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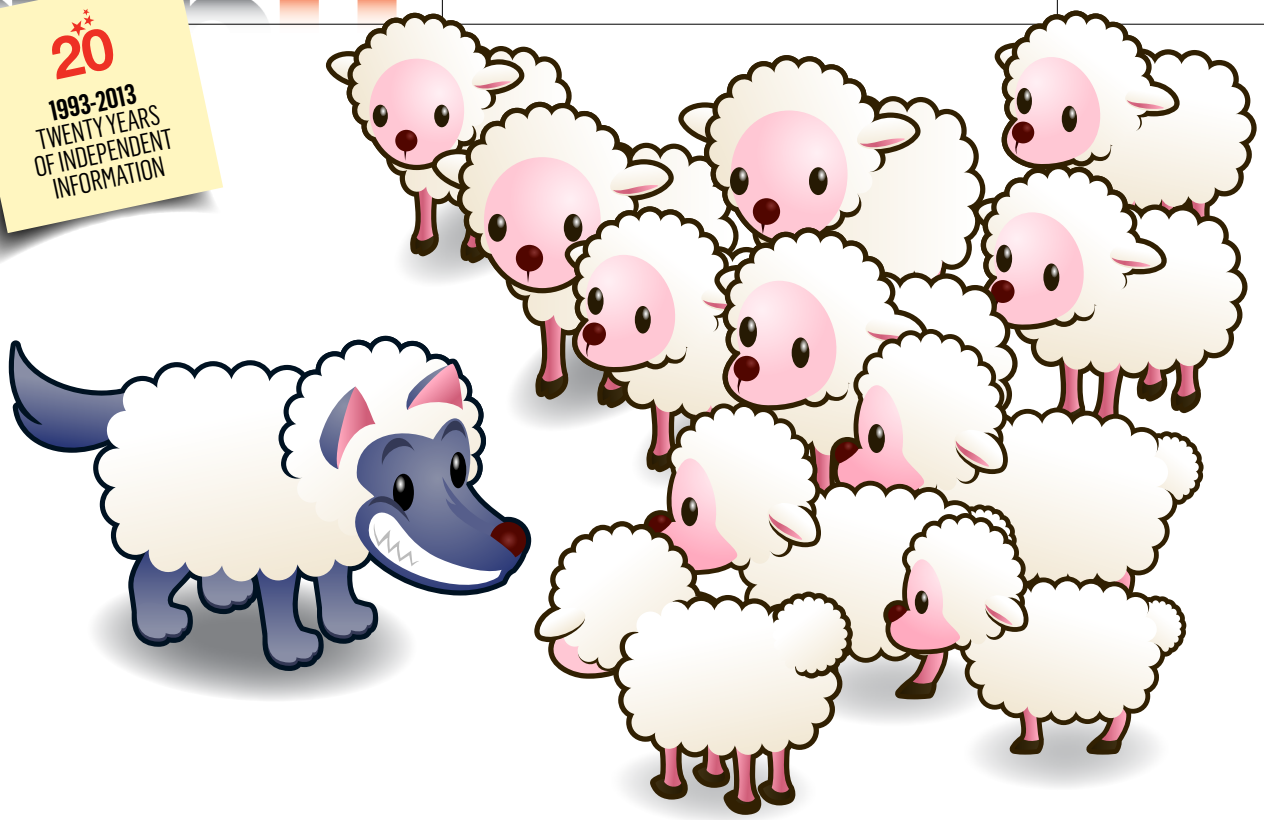

