Pharmacological treatment optimisation for stable COPD: an endless story?

Proposals from the Société de Pneumologie de Langue Française

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In recent years, several global and local guidelines, recommendations and proposals on chronic obstructive pulmonary disease (COPD) management have been published [1–14]. They illustrate the great interest in this disease that, although no cure exists, is no longer considered untreatable. They also reflect its major and growing burden from both public health and individual perspectives. Finally, they parallel the increasing knowledge of its pathophysiology, clinical characteristics and natural history, as well as of treatment effects, with the goal of personalising care as much as possible. Here, we aim to present recent proposals of the French-Language Respiratory Society (Société de Pneumologie de Langue Française (SPLF)) and put them in perspective with the similarly recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) document, which represents a major revision of GOLD proposals. It is also crucial to take this opportunity to emphasise here that the story of a guideline does not end with its production: the implementation phase is even more important and truly never ends until the next guideline, resulting in an endless cycle.

Background

In 2011, the GOLD document introduced a major change in the proposed way to assess and treat patients with COPD: the new paradigm was based on a combined assessment scheme in which patients were allocated to one of four quadrants (A, B, C and D) depending on their level of symptoms and clinical impact, their risk of exacerbations determined by their exacerbation history and forced expiratory volume in 1 s (FEV_1)-defined grade of airflow limitation. Symptoms and clinical impact were to be assessed by the modified Medical Research Council (mMRC) dyspnoea scale and/or the COPD Assessment Test (CAT), to which the Clinical COPD Questionnaire (CCQ) was subsequently added [15]. This represented an advance

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through the formal introduction of clinical parameters in the recommended assessment process. However, several aspects of this proposition were challenged, including the lack of firm evidence linking this classification to treatment effects, the unclear concordance between mMRC and CAT cut-offs to distinguish patients with low *versus* high impact or symptom burden, and the heterogeneity of the magnitude of increase in exacerbation risk depending on the considered criteria (low lung function, exacerbation history or both). As a consequence, several scientific societies and groups developed alternative classifications or kept following their previous therapeutic recommendations. This applied to SPLF, which continued advocating the use of its 2009–2010 COPD guidelines, which were actually very close to the previous GOLD document [13, 16, 17]. During the five following years, a considerable body of evidence on the relevance and drawbacks of the GOLD ABCD categorisation scheme accumulated, ultimately leading to the major 2017 revision in which FEV_1 disappeared as a criterion to define exacerbation risk, due to the marked preponderance of exacerbation history as a predictor of future exacerbation risk [18] and the strong will towards simplification. In parallel, all guidelines kept reinforcing the key role of nonpharmacological interventions (especially help towards smoking cessation and physical activity) in COPD management and increasingly recognised the importance of integrating the treatment of comorbid conditions in COPD care. In 2014, GOLD and the Global Initiative for Asthma released a common document formalising the concept of asthma–COPD overlap (ACO) syndrome, defined as an entity featuring characteristics of both asthma and COPD in a roughly equivalent proportion. Other, more precise definitions were proposed subsequently, and again, significant amounts of data on the topic have accumulated since the first appearance of the term ACO syndrome in the medical literature [19].

The SPLF, considering the evolution of COPD treatment paradigms and the constantly increasing amount of results from studies on new medications, decided in 2014 to develop an update of its position on how to optimise pharmacological therapy in patients with COPD. This update was released at the end of 2016 [13], roughly at the same time as the 2017 GOLD update [12].

The development of these proposals was based on expert opinions informed by an extensive literature review. A working group composed of the authors of this editorial reviewed the literature published between January 2009 (date of the previous recommendations from the SPLF) and May 2016, with an appraisal of all the abstracts published in Medline or in the Cochrane library. The search terms used were "COPD [MeSH]" in association with "therapeutics [MeSH]", "therapy", "drug therapy [MeSH]" or "treatment outcome [MeSH]". Randomised trials and meta-analyses published in English and French were selected. Only the medications available in France at the end of December 2016 were discussed. The proposal was reviewed by a panel of pulmonologists and general practitioners, and finally, by the scientific committee of the SPLF. Since the process did not rely on a formal Grading of Recommendations Assessment, Development and Evaluation-like methodology, it was decided to qualify the result as proposals rather than guidelines. The mission assigned to the working group was to follow certain basic principles and goals, which are listed below.

