



SPECIAL ARTICLE

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Patient benefit as a goal of humanization**El beneficio del paciente como objetivo de la humanización**Manuel David Gil-Sierra¹, María del Pilar Briceño-Casado², Eduardo López-Briz³¹Pharmacy Department, Hospital Universitario de Puerto Real, Puerto Real (Cádiz). Spain. ²Pharmacy Department, Hospital Universitario de Jerez de la Frontera, Jerez de la Frontera (Cádiz). Spain. ³Pharmacy Department, Hospital Universitari i Politècnic La Fe, Valencia. Spain.**Author of correspondence**

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Abstract

Patient empowerment is one of the main pillars of humanisation. Therefore, consideration of patients' preferences and expectations should be taken into account during the practice of any healthcare professional. Improving overall survival and quality of life are the main wishes of patients. Indeed, the recent emergence of Patient Reported Outcomes has become an important focus for healthcare providers. The hospital pharmacist specialised in drug evaluation is a professional who evaluates the efficacy, safety, appropriateness and efficiency of treatments prescribed by physicians, and decision-making must be based on both technical factors and the four principles of bioethics. The correct application of evidence-based clinical practice allows to provide patients with increases in survival and/or quality of life, adapting the convenience and costs to the current situation. With this in mind, it could be said that the evaluation of medicines involves a strong commitment to humanisation. On the other hand, organisations that promote the rigorous evaluation and selection of medicines stand as allies of patients, as they have a direct impact on them and an indirect impact on society. Regulatory agencies in charge of approving and financing medicines in healthcare systems play a key role in the process of humanising clinical decision-making and empowering patients. If these agencies approve the use of new medicines based on data that do not measure quality of life or survival of patients when there are already other therapeutic alternatives for these pathologies, they are indirectly failing to meet patients' expectations and are infringing bioethical principles. This can have a considerable influence on the benefit-risk ratio of drugs, and

Resumen

El empoderamiento del paciente supone uno de los principales pilares de la humanización. Por ello, la consideración de las preferencias y expectativas de los pacientes debería ser tenida en cuenta durante el ejercicio de cualquiera de los profesionales de la salud. Mejorar la supervivencia global y la calidad de vida son los deseos principales de los pacientes. De hecho, la reciente aparición de los llamados *Patient Reported Outcomes* ha supuesto un importante foco para los agentes involucrados en la asistencia sanitaria. El farmacéutico hospitalario especializado en la evaluación de medicamentos es un profesional que evalúa la eficacia, seguridad, adecuación y eficiencia de los tratamientos prescritos por facultativos, y debe basar la toma de decisiones tanto en factores técnicos como en los cuatro principios bioéticos. La correcta aplicación de la práctica clínica basada en la evidencia permite proveer a los pacientes de incrementos de supervivencia y/o calidad de vida, adecuando la conveniencia y costes a la situación actual. Teniendo en cuenta esto, podría decirse que la evaluación de medicamentos supone un fuerte compromiso con la humanización. Por otra parte, las organizaciones que promueven la evaluación y selección de medicamentos rigurosamente se erigen como aliados de los pacientes, ya que repercuten de forma directa en éstos y de forma indirecta en la sociedad. Las agencias reguladoras encargadas de la aprobación y financiación de medicamentos en los sistemas sanitarios protagonizan un papel fundamental en el proceso de humanización de la toma de decisiones clínicas y empoderamiento de pacientes, ya que si aprueban el uso de nuevos medicamentos según datos que no miden la calidad de vida o supervi-

KEYWORDS

Patient; Humanisation; Patient-centered care; Empowerment; Bioethics; Evidence-based medicine; Drug evaluation.

PALABRAS CLAVE

Paciente; Humanización; Atención centrada en el paciente; Empoderamiento; Bioética; Medicina basada en la evidencia; Evaluación de medicamentos.



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patients may be treated with regimens that do not provide benefit, or may even harm them. Therefore, where should the process of humanisation be oriented? It seems reasonable that the benefit of the patient should be the fundamental objective of the process of humanisation of healthcare, evidently.

