Characteristics of Newly Diagnosed COPD Patients treated with Triple Inhaled Therapy by General Practitioners: a Real World Italian Study.

Fabiano **Di Marco**[1], Pierachille **Santus**[2], Silvia **Terraneo**[1], Elena **Peruzzi**[3], Elisa **Muscianisi**[4], Claudio **Ripellino**[5], Valeria **Pegoraro**[6]

COPD new patients and triple therapy: a RWE Italian Study

[1] Department of Medical Sciences. Università degli Studi di Milano. Respiratory Unit. San Paolo Hospital, Milan, Italy

[2] Department of Medical Sciences. Università degli Studi di Milano. Pulmonary Rehabilitation Unit. Fondazione Salvatore Maugeri, Scientific Institute of Milan-IRCCS. Milan, Italy.

[3] Epidemiology and Outcome Research Manager . Novartis Italia. Origgio (VA), Italy.

[4] Medical Franchise Leader Respiratory. Novartis Italia. Origgio (VA), Italy.

[5] Real World Evidence Consultant. IMS Health Information Solutions Italy srl. Milan, Italy.

[6] Real World Evidence Consultant. IMS Health Information Solutions Italy srl. Milan, Italy.

33   **Corresponding Author**

34   Valeria Pegoraro

35   vpegoraro@it.imshealth.com

36   IMS Health Information Solutions Italy S.r.l.

37   Via Fabio Filzi 29, 20124 Milan, Italia

38   Phone: +39 02 69 78 6237|| Fax: +39 02 70 03 9919

39   **Abstract**

40

41   Factors predicting prescriptions of triple therapy were investigated in a large group of

42   general practitioners (GPs) in Italy. In the population treated by identified GPs, a cohort of

43   newly diagnosed COPD patients was extracted from IMS Health Longitudinal Database

44   during the period 2010-2013. From the diagnosis, one-year follow-up was evaluated.

45   32,046 newly diagnosed COPD patients were evaluated (57.7% male, mean age 67 years).

46   During two years prior to diagnosis less than 13% of patients were requested with a

47   pulmonology evaluation and less than 5% with a spirometry; 65.1% cases were prescribed

48   with a respiratory drug, which in 9.6% of cases was inhaled corticosteroid/long-acting β_2-

49   agonist fixed-dose combination (ICS/LABA FDC). 2,028 patients (6.3% of the newly

50   diagnosed COPD patients) were treated with triple therapy during the first year of follow-

51   up, whose 858 (42.3%) starting immediately, and 762 (37.6%) following an initial

52   treatment with ICS/LABA FDC.

53   Being older, being requested with pulmonologist evaluation or spirometry, being

54   prescribed with a ICS/LABA FDC at diagnosis resulted independent predictors of triple

55   therapy use.

56

57   *Keywords:* COPD; triple therapy; Fixed Dose Combinations (FDC); LABA; ICS

58

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable

disease, characterized by persistent airflow limitation that is usually progressive and

associated with an enhanced chronic inflammatory response to noxious particles or gases

in the airways and lungs. Exacerbations and comorbidities contribute to the overall

severity of patients[1,2]. The destruction of lung parenchyma, increased by subtended

inflammatory processes, leads to loss of alveolar attachments to the small airways and

decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to

remain opened during expiration[3]. COPD management is a major healthcare problem, and

numerous recommendations/guidelines were created to increase appropriateness hence

to address the unmet need of patients remaining symptomatic, so to improve patients'

benefit and reduce exacerbations risk[3,4]. International recommendations, such as the

GOLD document, and national guidelines such as the ones provided by Agenas (Italian

National Agency for Regional Health Care Services), provide guidance to physicians in

treating COPD[4]. Once COPD is diagnosed and its severity is established, pharmacological

treatment aims primarily to improve dyspnea and quality of life, to prevent disease

progression and exacerbations, and to reduce mortality[5]. Inhaled long-acting

bronchodilator therapy consists of long-acting β_2 agonists (LABAs), and/or long-acting

muscarinic antagonists (LAMAs)[6,7,8,9]. The choice within each pharmacological class relies

on the availability and cost of the medication, and on the patient's response, strictly linked

to severity of symptoms, airflow limitation and rate and severity of exacerbations[3]. Inhaled

corticosteroids (ICS) are usually added as anti-inflammatory agents in case of exacerbation