1) To aim to format the proposals as a single algorithm covering the most frequent situations and based on patients' characteristics easily accessible to all practitioners caring for patients with COPD, including respiratory specialists and general practitioners with more limited access to repeated spirometry; the purpose here was to present the progression of treatments as a function of the progression of the disease-related clinical burden, given that COPD medications mainly target symptoms with limited impact on the natural history.

2) To develop an alternative presentation of treatments' indications with a tabular format, to adapt to the preferences and functioning of target physicians.

3) To weight the benefit–risk balance to inform proposed therapeutic choices; specifically, to avoid proposing treatment initiation with multiple pharmacological agents in the absence of firm evidence of general superiority over treatment initiation with a single agent.

4) To focus on "pure" COPD, *i.e.* to exclude patients with features of asthma from the target population, in order to avoid confusion. The goal here was to favour a systematic, thorough differential diagnosis process between asthma and COPD. Patients with evidence of asthma features were to be treated following asthma guidelines.

5) As a correlate, to request that the diagnosis is confirmed by spirometry before or soon after treatment initiation.

6) To mention clearly the measures that need to be implemented together with prescription of medications, even if the literature appraisal was restricted to pharmacological treatments.

Proposals

The literature review allowed the identification of several key features of available therapeutic options, which were subsequently used to build the proposals and are summarised here. Several areas of

uncertainty were also identified on the following topics, including: 1) respective effects of long-acting β_2-agonists (LABA) plus long-acting muscarinic antagonists (LAMA) and LABA plus inhaled corticosteroids (ICS) on exacerbations in patients with few symptoms and high risk of exacerbations (GOLD C category); 2) added value of ICS on top of LABA+LAMA; 3) effects of antioxidant mucolytics in patients from non-Asian populations receiving standard inhaled therapy; and 4) optimal duration of preventive macrolide therapy.

Figure 1 presents the resulting proposition of decision-tree, while figure 2 shows corresponding treatment indications. Crucial accompanying measures are summarised in table 1.

Narrative summary

Any COPD diagnosis based on pulmonary function tests (presence of airflow limitation as defined by FEV1/FVC <70%) should lead to smoking cessation counselling, influenza and pneumococcal vaccinations, encouragement of physical activity, pulmonary rehabilitation in the case of activity limitation, and as-needed short-acting bronchodilators for symptomatic relief. The level of symptoms and exacerbation frequency should guide therapeutic choices. In the case of dyspnoea during daily activities (mMRC ⩾1) and/or frequent exacerbations (*i.e.* at least two in a year or one leading to hospitalisation), the recommendation is to start with a single inhaled long-acting bronchodilator

