolute numbers of patients on triple therapy in MedicineInsight was lower than seen in the PBS 10% sample (8,223 versus 8,739 patients in total, respectively). This is likely due to prescriptions from specialist practitioners, which are included in the PBS 10% sample, but are not captured in MedicineInsight.
- In the MedicineInsight general practice data we found a higher proportion of patients initiated on MITT during the study period than SITT whereas in the PBS data more patients were initiated on SITT than MITT during the study period. This finding was despite the same definition of ‘initiation of SITT’ and ‘initiation of MITT’ being applied to both the MedicineInsight prescribing data and the PBS dispensed prescription data. Inherent differences between the two data sources most likely explain this finding. The PBS data includes prescriptions written by both specialists and GPs whereas MedicineInsight only includes prescriptions by GPs. In this study SITT was initiated by specialists (55.3%) slightly more frequently than MITT was initiated by specialists (53.4%) and conversely MITT was initiated by GPs (46.6%) slightly more frequently than SITT was initiated by GPs (44.7%) (Table 13); this might partly explain why triple therapy with MITT was initiated more frequently than SITT in the MedicineInsight general practice data, but not the PBS data. Specialists are more likely to prescribe with a more complete knowledge of patient hospitalisation history, and are more likely to be seeing a patient as a result of a recent hospitalised exacerbation. Specialists may also be more confident of prescribing a new therapy than GPs. Additionally, as MedicineInsight data only includes what was prescribed and not what was dispensed, another potential/theoretical explanation for the more common initiation of MITT in MedicineInsight data compared to PBS data, could be that less patients fill prescriptions for MITT compared to prescriptions for SITT.

Initiation of SITT or MITT between 1 July 2018 and 31 October 2019 in patients with COPD

- More patients who initiated SITT had a recorded (MedicineInsight cohort) or inferred (PBS cohort) diagnosis of COPD than patients who initiated MITT. In MedicineInsight data, 88% of patients who started SITT had a recorded diagnosis of COPD compared with 70% of patients who started MITT. Of MedicineInsight patients who had no recorded diagnosis of COPD, almost three quarters (74.2%) of patients who initiated MITT had a diagnosis of asthma, compared to slightly more than half (51.0%) of patients who initiated SITT. MITT is indicated for moderate-severe asthma not controlled on ICS-LABA, and is advocated in clinical guidelines.
- In the PBS 10% sample, 92% of patients who started SITT had an inferred diagnosis of COPD compared with 75% of patients who started MITT.

Sociodemographic characteristics of patients with COPD initiated on SITT or MITT

- The mean age of patients who initiated SITT in both the MedicineInsight and PBS data was 70 years, more patients were male (51% of MedicineInsight patients and 52% of PBS 10% sample patients) and most were concession card holders (83% of MedicineInsight patients; 85% of PBS 10% sample patients).
- Compared with the MedicineInsight general study population patients initiated on SITT were more likely to be male, reside in inner and outer regional areas and socioeconomically disadvantaged areas, reflecting the higher prevalence of COPD in males, regional areas and socioeconomically disadvantaged areas.
- The mean age of patients who initiated MITT in both the MedicineInsight and PBS data was 68 years. In contrast to patients initiating SITT, fewer patients initiating MITT were male (46% in both the MedicineInsight and PBS data) than female (54% in both the MedicineInsight and PBS data).
- Patients who initiated MITT were less likely than those initiating SITT to be concession card holders (79% in both MedicineInsight and PBS data, compared to 82.5 and 85.2% in MedicineInsight and PBS data, respectively).
- Like the SITT cohort, more patients initiating MITT resided in inner and outer regional areas and socioeconomically disadvantaged areas than the general study population.
- Patients with COPD who were initiated on SITT in the 3-month period immediately after PBS listing in 2018 were slightly older than those who initiated SITT in the same 3-month period in 2019 (mean age MedicineInsight: 70.7 years vs 68.7 years, respectively). In MedicineInsight data 5.3% of 2018 SITT initiators were aged 35-54 years compared with 11.0% of 2019 SITT initiators and in PBS data 6.0% of 2018 SITT initiators were aged 35-54 years compared with 7.4% of 2019 SITT initiators.

