Study Protocol

Predictors of treatment choice in patients with COPD

A retrospective observational cohort study that investigates predictors of initial treatment choice in COPD patients.

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TITLE	Predictors of treatment choice in patients with COPD
Subtitle	A retrospective observational cohort study that investigates predictors of initial treatment choice in COPD patients.
Protocol version number	V1.0
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Study aims and objectives	This study aims to examine the changes in prescriptions patterns over time, in order to determine the potential driving factors behind GP prescribing for newly diagnosed COPD patients. The objective of the study is to highlight predctors over time in GP prescription of: • any initial COPD therapy vs. • no COPD therapy **and** • maintenance therapy versus • short-acting agents/no therapy
Country of study	United Kingdom
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1.0 Background

Currently COPD places a high burden on the National Health Service (NHS) in the UK. Current international guidelines for COPD recommend long-acting inhaled bronchodilators, including b2-agonists (LABA) and antimuscarinic agents (LAMA) on a regular basis as monotherapy or in combination with inhaled corticosteroids (ICS) for the symptomatic management of COPD and the prevention of exacerbations. However, it is now widely agreed upon that prescription patterns for Chronic Obstructive Pulmonary Disease (COPD) do not follow international guidelines that are based on randomized clinical trials (RCTs) and more evidence is needed to understand why there is a significant dissociation between guideline recommendations and clinicians' practice.

There is an abundance of literature available from large scale primary care database that provides information on how COPD patients are treated real-life. Indeed a paper recently published by Research in Real Life (RiRL)[4] gives comprehensive real world findings of how COPD patients are currently being managed with pharmacological therapy. The study reflected that some patients receive no treatment despite experiencing symptoms. Among those on treatment, most received ICS irrespective of severity of airflow limitation, asthma diagnosis, and exacerbation history. Many patients on treatment continued to have symptoms. This highlights the persistent uncertainties of physicians and emphasized that more efforts are required to improve education on and the implementation of COPD guidelines regarding COPD therapies.

Therefore, this study aims to take the work further by exploring the predictors of such prescribing. There may be several reasons for the discrepancy between guidelines and clinical practice including the limited encouragement to implement Guidelines in clinical practice and the individual clinician seeing the Guidelines as an interference to their own clinical judgement. This study will eplore in further detail the potetial predictors in GP prescribing to determine what could be the driving factors behind GP prescribing to COPD patients (espcially in those patients who do not warrant the treatment prescribed).

2.0 Study Overview

2.1 Study aims & objectives

This study aims to examine the changes in prescriptions patterns over time, in order to determine the potential driving factors behind GP prescribing for newly diagnosed COPD patients.

2.2 Study design

A retrospective observational database study using the Optimum Patient Care Research Database. The data utilised in this study ranges from 1997 – 2013. Eligible patients must have a minimum of one year of data prior to their initial date of COPD diagnosis for baseline period, and a minimum of two years of data post their initial COPD diagnosis for outcome period to assess patient characteristics and pharmacological treatment prescriptions.

Cohorts will chosen to assess how prescription patterns have changed over time and if certain factors such as the introduction of QoF[1] in 2004 and Tiotropium (LAMA) becoming licensed in UK in January 2002 influence prescribing behaviour.

Patients will split into three cohorts based on their date of initial COPD diagnosis:

- 1997 – 2001
- 2002 – 2006
- 2007 – 2010

COPD initial therapy will be defined as pharmacological therapy prescribed during one year prior to and at the initial date of COPD diagnosis (baseline period). COPD therapies will be grouped by treatment class:

- Inhaled corticosteroid (ICS),
- long-acting β_2-agonist (LABA),
- long-acting muscarinic antagonist (LAMA),
- short-acting β_2-agonist (SABA),
- short-acting muscarinic antagonist (SAMA) (in single, dual or triple therapy
- Other respiratory pharmacological therapies (theophylline)
- None (no prior baseline pharmacological therapy).

To identify possible drivers of treatment choice, analyses will be conducted in subgroups according to:

- Year of initial COPD diagnosis
- Comorbid asthma diagnosis
- Lung function grade (GOLD stage 1, 2, 3 or 4 [2])
- mMRC dyspnea scale score
- Baseline exacerbation rate.