abstract

Objective: to review the information regarding the efficacy and safety of roflumilast and verify the positioning of this drug in clinical practice guidelines: GOLD guidelines (updated 2013), COPD guidelines of GuiaSalud and the GesEpoc guidelines. **Methods:** a bibliographical research in PubMed, updated on the 30 April 2013 was carried out with the following criteria: *"roflumilast" and "pulmonary disease, chronic obstructive".* The search was filtered by type of study (clinical trial or meta-analysis). The North American registry of clinical trials *(clinicaltrials.gov)* was consulted with the aim of finding completed or ongoing studies on roflumilast in the management of COPD. In addition, Tripdatabase, the EMA, FDA and Guiasalud websites were consulted and an open internet search was made for gray literature unindexed in traditional databases. **Results:** in the management of stable COPD, roflumilast has only shown an improvement in lung function and a modest reduction in exacerbations when compared to placebo. However, there are no data on roflumilast efficacy incorporated into therapeutic regimens commonly employed in clinical practice. There is concern regarding the safety profile of the drug and it is under an extensive risk management plan. The positioning of roflumilast is different in the three aforementioned guidelines: 1) as an alternative to inhaled cortisteroids in patients with severe or very severe COPD and with high risk of exacerbations in cases of chronic bronchitis (Gold guidelines, 2013); 2) only in the context of clinical research (Guia Salud), and 3) at the same level as inhaled corticosteroids and employed in multiple combinations in patients with a mixed phenotype COPD-asthma and patients characterised by acute exacerbations of chronic bronchitis (GesEPOC guidelines). **Conclusions:** the positioning of roflumilast in the clinical practice guideline of GesEPOC is rather hasty and is not coherent with the available scientific evidence. **Key words:** COPD, roflumilast, clinical practice guidelines, therapeutic place.

Roflumilast for stable COPD, another example of hasty positioning in (some) Clinical Practice Guidelines

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The drug market for the management of chronic obstructive pulmonary disease (COPD) has been very active in recent times. After a long period with no introduction of new agents, -except for indacaterol- in just over two years, two new inhaled antimuscarinic agents have appeared, aclidinium bromide and glycopyrronium bromide. This has arrived at an opportunistic moment when the tiotropium patent expires. In addition, roflumilast has been introduced and presents a different mechanism of action compared to known drugs for COPD with the peculiarity of an oral administration route.

There is also novelty regarding Clinical Practicve Guidelines for the management of COPD. Besides the 2013 update of the *Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease* (GOLD guidelines)[1], two other Spanish national guidelines have been introduced: The Clinical Practice Guideline for the diagnosis and treatment of COPD, Spanish COPD guideline (GesEPOC)[2], and the Clinical Practice Guideline for COPD management[3] of the National Health Services project for clinical guidelines, GuíaSalud.

Given that the three guidelines have been issued after the commercialization of roflumilast, we will attempt to verify the positioning of this drug in each of these guidelines and the evidence that supports the upheld stance.

Is roflumilast an improved theophyline?

Roflumilast is an oral non-steroidal anti-inflammatory drug that acts by inhibiting 4-phosphodiesterase (PDE4), the predominant isoenzyme in the majority of structural and inflammatory cells implicated in the pathogenesis of COPD[4]. By blocking its action, roflumilast and its active metabolite, N-oxide roflumilast, provoke the intracellular accumulation of AMPc, reducing the recruitment of different inflammatory cells in the bronchi, such as neutrophils and macrophages[4].

Two drugs belonging to the PDE4 inhibitors class -cilomast and roflumilast- have been tested in clinical trials run to determine their efficacy and safety profile in the management of COPD[5].

We should keep in mind that theophylline presents a very similar mechanism of action to roflumilast –although less selective– as it inhibits PDE inespecifically.[6] Currently theophylline has been relegated as a fourth line treatment option, given its unfavourable adverse effects, the narrow therapeutic margin and its implication in numerous pharmacological interactions. The question we pose is whether the higher selectivity of roflumilast to an enzyme related to the lung inflammatory response really improves the benefit-risk balance in the treatment of COPD in comparison to theophylline.