Since Berwick first coined the concept of *triple aim* as the goal of excellence in healthcare (optimal clinical outcomes, lower costs, improved patient satisfaction)¹, humanization has become one of its main objectives²⁻⁵. The concept *humanization* affects a range of activities, some of which have not been clearly defined^{6,7}. This lack of clarity hinders the implementation of measures that would enable patients to make their voice heard.

Patient empowerment is one of the main goals of humanization. At present, patient associations and companies (public and private) are making efforts to raise the visibility of this movement⁸⁻¹⁰. The *Guide for Humanization of the Spanish Society of Hospital Pharmacy* (SEFH) defines patient empowerment as one of the tenets of humanization¹¹. Pharmacy Services have undertaken a wide variety of initiatives aimed at the humanization of their areas of activity¹²⁻¹⁴. However, many more programs/strategies are needed to adequately incorporate humanization into processes such as drug approval, regulation, evaluation, selection and monitoring. As demonstrated by some studies exploring the opinions of patients about therapeutic decision-making, healthcare professionals should consider patient preferences and expectations. Patients primarily aim at improving their overall survival and quality of life^{15,16}. However, these endpoints are frequently neglected, which shows a failure to meet the principles of Beneficence and Autonomy. This is striking, especially in some types of cancer or rare diseases¹⁷.

Whereas assessing survival in early stages of neoplastic or rare diseases with a long life expectancy is challenging due to the lack of data¹⁸, evaluating quality of life is not an insurmountable obstacle. Hence, endpoints related to quality of life should be included in pivotal trials as a primary (or at least secondary) endpoint, which rarely occurs. Secondly, although quality-of-life data should be thoroughly interpreted, it is frequently mentioned briefly at the end of the "Results" section. For this reason, the recent emergence of the so-called *Patient-Reported Outcomes* (PROs) has become the focus of patients, scientific societies, researchers and the pharmaceutical industry^{19,21}. This would involve the principles of Beneficence and Autonomy. To analyze these outcomes, it is necessary that healthcare professionals determine whether the endpoints assessed are clinically relevant and have been measured using validated instruments. Moreover, evaluators should avoid considering irrelevant findings that benefit external agents other than patients²². Additionally, patient opinions should be individually assessed and considered as a complementary—rather than substitute—element during clinical decision-making. An empowered patient would express his/her preferences for clinicians to take them into account for the selection of a drug therapy. This is especially relevant when several therapeutic options with similar efficacy but different safety profiles are available. This way, clinician's choice would be based on the aspects related to quality of life that will be most affected, and considering patient opinion. This would accomplish the principle of Autonomy. Likewise, an empowered patient has a better understanding of concepts related to clinical decision-making, efficiency and sustainability of the healthcare system. This would lead to greater equity in resource use and promote the bioethical principle of Justice.

The hospital pharmacist specialized in the evaluation and selection of medicines assesses the efficacy, safety, convenience and efficiency of the treatments prescribed by other physicians²³. The work of these professionals has a transverse impact on other areas of the Pharmacy Service, such as Oncology or Outpatient Pharmacy. Clinical decision-making should not only be based on technical factors, but also on bioethical criteria^{24,26}. Medical and pharmaceutical ethics evaluate interventions based on the four Principles of Bioethics: Beneficence, Non-Maleficence, Autonomy, and Justice^{27,28}. There is a relationship between the technical criteria that determine the place of drugs in therapeutics and the fundamentals of bioethics.

vencia de los pacientes cuando ya existen otras alternativas terapéuticas para estas patologías, indirectamente no estarán dando respuesta a las expectativas de los pacientes y conculcarán los principios bioéticos. Esto puede tener una considerable influencia en la relación beneficio-riesgo de los fármacos, pudiendo tratar a pacientes con esquemas que no aportan beneficio, o incluso podrían perjudicarles. Por tanto, ¿hacia dónde debiera ir orientado el proceso de humanización? Parece razonable que el beneficio del paciente sea el objetivo fundamental del proceso de humanización de la asistencia sanitaria, evidentemente.