[10,11,12,13], but, in the fixed association with LABA, they have recently been demonstrated as

less effective in moderate-severe patients if compared to LAMA/LABA association in terms

of prevention of exacerbations[14]. The current GOLD strategy document recommends that

the use of ICS is reserved for patients with severe or very severe airflow limitation and/or

≥2 exacerbations per year (GOLD groups C and D)[5]. This recommendation is based on data

86   from available studies, which indicated that patients with a history of frequent

87   exacerbations were more likely to benefit from ICS treatment. Provided the availability of

88   new compounds, during latter years, the pharmacological treatment of COPD moved

89   towards a more personalized approach, such as targeting the eosinophils, the asthma and

90   COPD overlap syndrome (ACOS) or the so-called phenotype of the frequent exacerbator [15],

91   and bringing triple ICS/LABA/LAMA therapy to phase III[16,17].

92   Nevertheless, despite GOLD recommendations and even more recent evidences

93   underlining the efficacy of LABA/LAMA FDC vs. ICS/LABA fix dose combination (FDC)[14,18],

94   and despite a clear identikit of severe COPD patient possibly benefitting from adequate

95   triple therapy with ICS/LABA/LAMA, ICS and ICS/LABA FDCs are often prescribed in the

96   early stage of the disease[19,20]. Even if national recommendation in Italy suggest

97   GP/specialist interaction, currently GPs are allowed to manage both the diagnosis

98   (requesting spirometry or, in limited cases, performing spirometry themselves), and the

99   treatment of COPD, with the only exception of the prescription of LABA/LAMA FDCs, and

100   roflumilast which need currently specialists' indication.

101   The aim of the present study was to describe newly diagnosed COPD patients

102   according to their characteristics observed during two years prior to diagnosis and to

103   identify factors that could predict progression to triple therapy in the first year after

104   diagnosis in a real-life context of GPs setting in Italy.

Results

From the analysis of IMS Health LPD database, 32,046 newly diagnosed COPD patients have been found, whose 2028 (6.3%) have been treated with triple inhaled therapy in the year of follow-up.

Feature of overall population

Characteristics of the overall cohort are shown in Table 1. The majority of patients were male, with a mean age of 67 years, and the majority of them expressing comorbidities (94.0%): as expected, a high rate of cardiovascular diseases (65.0%) and diabetes (16.8%), but also anxiety, and depression were found (6.3 and 5.8%, respectively). The registration of smoking history was low, since in more than one out of four patients this information was not collected. Moreover, more than one out of four patients presented with obesity (i.e. BMI ≥ 30 Kg/m², Table 1, information registered in 76.4% of cases). In the two years before diagnosis (i.e. pre-selection period), less than 13.0% of patients were requested with a pulmonology evaluation and less than 5% of the patients were requested with a spirometry. It is noteworthy that the same approach was used also for patients treated with at least one respiratory drug in the two years prior to diagnosis (65.1%), since more than 80.0% were not requested a specialist evaluation nor a spirometry (Table 1). 3,069 patients have been treated during the two-year period before diagnosis with ICS/LABA FDC (9.6% of the overall population, and 14.7% of patients prescribed with any therapy, Table 1).

Features of patients treated with triple therapy

At the end of the first year of follow-up period, 2,028 patients (6.3% of the newly diagnosed COPD patients) were treated with triple therapy, whose 858 (42.3%) starting immediately at the time of diagnosis, whilst 762 (37.6%) following an initial treatment

131   with ICS/LABA FDC. Mean time to triple therapy since first COPD diagnosis was estimated

132   in 61±91 days, with median time of 14 days.