It should be kept in mind that the concomitant treatment with roflumilast and theophylline is not recommended given the lack of clinical data to support it.[4]

Marketing authorization and clinical indication

The European Medicines Agency (EMA) authorized the commercialization of roflumilast in April 2010 after an extraordinary meeting of experts[7] of which no names or conflicts of interest are known. On the other hand, the Food and Drug Administration (FDA) denied roflumilast approval in 2010, given the modest benefit of the drug and the potential adverse reactions. Later on, in March 2011, it was approved after a second petition.[8,9] In both cases the regulatory agency restricted the indication to a subgroup of COPD patients with specific characteristics.

In the European Union, the authorized indication is for maintenance treatment of severe COPD (post-bronchodilation forced espiratory volume, $FEV_1 < 50\%$) associated with chronic bronchitis in adult patients with a history of frequent exacerbations and as an add on therapy to bronchodilators.[4,7]

As formulated, this indication raises several questions concerning the management schema in which roflumilast has been added. For example, how do we interpret "bronchodilator treatment" in COPD?, does it refer to long-acting beta-adrenergic treatment (LABA) or long-acting antimuscarinic treatment (LAMA)? Or could it refer to combined therapy with LABA and LAMA? And can a inhaled corticosteroid (IC) be associated to bronchodilatory treatment?

We consider that these questions have not been adequately addressed and clarified by the clinical research available on roflumilast, and so there is still uncertainty with regard to its place in the management of COPD patients and the therapeutic regimens in which it could be included. This same line of thought has been expressed

by other institutions and working groups dedicated to independent reviews, such as the committee for new drugs assessment in Navarre[10], the Prescrire journal[11] and the *National Institute for Health and Care Excellence* (NICE).[12]

Clinical research with roflumilast

According to the EMA's requirements for drug approval in COPD, efficacy in clinical trials can be measured through some of the following variables: lung function determined through spirometry (mainly pre-bronchodilation FEV_1), frequency of exacerbations, quality of life, dyspnoea, symptom scores, capacity for exercise, use of rescue medication, or imaging techniques.[13] The most commonly employed parameters include the increase in FEV_1 and the incidence of exacerbations, which were used in clinical trials studying roflumilast.[7] Given that roflumilast is not in a strict sense a bronchodilator, it would be more important to show a reduction in exacerbations associated with its use, rather than an effect on lung capacity. Moreover, exacerbations reduction is a harder patient-oriented endpoint in comparison to FEV_1, a soft disease-oriented variable.[7]

Clinical research with roflumilast began 15 years before its approval and during this period numerous studies have been carried out on the management of COPD and other diseases, such as asthma, allergic rhinitis, or rheumatoid arthritis.[6,7] However, the regulatory agencies –including the EMA[7]–, only considered six of these trials for approval (see table 1). What is surprising is that only two of them (pivotal or main studies) were carried out in similar populations in which the indication has been restricted to.

Clinical studies carried out before the approval for commercialization

In 2005, the first phase II clinical trial with roflumilast in the managemet of COPD was published.[14] This trial compared two doses of the drug (250 mcg and 500 mcg) with placebo during a 24-week period. Roflumilast increased post-bronchodilator FEV_1 of patients at the end of the study, but only reduced the frequency of mild exacerbations. The 500 mcg daily dose was determined as the therapeutic dose to employ in successive clinical trials.

The following two trials aimed at proving the hypotheses that roflumilast 500 mcg daily was effective in patients with moderate or severe COPD. Both studies were considered by the regulatory agencies for drug approval, but only one of them was published in 2006. It included patients with $FEV_1 \leq 50\%$ treated with roflumilast 500 mcg daily or placebo for one year. Moreover, they could receive concomitant treatment with inhaled corticosteroids (IC) and short-acting beta-muscarinic agents (SAMA), whenever they were employed at maintenance doses before the onset of the study, and a short-acting beta-adrenergic (SABA) drug as rescue medication. However, it is curious that no LABA was allowed, taking into account the severity of the patients included in the study and the fact that these drugs are the basis of COPD management. In the published trial, the group under treatment with roflumilast presented a modest increase in post-bronchodilator FEV_1 when compared to the group under placebo (39 mL), but no positive effects in the reduction of moderate and severe exacerbations were observed. No efficacy in the frequency of exacerbations was seen in the unpublished trial either.[7]