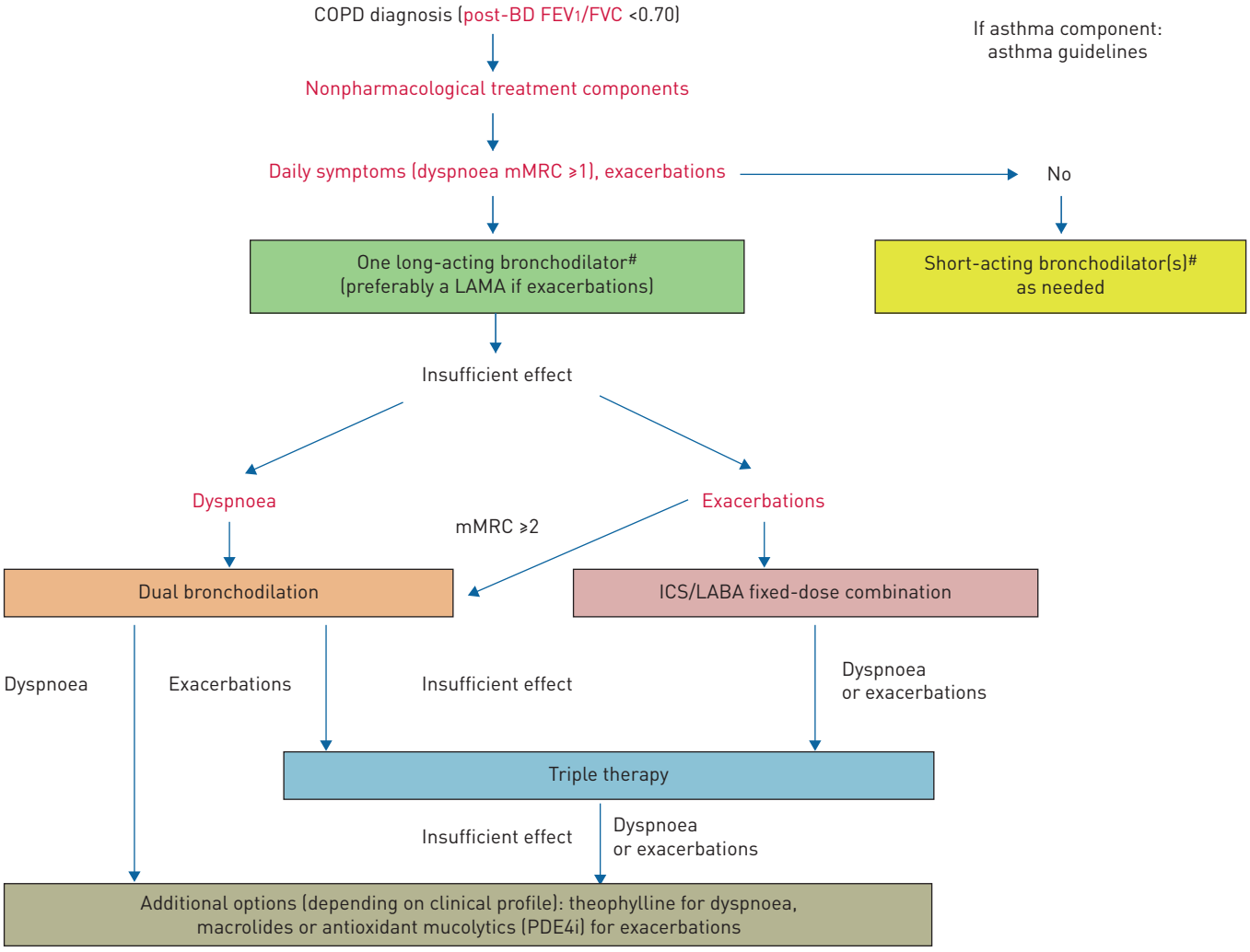

FIGURE 1 Proposed algorithm for the pharmacological therapeutic management of chronic obstructive pulmonary disease (COPD). For patients with exacerbations despite a long-acting bronchodilator but low levels of dyspnoea (modified Medical Research Council (mMRC) score <2), the choice can be either a long-acting β_2-agonists (LABA) plus long-acting muscarinic antagonists (LAMA) or an inhaled corticosteroids (ICS) plus LABA combination. For patients with dyspnoea on two long-acting bronchodilators, applicable components of the lowest box are theophylline and additional rehabilitation (since at this point, these patients should have already undergone rehabilitation as part of the "nonpharmacological treatment components" mentioned at the top of the figure). BD: bronchodilator; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PDE4i: phosphodiestase-4 inhibitors. #: β_2-agonist or anticholinergic.