133   Results from the comparison between patients initiated to triple therapy within

134   one year since the first diagnosis and those who did not are shown in Table 2. Patients

135   prescribed with triple therapy resulted on average 5 years older, more frequently male,

136   and affected by one or more comorbidities. As described in Table 2, COPD symptoms

137   frequency varied a lot accordingly with being prescribed with triple therapy, with 56.8%

138   and 35.7% of patients with at least one COPD symptoms in the subgroup of patients that

139   went to triple therapy, and in the subgroup of patients who didn't, respectively (P<0.001,

140   Table 2). In the two years before diagnosis, the approach of the GPs resulted different in

141   the two subgroups, since more patients initiated to triple therapy had at least one

142   pulmonologist visit, one spirometry, or have been treated with a respiratory treatment

143   (P<0.001 for all comparisons, Table 2). Also, the proportions of patients who had at least

144   one ICS/LABA FDC prescription at COPD diagnosis resulted very different: among patients

145   prescribed with triple therapy, 762 (37.6%) had at least one ICS/LABA FDC prescription in

146   comparison with 7.7% among those who were not prescribed with triple therapy

147   (P<0.001).

148   Multivariate Cox regression model showed a statistically significant association

149   between triple therapy and all the studied covariates included in the model, with none of

150   them excluded according to the stepwise approach adopted (Table 3). Being so, male

151   patients, elderly patients and patients requested with a pulmonology visit or just a

152   spirometry were more likely prescribed with triple therapy than other patients. Moreover,

153   patients who presented COPD symptoms during the pre-selection period were more likely

154   prescribed with triple therapy, whereas comorbidities presence had the opposite effect.

155   Furthermore, being prescribed with a ICS/LABA FDC at the first COPD diagnosis seemed to

156   be a strong predictor of being prescribed with triple therapy within one year since

157   diagnosis, with a HR of 5.10 (95% CI: 4.65-5.60, Table 3).

Discussion

<u>Main findings</u>

In this large GPs setting, following results were found: 1) symptomatic, males, older patients, patients with less comorbidities and patients prescribed with a pulmonology visit or just a spirometry were more likely prescribed with triple therapy; 2) prescription of ICS/LABA FDC at the time of diagnosis and older age seemed to be the strongest predictors for triple therapy use. 3) in the two years before the diagnosis few patients were requested with a pulmonology evaluation or a spirometry, even if treated with a respiratory drugs.

<u>Interpretation of findings in relation to previously published work</u>

Our newly diagnosed COPD patients' cohort presents demographic characteristics similar to those found in a cohort of patients collected in an analogue real world evidence study conducted in UK[21], with both studies describing a mean age of about 67 years and a mean BMI of 27 kg/m^2 for patients at their first COPD diagnosis. Results in terms of comorbidities are in line with those found by the INDACO study[22], reporting a high prevalence of comorbidities among COPD patients, with more than 80% presenting with at least one comorbidity. Patients with recorded symptoms before being diagnosed with COPD represented 37%. Considering that symptomatology recorded in the database is not mandatory unless leading to a prescription, specialist visit or exam request, this proportion should be regarded as quite high. In addition, it should be kept in mind that the analyzed setting is the one of GPs. Pulmonologist visit including FEV1 evaluation were found just in a small group of patients. Pulmonologists visits and FEV1 evaluations could increase the probability of a better management as well as to a reduced delay in proper diagnosis. In addition patients that had at least one respiratory treatment before diagnosis, represented 65.1% of the total population. Delay in COPD diagnosis by GPs has been confirmed also in previous studies. When comparing results about the proportion of

185 patients prescribed with ICS/LABA FDC at the time of the first COPD diagnosis, results

186 from the present study showed a approximate 10% lower proportion than the one found

187 in the above mentioned UK study (approximately 43%)[21]. It should be taken in account

188 that for the UK study is not specified whether LABA and ICS combinations are fixed,

189 extemporaneous or both, while in the present study only fixed combinations have been

190 evaluated. Nevertheless, when evaluating the proportion of patients that within one year

191 progress to triple therapy among those prescribed with ICS/LABA FDC at the time of first

192 diagnosis, the present study revealed a higher percentage (25% coming from 762 patients

193 over 3,069 prescribed with ICS/LABA FDC *vs.* 17% from UK study). Proportions become

194 more similar when comparing the 25% of patients going to triple therapy within one year

195 (Italy), with the 24% of patients going to triple therapy within two years (UK), leading to

196 the consideration that, probably, Italian GPs are more cautious at prescribing ICS/LBA FDC

197 as a first line therapy, but at the same time the step up in therapy happens faster when

198 compared to the English setting. The rapidity Italian GPs escalate therapy as observed in

199 the present study, could be related to the fact that ICS/LABA are prescribed as fixed dose

200 combinations.