After 15 years of research on roflumilast, the scientific evidence available is of poor quality

A *post-hoc* analysis[16] of these two trials was carried out with the aim of finding statistical significance in the reduction of the frequency of exacerbations and identify a subgroup of patients in which the results on this variable were more favourable. In this pooled analysis, the incidence of exacerbations per year were 0.52 vs 0.61 ($p=0.026$), in the roflumilast and placebo groups, respectively. The reduction of exacerbations was greater in the subgroup of patients with chronic bronchitis, with or without emphysema and in those under IC therapy.

These findings led to the idea that clinical research on roflumilast should focus on a more selective subgroup of COPD patients in which the expected results in terms of a reduction of exacerbations were more favourable than those obtained up to now. For this reason, the two following clinical trials, of equal design were carried out in COPD patients with frequent exacerbations and a history of chronic bronchitis. These are the studies that regulatory agencies consider pivotal or main trials, and as a consequence, the characteristics of the subjects included in them are the ones which finally determine the group of COPD patients contemplated in the clinical indication approved.

The pivotal studies[17] were carried out between 2006 and 2008 and were published together. They include patients with severe or very severe COPD ($FEV_1 \leq 50\%$) that present confirmed symptoms of chronic bronchitis and at least one moderate or severe exacerbation documented in the previous year before the study. The patients were treated with roflumilast 500 mcg daily or

Table 1: Clinical trials on roflumilast considered by regulatory agencies for approval in the management of COPD (adapted from reference 9).

Clinical trial	Patients (n)	Mean FEV_1 of patients at the onset of the study (% of theoretical value)	Inclusion Criteria		Duration (weeks)	Treatment groups	Other drugs for the treatment of COPD permitted in the trial	Results*	
			Presence of bronchitis (chronic productive coughing)	Exacerbations in the previous year				Increase in FEV_1 at the end of the study (pre-bronchodilatador)	Difference in the number of annual exacerbations (roflumilast *vs.* placebo)
Not published (M2-111)	1,173	36	NO	NO	52	Roflumilast *vs.* placebo	IC (beclometasone up to 2000 mcg or equivalent) and SAMA if there were already employed before entering the study. SABA as rescue therapy.	51 mL	n.s. (moderate or severe)
Calverley 2007 (M2-112)	1,513	41	NO	NO	52				
Calverley 2009 (M2-124)	1,523	38	YES	YES	52	Roflumilast *vs.* placebo	LABA and SAMA if there were already employed at the start of the study. SABA as rescue therapy.	39 mL	1.08 *vs.* 1.27 (moderate or severe)
Calverley 2009 (M2-125)	1,568	35	YES	YES	52			58 mL	1.21 *vs.* 1.49 (moderate or severe)
Fabbri 2009 (M2-127)	933	55	79% with productive coughing	NO	24	Roflumilast + salmeterol *vs.* placebo + salmeterol	SABA as rescue therapy.	49 mL	n.s. (total exacerbations)
Fabbri 2009 (M2-128)	743	56	NO	NO	24	Roflumilast + tiotropium *vs.* placebo + tiotropium		80 mL	n.s. (total exacerbations)

n.s.: not significant. (*) In the M2-111 and M2-112 trials the results offered are form the overall analysis as there are no data available on the M2-111 trial separately.

placebo for one year. Both groups could be under LABA therapy (around 50% of the patients used LABA during the trial) and could also take SABA or LAMA at stable doses. However, since both roflumilast and ICs have anti-inflammatory effects, the use of ICs was not allowed to avoid confounding. Here again a different therapeutic regimen is employed compared to clinical practice, since severe or very severe COPD patients who present frequent exacerbations are recommended treatment with ICs. The exacerbations were considered moderate when systemic corticoids were needed and severe when associated with hospital admission or death.