3.0 Study population

3.1 Inclusion and exclusion criteria

Inclusion criteria
COPD diagnosis with QoF approved read codes
Age ≥ 40 years
Patients have one year of practice data prior COPD diagnosis and 2 years of practice data after COPD diagnosis
Spirometry data supportive of a COPD dx in the 5 year window around date of diagnosis. Patients must be diagnosed within the last 15years
Exclusion criteria
Patients aged less than 40 at diagnosis
No valid spirometry data available
Patients diagnosed earlier than 1997

Table 1: Inclusion and exclusion criteria

3.2 Data source

The study will use patient data from the Optimum Patient Care Research Database (OPCRD). The study team work with fully anonymised data, removed of any patient identifiable information. The OPCRD is developed, maintaned and owned by Optimum Patient Care, a social enterprise company that aims to improve patient outcomes through medical research and services. OPC provides evidence based reccomendations to UK general practices through bespoke software and practice reports.

The OPCRD currently comprises longitudinal medical records for over 2.2 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data:

- routinely recorded clinical data and
- questionnaire responses from over 40,000 respiratory patients.

The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life and unique adherence measures. Indeed the OPCRD is the only database in the UK which compliments routinely recorded disease coding and prescribing information with patient reported outcomes. OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). It is governed by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG) to govern the standard of research conducted on internationally renowned databases. All research using OPCRD will be registered on recognised study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

4.0 Study variables and study outcomes

4.1 Demographic and baseline variables

Refer to Appendix for mock tables of demographic and baseline variables.

4.2 Primary outcome

Predictors of initial treatment patterns

Primary outcome will identify predictors of GP prescribing behaviour when treating newly diagnosed COPD patients with their first pharmacological therapy. It will assess the odds of being prescribed:

- any initial COPD therapy vs.
- no COPD therapy

A further analysis will be conduted in regard to the odds of being prescribed:

- maintenance therapy versus
- short-acting agents/no therapy

4.3 Secondary and exploratory outcomes

Initial treatment patterns

To obtain the data required for exploring the primary outcomes, exploratories will be conducted to investigate the distribution of COPD pharmacological therapy in the main potential predictors (see appendix for full list). Results will be summarised and tested using chi-square to identify whether variation occurs among the categories.

5.0 Statistical analysis

5.1 Software used and power calculation

Baseline patient characteristics and outcome analysis (Logistic Regression) will be carried out using SPSS version 20[2], SAS version 9.3 and Microsoft Office EXCEL 2007.

5.2 Significance testing

Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \leq p < 0.10$.

5.3 Baseline characterisation

Summary statistics will be produced for all baseline and outcome variables (see appendix), as a complete dataset and by treatment groups. For variables measured on the interval or ratio scale, these will include:

- Sample size (n)
- Percentage non-missing
- Mean
- Variance / Standard Deviation
- Range (Minimum / Maximum)
- Median
- Inter-quartile Range (25th and 75th percentiles)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Range (if applicable)
- Count and percentage by category (distribution)

5.4 Analysis of study outcomes

COPD initial treatment patterns

Logistic regression analysis for all patients receiving first COPD therapy. This analysis will be conducted on:

a. All patients receiving first COPD therapy
b. The subgroup of patients who receive their first therapy on their date of COPD diagnosis

This will be carried out as follows:

Investigate the COPD therapy distribution of by the following main potential predictors:

a. Year of initial COPD diagnosis (1997-2001; 2002-2006; 2007-2010)

b. Presence of co-morbid asthma diagnosis

c. Lung function grade (please note that GOLD stage 2 will be used as the reference). This will also be repeated for the earlier analysis investigating predictors of initial therapy choice for all patients receiving first COPD therapy

d. mMRC score

e. Annual exacerbation rates

f. GOLD group with the following comparisons:
   - B vs A
   - D vs C
   - A+B vs C+D

For each potential predictor consider:

- the distribution of initial COPD therapy (number and percentage of patients and bar chart) will be summarised

- Need to test to see if it varies among the categories of each potential predictor with a chi-square.