201 The reduced likelihood of being prescribed with triple therapy observed for

202 patients affected by other comorbidities is an interesting finding that should be

203 contextualized in the GPs' setting: research and guidelines on the management of long

204 term conditions have routinely focused on single diseases[23], whilst patients with

205 comorbidities are usually excluded from randomized controlled trials[24]. This has led to

206 individual disease management rather than a more holistic approach that, on the other

207 hand, should be the approach adopted by GPs. The more chronic conditions a patient has,

208 the more medications they are likely to be prescribed[25,26]. Multiple therapies commonly

209 lead to drug disease interaction and drug-drug interactions [27,28,17]: these issues, as well as

210 the fear of adverse drug reactions, are the factors probably preventing GPs' from

211 prescribing triple therapy to patients affected by comorbidities, possibly due to the

212 conception of COPD as less important than other chronic disease (e.g. cardiovascular

213 disease or diabetes). However, drugs for COPD are inhaled, thus much less likely to cause

214 systemic adverse effects and drug interactions than systemic ones.

215

216 <u>Strengths and limitations of this study</u>

217 The large number of patients included in the analysis has to be considered among

218 the study strengths', together with the longitudinal nature of data collected, the

219 generalizability of Italian general practice population, and the usage of validated codes for

220 identifying COPD patients. Among study limitations, it should be addressed that smoking

221 habits information were not considered since in the database data about this issue are not

222 complete. These data confirm a study by Bryant et al., describing that accurate detection of

223 smoking habits occurs in less than two-thirds of all patients, despite significant investment

224 to increase GPs' intervention for lifestyle risk factors[29], even if the possibility that GPs

225 discussed this aspect with their patients without including it in the medical records cannot

226 be ruled out. Moreover, this kind of information in a real practice context could not be

227 reliable due to the fact that, being based on what patients report to the GPs, they are self-

228 reported measures, and it is known that self-reported information about smoking status

229 are biased.[30] The study was also limited by the lack of available information on FEV_1 values,

230 as well as hospitalizations and exacerbations, which would have provided a more

231 comprehensive picture of COPD patients' management and would have allowed a

232 stratification by disease severity. Nevertheless, results from a previous study using the

233 same source of data, where FEV_1 was recorded to define disease severity as per GOLD

234 guidelines, suggest that the presence of FEV_1 value does not constitute a bias: patients

235 resulted to be distributed among disease severity classes, with mild and moderate patients

236 accounting for about 80% of the cohort[31]. Another limitation is the lack of spirometry

237 assessment to diagnose COPD: this approach is common for all "real life" studies, currently

238 proposed also to evaluate the effectiveness of new treatments (Salford study). This bias,

239   which should not affect the interpretation of the results, is in line with the aim to evaluate

240   the behavior of GPs in real clinical practice. Then, "Chronic bronchitis", a condition

241   different from COPD in absence of obstruction, was also included in the analysis, given the

242   term often used as a synonymous for COPD. Finally, the role of GPs is different in several

243   Countries, condition which limits the external validity of our study.

244

245   <u>Implications for future research, policy and practice</u>

246   Even if there is an Italian document/guideline on COPD diagnosis and treatment,

247   the results of our study failed to demonstrate an appropriate management of patients[32]

248   suffering from this disease. In this respect, new campaigns of information are desirable:

249   following such an informative approach, a new study to evaluate whether the approach to

250   COPD has improved is needed, mainly in terms of early diagnosis with spirometry, and

251   appropriate treatment and follow-up. Then, accessibility of spirometry in primary care has

252   to be facilitated.