In the two trials, a positive effect was once again observed regarding pre-bronchodilator FEV_1 (48 mL in the pooled analysis; 95% CI, 35-62 mL) and also a statistically significant but modest difference between treatment groups in the incidence of moderate or severe exacerbations, 1.14 vs 1.37 cases-year (roflumilast vs placebo, respectively), RR=0.83; 95%CI, 0.75-0.92. However, no differences were found in the frequency of severe exacerbations. Moreover, according to the FDA analysis, this reduction in the frequency of exacerbations attenuated or disappeared after 8 weeks of treatment.[8,10] A post-hoc analysis of the pivotal studies shows that management with roflumilast is more effective in those patients under a therapeutic regimen that includes an LABA.[18]

Almost at the same time as the pivotal studies, two other clinical trials were carried out to evaluate the combination of roflumilast and LABA or LAMA,[19] although in this case the population did not correspond to that of the approved clinical indication. The selected patients presented moderate to severe COPD (FEV_1 = 40-70%).

In one of the studies, the combination salmeterol + roflumilast was compared to salmeterol + placebo, and in the other, tiotropium + roflumilast was compared to tiotropium + placebo. Both studies lasted 6 months. Concomitant use of ICs was prohibited although probably many of these patients would have received them in common clinical practice. In both cases, the regimen including roflumilast showed an increase in FEV_1 (the increase was greater with tiotropium, as in this trial the patients presented symptoms of chronic bronchitis), but no differences were found on the frequency of annual exacerbations (including mild, moderate and severe).

In summary, in the trials reviewed before the approval, roflumilast was shown to improve FEV_1 –although the clinical relevance of the improvement is questionable[7,12] – and reduce the frequency of exacerbations compared to placebo, but only in moderate cases and in patients with specific characteristics. There is no evidence of clinically significant improvements in the degree of dyspnoea, quality of life, or in mortality.[12] No comparisons have been made with either theophylline or ICs.

In addition, roflumilast is not recommended in numerous population groups that were excluded from the clinical trials: cancer patients (carcinogenic toxicity has been observed in the mucosa of rodents), patients with NYHA grade 3 or 4 congestive heart failure, patients with severe immune disease, patients with acute and severe infections and patients under immunosupressor therapy.[4]

The benefit-risk balance of roflumilast is questionable

Ongoing clinical trials

When the EMA and the FDA approved roflumilast they made a condition to carry out a phase III/IV clinical trial to investigate whether the addition of the drug to the association of LABA + IC -to which a LAMA could be added if necessary (triple therapy)-, would improve clinical results in patients with severe or very severe COPD, with symptoms of chronic bronchitis and at least two exacerbations in the previous year.[7,9] This study[14] is recruiting patients at present and results are expected in 2015.[9]

However, the impression is that this trial has come late, and should have been a *sine qua non* requisite for the regulatory agencies to approve the use of roflumilast in the management of COPD. The patients with FEV_1 ≤50%, chronic bronchitis and a history of frequent exacerbations (the indication approved for the drug), will most likely be under treatment in real clinical practice with a combination of LAMA+IC or LAMA+LABA, and an important proportion of them would be under triple therapy (LAMA+LABA+IC). That is, the conditions in which roflumilast is probably employed does not coincide with those contemplated in the clinical trials that support the decision to authorize the drug, and therefore, we can say that the necessary clinical phase for the approval was incomplete. The uncertainty with regard to the efficacy of roflumilast combined with tiotropium+IC still prevails over time, as there are no data either from previous trials or from the ongoing trial.