	Inhaled treatment	Clinical situation
	SABA and/or SAMA	All patients Sole treatment for low-symptoms, low-risk patients
First step	One single long-acting bronchodilator	
	LABA	Dyspnoea during usual activities (mMRC ⩾1)
	LAMA	Dyspnoea or exacerbations
Second step	Two treatments	
	LABA+LAMA	Dyspnoea (mMRC ⩾2) ± exacerbations despite first-step treatment
	LABA+ICS	Exacerbations with no marked dyspnoea despite first-step treatment
Third step	Triple therapy	Exacerbations despite second-step treatment Dyspnoea despite LABA+ICS

FIGURE 2 Pharmacological treatment indications corresponding to the algorithm proposed in figure 1. Steps refer to maintenance therapy, as-needed short-acting bronchodilators being indicated in all patients. SABA: short-acting β_2-agonists; SAMA: short-acting muscarinic antagonists; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists; ICS: inhaled corticosteroids; mMRC: modified Medical Research Council.

(β_2-agonist (LABA) or anticholinergics (LAMA)) rather than with a combination of bronchodilators. In the case of frequent exacerbations, LAMA should be preferred [20]. When symptoms or exacerbations persist, other causes of insufficient therapeutic efficacy need to be investigated (differential diagnosis, comorbidity, poor compliance, incorrect use of inhalation devices or persistent smoking) and lung function needs to be checked to ensure the lack of marked discordance with clinical features that would trigger the search for concomitant conditions (table 1). Then, a dual therapy can be suggested, the combination of two long-acting bronchodilators (LABA+LAMA) being preferred in the presence of more significant dyspnoea (mMRC ⩾2) with or without exacerbations [21, 22]. When the patient has exacerbations but low levels of dyspnoea (mMRC <2), the choice can be either LABA+LAMA or ICS+LABA, since there is no evidence suggesting that data from randomised controlled trials in patients with mMRC ⩾2 can be extrapolated to this population. In addition, the mechanisms by which bronchodilators prevent exacerbations could include decreased baseline airway resistance, stabilisation of bronchial tone or resetting of dyspnoea perception, which could be more prominent in patients with more impaired lung mechanics. Current evidence was not considered sufficient to recommend guiding treatment based on blood eosinophil levels at present, since only *post hoc* analyses suggested that these (with various thresholds) could predict better response to ICS-containing than to bronchodilator-only regimen [23]. The occurrence of pneumonia or other ICS-associated side-effects should cause reconsideration of the need for ICS [24].

Fixed-dose combinations could facilitate better adherence than free combinations (whether LABA+LAMA or ICS+LABA), although this potential benefit still needs to be formally demonstrated. When exacerbations persist despite one of these combinations or when dyspnoea persists on ICS+LABA, a triple combination (LABA+LAMA+ICS) should be tested [25]. Notably, an absence of response to any increase in treatment intensity may lead to a step back or (when possible) switch for another option because of potential side-effects. Other pharmacological treatment options include theophylline for dyspnoea, and macrolides or phosphodiesterase-4 inhibitors (not available in France) for exacerbations [26]. For patients with refractory dyspnoea, defined as persistent chronic dyspnoea occurring at rest or from minimal exertion despite optimal treatment of the disease, low-dose opioids (in the form of sustained-release morphine) can be initiated under close monitoring [27]).

A clinical and lung function re-evaluation, as described earlier, is suggested 1–3 months after any treatment modification and every 3–12 months according to the severity of the disease, and in the case of clinical worsening, leading to the exclusion of other causes of insufficient therapeutic efficacy and differential diagnosis.

From global to local guidelines: adopt or adapt?