253

254   <u>Conclusions</u>

255   In the studied population, the choice of treatment is driven by a set of factors that

256   include symptoms, general patients' features as well as functional and specialists

257   evaluation. However, the proportions of patients with a request for a specialist evaluation

258   or a spirometry are still very low. Even if the last version of GOLD document gives a high

259   level of importance to symptoms for the choice of the treatment, the same document

260   underline the importance of spirometry to confirm the diagnosis and to assess the level of

261   the flow limitation. In this setting educational programs should be implemented for GPs in

262   order to optimize the diagnosis treatment and follow up of patients with COPD.

263

264

265   **Methods**

266 <u>Data Source</u>

267   The data used in the present study were retrieved from the Italian General

268 Practitioners' (GPs) IMS Health Longitudinal Patient Database (IMS Health LPD)

269 established in 1998 primarily to carry out epidemiologic studies and to monitor drugs

270 prescriptions and drug safety. The database is fed by a constant representative doctors'

271 sample that agreed to take part to a research panel, has been trained for data entry and

272 uses standard patient management software to collect data directly during the

273 consultations. The information, which is gathered continually and in real time allows

274 patients and doctors to be longitudinally monitored and includes anonymous data about

275 patients' demographics, medical diagnoses, drug prescriptions, hospital referrals,

276 diagnostic investigations, and date of death. Medical diagnoses and drugs prescriptions,

277 both coded directly by GPs, comply with the ninth edition of International Classification of

278 Disease (ICD-9-CM), and the Anatomical Therapeutic and Chemical (ATC) classification

279 system respectively. All medical records are linked together with a unique encrypted

280 patient code. In Italy, IMS Health LPD consists of a panel of about 900 GPs homogenously

281 distributed throughout the national territory; it collects information about 1 million

282 patients per year and it is representative of the Italian general population. IMS Health LPD

283 database reliability has been recognized by the pharmaceutical industry and Medicine

284 Agencies[33].

285

286 <u>Cohort selection</u>

287   Newly diagnosed COPD Cohort was selected in the period from 1 January 2010 to

288 31 December 2013, as patients with a COPD diagnosis, defined as "Chronic bronchitis",

289 "Emphysema" or "Chronic airway obstruction, not elsewhere classified". The presence of at

290 least one registration within the database of one of the abovementioned ICD-9-CM codes

291 was the only criteria to define COPD diagnoses (i.e. not necessarily confirmed by

292 spirometry). In order to identify the first diagnosis, patients with a diagnosis during the

293 previous three-year period were excluded from the analysis. The date of the first COPD

294 diagnosis (i.e. index date) during the selection period was set as the one years follow-up

295 period start.

296

297 <u>Variables analyzed during the pre-selection period</u>

298   For each patient, information about COPD symptoms (see Appendix), spirometry

299 execution, respiratory treatments (see Appendix), comorbidities (defined by means of ICD-

300 9 codes registrations), and pulmonologist visits requests over a two-year period before the

301 first COPD diagnosis (i.e. pre-selection period) were collected and analyzed to characterize

302 patients and used as covariate in the analysis.

303

304 <u>Follow-up and outcomes</u>

305   Each cohort member was followed from the date of first COPD diagnosis until

306 outcome onset (see below), censoring, i.e. death, emigration, or end of follow-up (i.e. 12

307 months after the date of first COPD diagnosis), whichever date occurred earlier. Main

308 outcome (i.e. triple therapy presence during follow-up) was defined as the presence of

309 concomitant prescriptions of LABA, LAMA and ICS. Prescriptions were considered

310 concomitant when the lapse of time between them was less than 30 days. Time to triple

311 therapy was calculated as the difference, in days, between the date of the first prescription

312 that defined a triple therapy presence during the follow up period, and the first COPD

313 diagnosis date.