The research work never carried out

The NICE elaborated an assessment report on roflumilast[12] in 2012, and during this process, the manufacturer suggested that the drug should be used in daily clinical practice in the following therapeutic regimens: roflumilast added to triple therapy (LABA+IC+LAMA)

or roflumilast added to double therapy (LABA+LAMA) in patients who do not tolerate IC. As we have already commented, the problem is that none of these two combinations nor the (LABA or LAMA) + IC + roflumilast were employed in the clinical trials mentioned. A network meta-analysis was carried out to compare the efficacy of different treatments containing roflumilast, including those above mentioned, in the reduction of exacerbations in COPD.[21] However, the NICE rejected this study alleging that the population included was not the same as that in the approved clinical indication, and that the model chosen was not valid to estimate the magnitude of the effect of roflumilast associated with each of the therapeutic regimens.[12]

The reality today is that we do not know how effective roflumilast is in the therapeutic regimens in which it is employed in clinical practice. Neither do we know about its efficacy in the management of patients with severe COPD and bronchitis and a history of frequent exacerbations compared to IC therapy or to theophylline (in both cases associated with LAMA and/or LABA and short-acting bronchodilators).

Roflumilast (un)safety

Roflumilast is metabolised through the CYP3A4 and CYP1A2 isoenzymes of the P450 cytochrome, and so -just like theophylline- has a great potential for pharmacokinetic interactions.[4,11]

In the clinical trials a greater rate of dropouts due to adverse reactions was observed in patients under roflumilast (14%) compared to placebo (8.5%). [8,11] Adverse effects included gastrointestinal disorders (diarrhoea in 5.9% of the cases, nausea, abdominal pain), weight loss and neuropsychiatric alterations (headache, anxiety, and depression).[4,7] The diarrhoea could be severe in some cases.[20] There were also more cases of gynecomastia, pancreatitis, cancer and atrial fibrilation in the group treated with roflumilast compared to placebo.[11,22] It can rarely produce angioedema.[4]

The most worrisome adverse reactions were weight loss and suicidal behaviour.

Weight loss

In the pivotal clinical trials, 62% of the patients with roflumilast lost weight compared to 38% of those under placebo.[8,11] Weight loss was 2 kg on average per patient among those under roflumilast. This effect occurred at treatment onset and most patients recovered weight three months after discontinuing treatment.[7] However 7.1% of the patients under roflumilast in the pivotal trials suffered severe weight loss, that is, more than 10% of their initial weight.[8,22]

There is serious concern about roflumilast safety profile

Weight loss in COPD patients is of considerable concern because it is associated with a worse prognosis of the disease.[11] So when patients treated with roflumilast suffer from clinically relevant weight loss not justified by other causes, treatment should be discontinued and the patients weight status monitored over the following months.[4]

Suicide risk

During the clinicial trials there were five cases of suicide attempts (three deaths and 2 failed attempts) among those patients under roflumilast while no case was observed among patients under placebo.[7] For this reason, roflumilast is not recommended in patients with a history of depression associated with suicide ideation or behaviour and special attention should be given to changes in behaviour in those patients under this drug.[4,7]

Nevertheless a recent review of the unpublished data after approval shows that the suicidal behaviour was observed both in patients with a history of depression and in those with no history, and this ocurred especially in the first few weeks of treatment with roflumilast. Based on this information, the British *Medicines and Healthcare products Regulatory Agency* has issued an alert to health care professionals recommending special precaution in order to avoid the risk of suicide in their patients.[23]

According to the European data base of suspected adverse reactions, up to now 42 cases have been notified through the existing pharmacovigilance systems: 34 of suicidal ideation, two cases of suicide behaviour and 6 suicide attempts.[24]

Given the existing uncertainty derived from the nature, severity and incidence of roflumilast risks in different situations, the EMA approved the drug with restrictions that should be applied with the aim of guaranteeing safe and effective use.[7,25] These particular conditions of approval are described in an extensive risk management plan that requires very close monitoring of the important risks already identified (weight loss and psychiatric disorders), important potential risks (cancer, infections, coronary disease, etc.) and the risks in the population excluded from the clinical trials already mentioned.[4,7]

The risk management plan also includes the elaboration and dissemination of safety information to health care professionals and patients as well.[7]

Positioning of roflumilast in Clinical Practice Guidelines

Pharmacological management of stable COPD has to be progressive in relation to the severity of the patient. Traditionally, this severity was determined according to the degree of airflow obstruction defined by the GOLD initiative (see table 2). However, the severity of the condition does not depend only on this variable, but also on symptoms, frequency, and severity of exacerbations and the general wellbeing of the patient. The last guidelines already use treatment algorithms that combine traditional stages of GOLD severity classification with other parameters related to symptoms or exacerbation risk.