Risk factors among patients with COPD initiated on SITT or MITT (MedicineInsight)

- Among patients who initiated SITT:
 - 24.6 % were current smokers and 62.5% were past smokers
 - 23.4% were overweight and 31.2% were obese
 - 84.4% had an influenza vaccine recorded within the previous 2 years
 - Significantly more initiators in 2018 had an influenza vaccine recorded in the past 2 years (89.5%) than later initiators in 2019 (79.1%)

- 44.6% had a pneumococcal vaccine recorded in the previous 5 years (although some patients may not have 5 years of history at the practice and may have received a vaccine from another provider)
- Compared with patients who initiated SITT, among patients who initiated MITT:
 - more were non-smokers (16.6% MITT, 11.0% SITT)
 - more were obese (34.8% MITT, 31.2% SITT)
 - influenza vaccine coverage was lower (78.7% MITT, 84.4% SITT)
 - pneumococcal vaccine coverage was lower (37.4% MITT, 44.6% SITT)

Comorbidities among patients with COPD initiated on SITT or MITT (MedicineInsight)

- Among patients who initiated SITT:
 - 45.9% had a recorded diagnosis of asthma
 - 45.4% had GORD
 - 42.6% had osteoarthritis and
 - 37.7% had depression
- Compared with patients who initiated SITT, among patients who initiated MITT the prevalence of the selected conditions was similar, except for asthma which was more prevalent (51.9% MITT vs 45.9% SITT).

Most recent maintenance therapy prior to SITT among patients with COPD

- In both the MedicineInsight and PBS studies MITT was the most frequently recorded COPD maintenance therapy immediately prior to initiating SITT (41.9% MedicineInsight data; 34.6% PBS data), followed by dual therapy (33.6% MedicineInsight data; 30.8% PBS data) and monotherapy (10.9% MedicineInsight data; 19.5% PBS data). 13.6% of the MedicineInsight SITT cohort and 15.1% of the PBS SITT cohort had no COPD maintenance therapy recorded in the 12 months prior to initiation with SITT.
- When broken down by the type of COPD regime utilised most recently prior to initiation of SITT:
 - in the MedicineInsight study MITT (41.9%) was most frequently recorded, followed by combinations of ICS/LABA (17.2%), LAMA/LABA (15.7 %) and monotherapy with a LAMA (8.9%).
 - in the PBS study MITT (34.6%) was most frequently recorded, followed by combinations of LAMA/LABA (16.8 %), ICS/LABA (13.1%) and monotherapy with a LAMA (17.7%).
- The pattern of most recent COPD maintenance therapy in the PBS 10% sample data was similar to that seen in the MedicineInsight data, with some notable differences. While MITT was also the most frequently recorded therapy prior to initiating SITT proportionally fewer patients in the PBS data were on MITT (34.6% PBS vs 41.9% MedicineInsight) and more patients in the PBS data were on monotherapy with a LAMA (17.7% PBS vs 8.9% MedicineInsight). A similar proportion of patients had no record of prior COPD maintenance therapy in the 12 months prior to initiating SITT (15.1% PBS vs 13.6% MedicineInsight).

Stratification by patient factors

- For patients in the youngest age group (35-44 years) the most frequently recorded COPD maintenance therapy immediately prior to initiating SITT was:
 - MedicineInsight study: dual therapy with ICS and LABA (39.6%), followed by triple therapy (22.9%) and no therapy (22.9%).
 - PBS study: triple therapy (25.7%) followed by dual therapy with ICS/LABA (24.3%), no therapy (21.6%) and dual therapy with LAMA/LABA (9.5%).
 - No other significant differences were evident for the other age groups
- Concession card holders were more likely than general patients (i.e. non-concession card holders) to be dispensed MITT prior to SITT (MedicineInsight 43.2% vs 36.8%; PBS 35.8% vs 27.4%) and less likely to be on no therapy prior to SITT (MedicineInsight 12.0% vs 20.4%; PBS 13.9% vs 21.9%).
- There was some evidence that patients with osteoporosis were more likely to be on MITT and less likely to be on no maintenance therapy prior to SITT than the total SITT cohort (MedicineInsight).
- Patients with the lowest CCI score were more likely to have no COPD medicine recorded prior to initiating SITT than the total SITT cohort (MedicineInsight).
- Patients with evidence of 3 or more AECOPD episodes were most likely, and patients with no record of an exacerbation or pneumonia were least likely, to be prescribed MITT immediately prior to initiating SITT. Conversely patients with evidence of 3 or more AECOPD episodes were least likely, and patients with no record of an exacerbation or pneumonia were most likely, to have no therapy recorded prior to initiating SITT (MedicineInsight).