Predictors of initial COPD treatment

Evaluate how the potential predictors outlined above could affect the choice of initial COPD therapy in terms of:

a. Odds of being prescribed any initial COPD therapy vs. no therapy

For each potential predictor:

- The distribution of initial COPD therapy (yes/no) (number and percentage of patients and bar chart) will be summarised and a test to see if it varies among the categories of each potential predictor with a chi-square will be completed.

- Odds ratios (ORs) with their 95% confidence intervals (CIs) will be calculated using an univariable logistic regression model and a multivariable logistic regression model with stepwise reduction to derive best-fitting model of non-collinear predictors

- Presence of co-morbid asthma diagnosis used both as adjustment and as stratification variable (two multivariable models)

- Collinearity analysis on all potential predictors and confounders

b. Odds of receiving initial COPD maintenance therapy vs. short-acting agents/no therapy

For each potential predictor:

- The distribution of initial COPD maintenance therapy (yes/no) (number and percentage of patients and bar chart) will be summarised and tested to see if it varies among the categories of each potential predictor with a chi-square.

- Odds ratios (ORs) with their 95% confidence intervals (CIs) will be calculated using an univariable logistic regression model and a multivariable logistic regression model with stepwise reduction to derive best-fitting model of non-collinear predictors

- Presence of co-morbid asthma diagnosis used both as adjustment and as stratification variable (two multivariable models)

- Collinearity analysis on all potential predictors and confounders

Refer to Appendix for mock tables of secondary/exploratory outcome results.

6.0 Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu.

7.0 Data dissemination

Initial results will be presented in poster and/or oral format at The Respiratory Effectiveness Group's (REG) International Summit. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine. Submission for publications will be made as soon as the analyses are completed and the results are verified.

8.0 Advisory group

Rupert Jones, Guy Brusselle, Kevin Gruffydd-Jones, Marc Miravitlles.

9.0 Research team

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10.0 Timelines

Action	Timeline
Protocol final definition	1 week
Data extraction	1 weeks
Baseline analysis (stage I)	2 weeks
Baseline report writing	2 weeks
Outcome analysis (stage II)	4 weeks
Final report writing	7 weeks
First draft of paper	4-6 weeks from final report

11.0 References

[1]Optimum Patient Care. ADEPT committee approval. Available at *http://www.optimumpatientcare.org/Html_Docs/adept.html*

[2] Quality and Outcomes Framework. Available at http://www.qof.ic.nhs.uk/

[3] Research in Real Life. Available at http://rirl.org/

[4] Price D, West D, Brusselle G et al 2014. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. Internation Journal of COPD 2014; 9:889-905

[5] Global initiative for chronic Obstructive Lung Disease (GOLD 2015). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2015. Available at http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015.pdf

12.0 APPENDIX

12.1 Appendix 1: Definitions

Variable Name	Description	Time Period
Year of COPD diagnosis	Year of First COPD diagnosis	n/a
IDD Cohort	Year of first COPD diagnosis split into three cohorts: 1997 -2001, 2002 - 2006, 2007 - 2010	n/a
Age	Age at COPD diagnosis	n/a
Gender	Gender of patient: Male, Female	n/a
Smoking Status	Smoking status recorded in routine medical notes closest to date of COPD diagnosis	Closest to date of COPD diagnosis
Body Mass Index (BMI)	BMI defined as: Underweight = < 18.499, Normal = ≥ 18.50 - 24.99, Overweight = ≥ 25.00, Obese = ≥30.00	Closest to date of COPD diagnosis
Exacerbation Rate	Exacerbations were defined as:	Calculated during the year prior to and including the date of COPD diagnosis.
	(i) COPD-related hospital admissions or Emergency Department attendance;	
	(ii) use of acute oral steroids;	
	(iii) General practitioner consultations for lower respiratory tract infections.	
	Two exacerbations occurring within 2 weeks of one another were counted only once.	
mMRC Score	mMRC scores were based on the 5-point 162 scale of the British Medical Research Council questionnaire assessing perceived breathlessness. Combined mMRC score from either routine medical notes or questionnaire data if available.	Closest to date of COPD diagnosis
Lung Function Group	Lung function grade was calculated using GOLD Stage 1, 2, 3 and 4 criteria	Closest to date of COPD diagnosis
Asthma Diagnosis	Presence / absence of a co-morbid diagnosis of Asthma in routine medical notes	Closest to date of COPD diagnosis
Rhinitis Diagnosis	Presence / absence of a co-morbid diagnosis of Rhinits in routine medical notes	Closest to date of COPD diagnosis
Gastroesophageal reflux disease (GERD)	Presence / absence of a co-morbid diagnosis of GERD in routine medical notes	Closest to date of COPD diagnosis
Heart Failure	Presence / absence of a co-morbid diagnosis of Heart Failure in routine medical notes	Closest to date of COPD diagnosis
Chronic Kidney Disease	Presence / absence of a co-morbid diagnosis of Chronic Kidney Disease in routine medical notes	Closest to date of COPD diagnosis
Osteoporosis	Presence / absence of a co-morbid diagnosis of Osteoporosis in routine medical notes	Closest to date of COPD diagnosis