Table 2: GOLD classification of COPD severity[1]

COPD classification according to severity of airflow obstruction (based on post-bronchodilator FEV_1) For patients with $FEV_1/FVC < 0.70$		
GOLD 1	mild	$FEV_1 \geq 80\%$
GOLD 2	moderate	$50\% \leq FEV_1 < 80\%$
GOLD 3	severe	$30\% \leq FEV_1 < 50\%$
GOLD 4	very severe	$FEV_1 < 30\%$

After reviewing the information above, we can conclude that roflumilast does not present a very favourable benefit-risk balance. There are no available data to support the use of the drug in the common therapeutic regimens and its efficacy in comparison to IC therapy or theophylline remains unknown. Given these conclusions, it would have been more reasonable to have taken a more prudent approach when positioning the drug in the recent Clinical Practice Guidelines and to have relegated its place to the last treatment option in patients with severe COPD and chronic bronchitis along with a history of frequent exacerbations.

It is widely documented that there is great variability between the recommendations in the different Clinical Practice Guidelines,[26] and in occasions, the positioning of new drugs in these guidelines is carried out rather hastily, as for example, dronedarone in the 2010 guidelines for atrial fibrillation issued by the European Cardiology Society.[27] Does history repeat itself in the case of roflumilast in the management of stable COPD?

2013 GOLD guidelines[1]

Just like the 2011[28] guideline, the review of the 2013 GOLD guidelines continues to adopt a model of classifying patients in terms of GOLD stages, symptoms and exacerbation risk, the latter two valued through scale scores. This model results in four groups of patients which form the basis for pharmacological management of stable COPD patients.[1] Roflumilast is considered in the following groups of patients:[1]

The recommendations for roflumilast in the GesEPOC guidelines are not based on scientific evidence

Group C (GOLD 3 or 4 stages, with a high risk for exacerbations and moderate symptoms)
The elective treatment is the combination of LABA+IC or LAMA+IC. As alternatives, LAMA+LABA and LAMA+roflumilast for patients with chronic bronchitis are proposed.

Group D (GOLD 3 or 4 stages, with a high risk of exacerbations and prominent symptoms)
The elective choice is LABA+IC or LAMA+IC or LAMA+LABA+IC. As an alternative, LABA+LAMA or LAMA+roflumist or LABA+IC+roflumilast for patients with chronic bronchitis. It is emphasized that the evidence to support the addition of roflumilast to the IC is less solid than the evidence for its combination with long-acting bronchodilators.

Therefore, the GOLD guideline does not select roflumilast as first-line treatment in stable COPD, and also indicates that this drug produces more adverse reactions than inhaled medications.[1]

GuiaSalud guidelines[3]

As mentioned at the start, the GuiaSalud guideline has been elaborated within the framework of a project of Clinical Practice Guidelines of the National Health Services, financed by the Spanish Ministry of Health. Although some authors of this guideline also appear in the GesEPOC guidelines and adopt the same model of classifying the disease by "phenotypes", we have been confirmed by the secretary of GuiaSalud, located at the Aragon Institute of Health Sciences that they are two different guidelines. The GuiaSalud was elaborated following the GRADE[27] system and the methodological manual was carried out by the Health Technology Evaluation Unit of the now former Lain Entralgo Agency (Madrid).

The guideline recommends that in COPD patients in a stable phase of maintenance therapy with bronchodila-

tors, additional therapy with roflumilast as an alternative to additional IC therapy should only be used in a research context.[3] This recommendation coincides with the conclusions of the report[12] on roflumilast issued by NICE in 2012.

