

Editorial

Clinical Practice Guidelines or Personalized Medicine in Chronic Obstructive Pulmonary Disease?☆



Guías de práctica clínica o medicina personalizada en la enfermedad pulmonar obstructiva crónica

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Chronic obstructive pulmonary disease (COPD) is enormously complex and heterogeneous.¹ Until relatively recently, diagnosis and treatment was based essentially on the presence and severity of airflow limitation, measured by forced expiratory volume in 1 second (FEV₁). However, we now know that many other factors (exacerbations, pulmonary hyperinflation, exercise tolerance, comorbidities, etc.) can affect the symptoms, course, and prognosis of the disease.^{1–3} All these, some of which are treatable and others not, vary from patient to patient, generating significant differences in the clinical expression of the disease. This variability ultimately creates a dichotomy between the standardized management of patients according to clinical practice guidelines (CPG), and a more personalized approach, tailored to the specific characteristics of each individual.

CPGs aim to set down specific recommendations generated from a synthesis of the best available scientific evidence.⁴ This approach is widely accepted by the scientific community: CPGs help to improve quality of care, ensuring uniform, standardized clinical interventions, and ultimately facilitate a broad consensus and peace of mind among medical professionals. However, despite their ample benefits, CPGs do have some limitations, the most important being lack of adherence by professionals, delays in incorporating new concepts in a rapidly advancing scientific environment, and most especially, difficulties in applying general indications to specific individuals. The highest level of evidence assigned to a CPG is based on the results of randomized controlled clinical trials (RCT). In general, RCTs have specific inclusion and exclusion criteria which are often a barrier to external validation, making it difficult to apply conclusions to a heterogeneous population with characteristics other than those examined in the trial. Although subgroup analyses are often undertaken for more specific populations, the scientific community does not consider them sufficiently reliable: when the results of the primary variable show

statistically significant differences, the result is often generalized to the whole population, while if it is negative, the intervention is not considered useful for any patient. One example of this problem can be observed in the Toward a Revolution in COPD Health study (TORCH),⁵ an RCT designed to evaluate the effect of combined salmeterol and fluticasone (SFC) on the survival of COPD patients. The study was negative, since no significant differences were found between the SFC and the placebo groups, although the *P*-value was .052. The main conclusion, namely that combined therapy did not reduce mortality in COPD, was later included in CPGs.^{2,3} However, it is very likely that the use of this treatment in a more specific population that might respond better to inhaled steroids could have produced different results.

Another drawback of standardized CPGs, and perhaps the most significant, is the failure of professionals to follow the recommendations. For example, a recent clinical audit conducted among pulmonologists found that the BODE index was only calculated in 12.4% of cases, and the inhalation technique was evaluated in 22.4%.⁶ Practitioners are constantly and loudly demanding more simple guidelines to improve compliance. However, it is hard to justify simplicity in a disease as complex as COPD.

Aside from the evidence-based approach offered by CPGs, there is growing recognition of the need for a shift toward more patient-centered medicine, that can take into account the heterogeneity of the disease and adjust treatment to the situation of each individual. In this context, the terms personalized, tailored, and precision are used indistinctly. Personalized medicine is defined as an approach in which a medical treatment is adjusted to the individual characteristics of each patient.⁷ Many professionals are uncomfortable with this definition because, true to Gregorio Marañón's mantra "there is no such thing as disease, only patients", they believe that medical practitioners have always tried to tailor medicine to the individual patient. For this reason, the term precision medicine is preferred, understood as the use of treatments that target the needs of individual patients on the basis of biomarkers and the genetic, phenotypic and psychosocial characteristics that let us differentiate one patient from another with similar clinical features.⁸ The ultimate objective of precision medicine is to improve clinical outcomes in an individual patient while minimizing adverse

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effects, treating those cases with greater likelihood of responding to a treatment. Biological therapies using monoclonal antibodies are a clear example of the development of precision medicine. In COPD, intense research is currently being undertaken to identify aberrant biological pathways and therapeutic targets of interest.

Reflecting the shift from traditional medicine to precision medicine, some CPGs, such as the Spanish COPD Guidelines (GesEPOC),² propose stratifying patients according to relevant clinical characteristics or clinical phenotypes. This approach involves some degree of personalization, even though it is based exclusively on dominant clinical features. Interestingly, some authors have proposed managing patients on the basis of treatable features or characteristics which would include not only clinical features, but also radiological, functional, and/or biological characteristics.⁹ The next therapeutic stage in this journey is to address the underlying biological mechanisms (endotype) and to identify biomarkers that will allow us to select the right candidate. One example of precision medicine is the selective use of an anti-interleukin-5 monoclonal antibody that is being investigated in patients with peripheral eosinophilia.¹⁰

Both precision medicine and stratified or traditional medicine are based on a reductionist concept of disease which attempts to pinpoint the failure of one single component in a particular system. Alternatively, personalized medicine could be defined as a holistic method in which the subject is seen as a complex biological system with multiple interactions and self-adjusting systems. In this context, disease is viewed as a dynamic inter- and intra-systemic interaction.^{11,12} Network medicine and systems biology offer just this type of integral, multilevel, dynamic approach to understand the complex molecular, functional, clinical and environmental network. This new approach will improve our understanding of biological complexity, and will possibly lead to a new disease classification in which therapeutic alternatives will be targeted to promote changes or restore balance. This holistic strategy can potentially help in the development of new, more appropriate, more effective, safer targets (not anticipated by reductionist medicine) for the treatment of different subgroups of patients, and thus release the full potential of personalized medicine. Although the accumulated evidence is still scant, we already have excellent reviews and publications that illustrate the enormous potential of this holistic vision.^{11,13–15} Agustí et al.,¹⁵ using this new approach, described the systemic inflammation of COPD and showed that smokers and COPD patients have different inflammatory patterns. In contrast to the accepted thinking, it appears that some COPD patients do not present accompanying systemic inflammation, while others (approximately 20%) have persistent inflammation. Three-year mortality in patients with persistent inflammation was 6 times greater than in patients without inflammation, suggesting a new target of therapeutic interest for some specific patients.

Before this new approach fully takes hold, evidence-based medicine will remain our best tool for the design of both the current CPGs and of those which will emerge from stratified medicine, precision medicine, or network medicine. CPGs will not disappear, they will be adapted, and evidence will always be necessary.

Conflict of interests

Juan José Soler-Cataluña has received fees for scientific consultancy and/or for speaking at conferences from AstraZeneca, Boehringer Ingelheim, Chiesi, Ferrer, GlaxoSmithKline, Laboratorios Esteve, Menarini, MundiPharma, Novartis, Rovi, and Teva.

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