314

315 <u>Statistical Analysis</u>

316   Newly diagnosed COPD patients were described in terms of demographic, and

317 clinical characteristics; qualitative variables were described using usual statistical

318 methodologies, which are frequencies and percentages, whereas quantitative variables

319 were described in terms of mean±standard deviation. Chi-square test was calculated to

320   compare patients who received triple therapy within one year since the first COPD

321   diagnosis to patients who did not. Comparison was based on presence/absence of

322   respiratory treatments, spirometry execution, pulmonologist visit requests, and COPD

323   symptoms during the pre-selection period and presence/absence of at least one LABA/ICS

324   FDC prescription at the first COPD diagnosis. To evaluate the potential association between

325   triple therapy and factors that could influence the likelihood of being prescribed triple,

326   age, sex, presence/absence respiratory symptoms before diagnosis, comorbidities,

327   pulmonology visit, spirometry and prescriptions LABA/ICS FDC at the first COPD diagnosis

328   were considered in both univariate and multivariate Cox regression models. For

329   multivariate models, each variable had been retained in the final model according to a

330   stepwise approach. A p-value below than 0.15 was the cut-off. For all the above mentioned

331   analysis, p-values below than 0.05 had been considered as statistically significant.

367   **References**

368   1   Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between
369   exacerbation frequency and lung function decline in chronic obstructive pulmonary
370   disease. *Thorax* 2002; **57**: 847–852.

371   2   Schwab P, Dhamane AD, Hopson SD, Moretz C, Annavarapu S, Burslem K *et al.*
372   Impact of comorbid conditions in COPD patients on health care resource utilization
373   and costs in a predominantly Medicare population. *Int J Chron Obstruct Pulmon Dis*
374   2017; **12**: 735–744.

375   3   GOLD. Global strategy for the diagnosis,management, and prevention of chronic
376   obstructive pulmonary disease. Available from http//www.goldcopd.org/ . 2015.

377   4   AGENAS Agenzia Nazionale per i Servizi Sanitari. Broncopneumopatia Cronica
378   Ostruttiva. Linee guida nazionali di riferimento per la prevenzione e la terapia.
379   http//www.agenas.it. .

380   5   Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A *et al.* Combined
381   salmeterol and fluticasone in the treatment of chronic obstructive pulmonary
382   disease: a randomised controlled trial. *Lancet* 2003; **361**: 449–456.

383   6   Jones PW, Willits LR, Burge PS, Calverley PMA, Inhaled Steroids in Obstructive Lung
384   Disease in Europe study investigators. Disease severity and the effect of fluticasone
385   propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J*
386   2003; **21**: 68–73.

387   7   Mahler DA, Wire P, Horstman D, Chang C-N, Yates J, Fischer T *et al.* Effectiveness of
388   Fluticasone Propionate and Salmeterol Combination Delivered via the Diskus
389   Device in the Treatment of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit*
390   *Care Med* 2002; **166**: 1084–1091.

391   8   Jochmann A, Neubauer F, Miedinger D, Schafroth S, Tamm M, Leuppi JD. General
392   practitioner's adherence to the COPD GOLD guidelines: baseline data of the Swiss
393   COPD Cohort Study. *Swiss Med Wkly* 2010. doi:smw-12988.

394   9   Montuschi P, Ciabattoni G. Bronchodilating Drugs for Chronic Obstructive
395   Pulmonary Disease: Current Status and Future Trends. *J Med Chem* 2015; **58**: 4131–
396   4164.

397   10   National Institute for Health and Clinical Eccellence. NICE Clinical Guideline 101.
398   Available from http//www.nice.org.uk/guidance/cg101. 2014.

399   11   American Thoracic Society/European Respiratory Society. Standards for diagnosis
400   and management of patients with COPD. http//www.thoracic.org/clinical/copd-
401   guidelines/resources/copddoc.pdf. 2013.

402   12   Osthoff M, Jenkins C, Leuppi J. Chronic obstructive pulmonary disease – a treatable
403   disease. *Swiss Med Wkly* 2013. doi:10.4414/smw.2013.13777.

404   13   Fuso L, Mores N, Valente S, Malerba M, Montuschi P. Long-acting beta-agonists and
405   their association with inhaled corticosteroids in COPD. *Curr Med Chem* 2013; **20**:
406   1477–95.

407   14   Sannigrahi S, Wang C, Zhou X, Zhang N, Humphries M, Wang L *et al.* LANTERN: a
408   randomized study of QVA149 versus salmeterol/fluticasone combination in patients

with COPD. *Int J Chron Obstruct Pulmon Dis* 2015; : 1015.