GesEPOC guidelines[2]

The GesEPOC guidelines form part of an initiative of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR), other scientific societies, the Spanish Patients Forum, and the Health Technology Evaluation Unit (HTEU) under the Lain Entralgo Agency. They also have support from pharmaceutical companies as strategic partners and collaborators.[2]

Although the guidelines provide an appendix with questions addressed by the HTEU, which coincide with those in the GuiaSalud and even incorporates some of them to the text in the same guideline, it does not always follow the recommendations from GuiaSalud, and in some occasions, gives discordant recommendations. In addition to the absence of a reference methodology in the elaboration of the guideline, there is no mention on either the quality of the scientific evidence or the strength of the recommendations in each case. This raises doubts on the procedure employed in elaborating the GesEPOC guideline.

In this guideline a COPD classification is established in terms of "phenotypes"[30] (see table 3), denominated as such to refer to the different clinical forms patients present with prognostic value and which, along with the degree of severity, determine a differentiated treatment of the disease.[2] Treatment with roflumilast is contemplated in the following groups of patients:[2]

Type B (COPD-asthma phenotype)
This phenotype is defined by the presence of a limitation of airflow not completely reversible, accompanied by signs or symptoms of increased reversibility of airway obstruction.[31] In these patients the guidelines recommend initial treatment with combined LABA+IC and adding tiotropium in more severe cases or if exacerbations. If chronic expectoration and frequent exacerbations, adding theophylline or roflumilast to the previous regimen is proposed. However, there is no evidence to support the use of roflumilast in those patients.

Type D (exacerbator with chronic bronchitis phenotype)
The elective choice in the stages of milder severity is a combination of LABA with an anti-inflammatory agent, that could be indistinctly either an IC or roflumilast, recommendation which is maintained in more severe stages. In this group of patients, the GesEPOC guideline puts roflumilast at the same level as IC, despite the inexistence of comparative clinical trials that show that roflumilast presents at least similar efficacy to IC. Curiously, in the guideline's text and below the previous recommendation, roflumilast use is restricted to a research context only.[2] This circumstance confounds the reader and raises doubts about the strength of the recommendation. As the degree of severity increases in this group, the following regimens including roflumilast are recommended: LABA+roflumilast, LAMA+roflumilast, LABA+LAMA+roflumilast, LABA+IC+roflumilast, LABA+LAMA+IC+roflumilast. As mentioned earlier there is no evidence of the efficacy and safety of the majority of the combinations, many of which will be investigated in the ongoing clinical trial.[20]

Without entering into discussion on whether the classification of COPD patients in "phenotypes" has prognostic value, what seems clear is that treatment recommendations based on the phenotypes described in the GesEPOC guidelines and the role given to roflumilast are not in accordance with the scientific evidence available. This is another instance of a hasty positioning in a Clinical Practice Guideline of a new drug with dubious benefit-risk balance.

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CONCLUSIONS

Roflumilast is a new drug for the management of stable COPD that has only shown an improvement in lung function and a modest reduction in exacerbations compared to placebo.

No data are available on roflumilast efficacy incorporated into the therapeutic regimens commonly employed in clinical practice.

The safety profile of roflumilast is still worrisome and the drug is subject to an extensive risk management plan.

The positioning of roflumilast in the GesEPOC Clinical Practice Guideline is rather hasty and is not supported by available scientific evidence.

Table 3: Clinical phenotypes of COPD according to the GesEPOC[2]

			Mixed phenotype COPD-asthma
Frequent exacerbator phenotype (≥ 2 exacerbations per year)	(C)	(D)	(B)
Infrequent exacerbator phenotype (< 2 exacerbations per year)	(A)		
	Emphysema phenotype	Chronic bronchitis phenotype	

Types of COPD patients. Type A: Non exacerbator with emphysema or chronic bronchitis. Type B: Mixed COPD-asthma, with or without frequent exacerbations. Type C: exacerbator with emphysema. Type D: COPD exacerbator with chronic bronchitis.

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