Exacerbations of COPD and pneumonia (MedicineInsight)

- The rate of AECOPD in patients initiated on SITT was 0.68 per year, compared to 0.45 episodes per year in patients initiated on MITT. Previous studies have estimated rates of AECOPD to be from as low as 0.5 episodes per year, up to 3.5 episodes per year.⁸ However, using a well-defined cohort of patients with COPD, a more recent study has reported rates of between 0.85 and 1.30 episodes per patient per year, with a rate of 1.20 mild to moderate AECOPD episodes per patient per year.⁹
- Details of hospitalisations, clinical notes from specialist practitioners, and patient progress notes are not available from the MedicineInsight data for analysis. Therefore these results only relate to exacerbations managed, or recorded, at the general practice, which is likely to result in the underestimation of exacerbations and potential misclassification of exacerbation status.
- Patients with COPD initiated on SITT were more likely to have evidence of at least one acute exacerbation of COPD or pneumonia in the 24-month period before initiating therapy, than patients initiating MITT (40.9% versus 31.7%, respectively).
- Patients with COPD initiating SITT were more likely to have 3 or more AECOPD recorded in the 24-month period before initiating therapy, than patients initiating MITT (15.5% versus 7.8%, respectively).

Assessment of appropriate use of SITT according to PBS criteria

According to the PBS clinical criteria when SITT was first PBS listed, patients must either have been stabilised on MITT prior to initiating SITT or they must have a history of repeated exacerbations despite being on dual therapy with a LAMA and LABA or an ICS and LABA. The updated PBS criteria specify the minimum number of exacerbations while on dual therapy to qualify for subsidy as at least one severe exacerbation requiring hospitalisation or at least two moderate exacerbations.

As severe exacerbations resulting in hospitalisations could not be identified in MedicineInsight, and medicines prescribed by specialists or other prescribers outside MedicineInsight are not captured this study might overestimate the proportion of patients who do not meet the PBS criteria. With that in mind according to the information recorded in MedicineInsight:

- The majority of patients who initiated SITT satisfied the PBS clinical criteria.
- just under a quarter of patients who initiated SITT did not satisfy the PBS clinical criteria as they were on monotherapy (10.9%) or no COPD maintenance therapy (13.6%) prior to initiating SITT.
- a further 20.0% of patients who initiated SITT did not satisfy the PBS clinical criteria because they had previously been on dual therapy with either a LAMA and LABA or an ICS and LABA but didn't have evidence of an exacerbation recorded in the 24 months before initiating SITT.

According to the information available in the PBS dataset:

- just over a third of patients who initiated SITT did not satisfy the PBS clinical criteria as they were dispensed monotherapy (19.5%) or no COPD maintenance therapy (15.1%) prior to initiating SITT.

CONCLUSIONS

Using both general practice and PBS dispensing data, this study has provided evidence of real-world use of SITT in Australia post-PBS listing, in comparison with new users of multiple-inhaler triple therapy (MITT) in the same time period. Though there were some limitations, particularly with regards to the ascertainment of exacerbations, the data from MedicineInsight and the PBS 10% sample have provided a comprehensive description of uptake of SITT and MITT in general practice in the Australian setting.

There remain a substantial number of patients who continue to be prescribed MITT, even following the PBS listing of SITT. The reasons for this are not possible to discern from this data and would require future studies such as a survey of GPs examining knowledge, attitudes and behaviours with regards to COPD medicines and management.

The differences in initiation of SITT versus MITT among GPs versus specialist is notable. This aligns with the idea that specialists tend to be earlier adopters of new medicines within their speciality area. Their role as opinion leaders and therefore influencers of GP prescribing is also important. For example, if a patient is referred to a specialist or has a hospital admission and comes back to see the GP after initiation on SITT, this may strongly influence subsequent prescribing.

There are important findings about the assessment of appropriate use of SITT according to PBS criteria. The majority of patients who initiated SITT were found to meet the PBS criteria. However, that a significant proportion of the SITT cohort of patients had been previously stabilised on MITT, and that 15.1% of patients had no record of PBS-dispensed COPD maintenance therapy prior to initiation of SITT is notable. There were also a number of patients who transitioned from LAMA monotherapy directly to SITT, suggesting inappropriate step-up prescribing in some cases. Even allowing for an underestimate of the number and rate of AECOPD in the patient cohorts, the results of this study suggest that there are a proportion of patients being prescribed SITT who may not qualify under the current PBS criteria.

While an assessment of MITT use according to PBS criteria was not within the scope of this report, there was evidence that exacerbation rate was lower in the MITT population, compared to patients who were initiated on SITT, which may suggest that the PBS criteria play a role in GP selection of SITT for COPD patients.

The findings indicate a need for further education and support, particularly for GPs, with regards to the management and treatment of COPD in accordance with clinical guidelines and reimbursement criteria.

This study was granted ethical approval from the RACGP NREEC (NREEC 20-004) on 27 May 2020.