15 Lange P, Halpin DM, O'Donnell DE, MacNee W. Diagnosis, assessment, and phenotyping of COPD: beyond FEV$_1$. *Int J Chron Obstruct Pulmon Dis* 2016; : 3–12.

16 Montuschi P, Malerba M, Santini G, Miravitlles M. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping. *Drug Discov Today* 2014; **19**: 1928–35.

17 Montuschi P, Malerba M, Macis G, Mores N, Santini G. Triple inhaled therapy for chronic obstructive pulmonary disease. *Drug Discov Today* 2016; **21**: 1820–1827.

18 Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT *et al.* Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD. *N Engl J Med* 2016; **374**: 2222–2234.

19 Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. *Eur Respir J* 2009; **34**: 13–16.

20 Cazzola M, Molimard M. The scientific rationale for combining long-acting β2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther* 2010; **23**: 257–267.

21 Wurst KE, Punekar YS, Shukla A. Treatment evolution after COPD diagnosis in the UK primary care setting. *PLoS One* 2014; **9**. doi:10.1371/journal.pone.0105296.

22 Fumagalli G, Fabiani F, Forte S, Napolitano M, Balzano G, Bonini M *et al.* INDACO project: COPD and link between comorbidities, lung function and inhalation therapy. *Multidiscip Respir Med* 2015; **10**: 4.

23 Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M *et al.* Prevalence, Determinants and Patterns of Multimorbidity in Primary Care: A Systematic Review of Observational Studies. *PLoS One* 2014; **9**: e102149.

24 Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; **380**: 37–43.

25 Taylor AW, Price K, Gill TK, Adams R, Pilkington R, Carrangis N *et al.* Multimorbidity - not just an older person's issue. Results from an Australian biomedical study. *BMC Public Health* 2010; **10**: 718.

26 Lehnert T, Heider D, Leicht H, Heinrich S, Corrieri S, Luppa M *et al.* Review: Health Care Utilization and Costs of Elderly Persons With Multiple Chronic Conditions. *Med Care Res Rev* 2011; **68**: 387–420.

27 Dumbreck S, Flynn A, Nairn M, Wilson M, Treweek S, Mercer SW *et al.* Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. *BMJ* 2015; **350**: h949–h949.

28 Moffat K, Mercer SW. Challenges of managing people with multimorbidity in today's healthcare systems. *BMC Fam Pract* 2015; **16**: 129.

29 Bryant J, Yoong SL, Sanson-Fisher R, Mazza D, Carey M, Walsh J *et al.* Is identification of smoking, risky alcohol consumption and overweight and obesity by General Practitioner's improving? A comparison over time. *Fam Pract* 2015; : cmv078.

450 30   Avanzini F, Marzona I, Baviera M, Barlera S, Milani V, Caimi V *et al.* Improving
451   cardiovascular prevention in general practice: Results of a comprehensive
452   personalized strategy in subjects at high risk. *Eur J Prev Cardiol* 2016; **23**: 947–955.

453 31   Katz, P. & Pegoraro V. L'utilizzo dei corticosteroidi nei pazienti con la
454   broncopneumopatia cronica ostruttiva: aspetti epidemiologici ed economici.
455   *Farmeconomia e percorsi Ter* 2009; **10**: 179–188.

456 32   Bettoncelli G et al. The clinical and integrated management of COPD: An official
457   document of AIMAR (Interdisciplinary Association for Research in Lung Disease),
458   AIPO (Italian Association of Hospital Pulmonologists), SIMER (Italian Society of
459   Respiratory Medicine), SIMG (Itali. *Sarcoidosis Vasc Diffus Lung Dis* 2014; : 3–21.

460 33   AIFA. L'uso dei farmaci in Italia - Rapporto OsMed 2012. Osservatorio nazionale
461   dell'impiego dei medicinali. *Rapp Naz*
462   2012.http://astrid.eu/farmaci/Rapporti/RAPPORTI-O/osmed2001.pdf.

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