Diabetes	Presence / absence of a co-morbid diagnosis of Diabetes in routine medical notes	Closest to date of COPD diagnosis
Anxiety - Depression	Presence / absence of a co-morbid diagnosis of Anxiety - Depression in routine medical notes	Closest to date of COPD diagnosis
Chronic Renal Failure	Presence / absence of a co-morbid diagnosis of Chronic Renal Failure in routine medical notes	Closest to date of COPD diagnosis
Ischaemic Heart Disease	Presence / absence of a co-morbid diagnosis of Ischaemic Heart Disease in routine medical notes	Closest to date of COPD diagnosis

Table 1: Full list of demographic, baseline and outcome variables to be examined in the study

12.2 Appendix 2: Mock baseline results tables

Characteristics	Total Study Population	Initial date of COPD diagnosis cohort **1997-2001**	Initial date of COPD diagnosis cohort **2002-2006**	Initial date of COPD diagnosis cohort **2007-2010**
Age, years, median (IQR)				
Gender, Male				
Smoking Status				
Non Smoker				
Ex-Smoker				
Current Smoker				
Body Mass Index (BMI)				
Underweight				
Normal Weight				
Overweight				
Obese				
Lung Function Grade				
1				
2				
3				
4				
GOLD Risk				
A				
B				
C				
D				

Table 2: Example table of how baseline findings will be presented

12.3 Appendix 3: Mock outcome results tables

		Initial Therapy		Total	p value*
		No	Yes		
Year of Initial Diagnosis	1997-2001 2002-2006 2007-2010				
	Total				
Comorbid Asthma Diagnosis	Yes No				
	Total				
mMRC Score	1 2 3 4 5				
	Total				
Annual Exacerbations	0 1 2 3+				
	Total				
Lung Grade	I II III IV				
	Total				
GOLD Risk	A B C D				
	Total				

Table 3: An Example of how Baseline data by Initial Therapy Indicator will be presented

	Reference Category	Category	Odds* of being prescribed any initial therapy		
			OR (95% CI)	p-value	Overall p-value
Comorbid asthma diagnosis	NO	YES	3.88 (3.43, 4.40)	<0.001	<0.001
Lung grade	II	I	0.87 (0.78, 0.97)	0.009	0.001
		III	1.10 (1.01, 1.20)	0.038	
		IV	1.13 (0.95, 1.36)	0.174	

mMRC score	0	1	1.17 (1.05, 1.31)	0.005	<0.001
		2	1.22 (1.08, 1.38)	0.001	
		3	1.26 (1.10, 1.46)	0.001	
		4	1.40 (1.12, 1.75)	0.003	
Annual exacerbation rate	0	1	2.33 (2.12, 2.56)	<0.001	<0.001
		2	3.60 (3.03, 4.27)	<0.001	
		≥3	4.62 (3.75, 5.69)	<0.001	

Table 4: An example of how findings from logistic regression modelling will be presented