As detailed above, SPLF proposals are presented using a single algorithm with no reference to any formal categorisation scheme, which differs from the GOLD document that uses the ABCD quadrants to propose four separate decision trees. Despite these differences, the content is very similar overall, although with two significant differences. Firstly, for patients at risk of exacerbations but mildly symptomatic (GOLD C), SPLF proposes ICS+LABA or LABA+LAMA treatment while GOLD prefers LABA+LAMA (except in patients with features of asthma). It must be emphasised that there has been no direct head-to-head comparison between these two options in this specific group of patients. The GOLD choice is based on the increased risk of pneumonia with ICS in COPD patients, while SPLF refers to trials showing the beneficial effect of ICS+LABA on exacerbations occurrence in patients who are not all symptomatic (since these trials did not require any minimal level of symptoms). Secondly, SPLF proposes to systematically consider a step-by-step approach, rather than initiating the treatment with multiple medication classes as recommended by GOLD for category D patients. This is based on a conceptual belief rather than on firm evidence since there has been no "strategy trial" in naïve patients, comparing various ways of initiating and escalating treatment. Overall, the differences reflect variations in preferences rather than disagreements over evidence interpretation. The same observation could be made when comparing the global GOLD document to various local (national) recommendations all over the world, which all move towards personalised medicine, *i.e.* tailoring treatment to individual patients' characteristics [1–11]. This raises an important question: should local bodies put effort, energy and funds in the development of guidelines when well-documented global proposals already exist, and could be adopted as they are? The proliferation of local initiatives with sometimes subtle, but always real, differences suggests that there is still a need to account for national specificities in terms of presentation preferences, evidence interpretation and clinical practice implications [28]. In other words, to ensure proper implementation of evidence-based guidelines, recommendations or propositions, adaptation may be more effective than pure adoption, since it could improve the way they are perceived, leading to increased adherence of physicians and other stakeholders.

TABLE 1 Measures that should accompany the implementation of pharmacological treatment recommendations

Situation	Action
COPD diagnosis	The diagnosis has to be spirometry-confirmed (post-bronchodilator FEV_1/FVC ratio <0.70)
In all patients	Smoking cessation assistance
	Vaccinations
	Physical activity advised
	Balanced diet
	Rehabilitation if persistent dyspnoea/disability despite appropriate medications
	On-demand short-acting bronchodilator(s) in case of dyspnoea
	Account for the patient's capabilities when choosing an inhalation device
	Reassess 1–3 months after therapy changes, then every 3–12 months
	At least annual lung function testing
If associated asthma	See asthma recommendations
Insufficient effect (persistent dyspnoea/disability and/or exacerbations under maintenance therapy)	Check
	Differential diagnosis
	Smoking cessation
	Pulmonary function
	Compliance/intake technique
	Therapeutic education/rehabilitation
	Comorbid conditions

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Conclusion

Local adaptions of global guidelines may favour their implementation as compared to pure adoption. All guides to the management of COPD agree on the first measures to implement, *i.e.* smoking cessation and encouraging regular physical activity. They also agree on pulmonary rehabilitation, which is indicated as soon as disability persists in daily life despite a bronchodilator treatment. Based on benefit–risk considerations, SPLF proposes a monotherapy with a long-acting bronchodilator as the first-step treatment for all patients, irrespective of their level of symptoms, exacerbations and lung function impairment. Then, if symptoms or and/or exacerbations persist, a second step is recommended with LABA+LAMA or LABA+ICS. A triple combination should be prescribed only as third-step treatment. This choice is based on the relatively limited magnitude of difference between mono-, double and triple therapy in terms of percentages of responders for the main outcome measures. Most importantly, clinical and lung function assessments are recommended on a regular basis and 1–3 months after any therapeutic modification or in case of worsening. Before considering any treatment step-up, possible reasons for treatment failure should be considered including poor adherence, inhaler misuse, persistent smoking and comorbidities. As in the GOLD document, FEV_1 is not present among the criteria considered to decide pharmacological treatment modulation. However, also as in the GOLD document, this does not mean that spirometry is not useful in patients with COPD: it is still required to diagnose the disease, assess its evolution (including the identification of rapid decliners warranting special attention), understand symptoms and treatment effects, and trigger supplemental investigations when there is a discordance with the patient's clinical status.

With respect to future research, effectiveness and safety data from well-conducted "real-world" studies are needed to complement the efficacy data from registration trials with strategies testing. Hopefully, ongoing research might lead to real precision medicine, based on biomarkers reflecting underlying pathophysiological mechanisms and predicting response to current and future treatments. Indeed, future studies should explore whether different maintenance treatments prevent different types of exacerbations (especially eosinophilic *versus* bacterial types) [29]. It is likely that the next generation of recommendations will introduce phenotyping earlier in the therapeutic management of COPD [30].

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