Thus, fulfillment of the principle of Non-Maleficence is guaranteed through the assessment of treatment efficacy and safety in clinical trials. This minimizes the possibility that patients receive an alternative therapy that may cause them an avoidable prejudice, favouring Non-Maleficence. On the other hand, the assessment of treatment appropriateness by drug evaluators would have a significant impact on patient Autonomy, since it favors the selection of therapies that minimize the number of visits to the hospital or have a more convenient route of administration. In this regard, patient opinion on the convenience of a treatment can be determining in decision-making. Finally, assessing the effectiveness of treatments guarantees compliance with the principle of Justice, since the rational use of medicines optimizes the use of resources of the healthcare system. This way, based on the concept of "cost-opportunity", the treatments with a lower economic impact would be used in some patients, without prejudice to the access of other patients to other therapies^{29,30}. Otherwise said, it prevents wasting resources that are needed for other patients³¹.

Drug evaluation is the first step in the process of disease management. An improper drug selection results in suboptimal outcomes being obtained in subsequent pharmaceutical interventions (i.e. pharmacotherapeutic or pharmacogenetic follow-up).

Taking the above into account, an appropriate drug selection certainly represents a strong commitment to humanization. The correct application of evidence-based clinical practice provides patients with treatments that improve their survival and/or quality of life. In addition, treatment convenience and costs are adjusted to each individual case, thereby meeting the three aims of Berwick. The creation of organizations and entities that promote a thorough and transparent evaluation and selection of medicines emerge as essential allies to patients³². Likewise, there are tools available for the adequate interpretation of data from clinical trials. These tools are based on objective criteria and enable correct therapeutic decision-making, which directly benefits patients and, indirectly, society^{33,34}. This, however, collides with some situations in which the non-funding or restriction of medicines in certain clinical contexts is denounced, without further investigation of the reasons why these decisions are taken. An example is belantamab mafodotin in patients with refractory multiple myeloma, a drug that has been demanded by some organizations, but which benefit is unclear, with a cost yet unjustified^{35,36}.

Although not directly, regulatory agencies in charge of approving and financing medicines in healthcare systems play a key role in the process of humanising clinical decision-making and empowering patients. These entities, such as the European Medicines Agency (EMA) or the United States Food and Drug Administration (FDA) evaluate the scientific evidence currently available about the effects of drugs for specific indications^{37,38}. Patient expectations are not met and some principles of bioethics are violated if these entities approve the use of new drugs based on clinical trial data for surrogate endpoints that do not measure quality of life or survival, when other alternative therapies are already available for these diseases. The assessment of surrogate endpoints in clinical trials is acceptable when there is an unmet need in a specific clinical setting where other drugs have not demonstrated a clinically relevant benefit, or when the patient has a good prognosis and the surrogate endpoints assessed correlate with final endpoints^{39,40}. The approval of new drugs based on immature results that do not meet these criteria might result in a patient receiving a therapy under an unacceptable level of uncertainty. This may influence the benefit-risk balance of a drug significantly. Thus, some patients could be treated with schemes that do not provide any clinical benefit or that may compromise their health, thereby violating the principles of Beneficence and Non-Maleficence. A recent example is the use of the combination of olaratumab and

doxorubicin in soft tissue sarcoma⁴¹, which marketing authorization was withdrawn due to an unfavorable benefit-risk balance.

Furthermore, accelerated access programs are being created to facilitate access to new medicinal products in clinical settings with unmet needs⁴². This very positive strategy, however, should be implemented with caution to prevent that entities authorize the use of new drug therapies based on interim data in diseases for which there is already a therapeutic option available⁴³.

Claims from patients for rapid access to new molecules could lead regulatory agencies to fail to complete the standard authorization procedures that guarantee the efficacy and safety of treatments. In this setting, a correct design of clinical trials assessing the efficacy and safety of new drugs represents a guarantee⁴⁴. A limitation of single-arm clinical trials is that they complicate the inference of causality between the administration of the drug and the outcomes observed. This limitation is overcome in phase III trials thanks to patient randomization and use of a control arm^{45,46}. In clinical trials, randomization prevents a potential misbalance of factors across patient cohorts. Additionally, it enables researchers to attribute clinical outcomes to a specific therapeutic intervention rather than to the natural course of the disease based on the characteristics of the patient. Therefore, data from single-arm studies (and their interpretation) are hardly generalizable to other populations.

A thorough drug evaluation also requires assessing its associated costs⁴⁷. However, some regulatory medicines agencies such as the EMA do not assess the economic impact prior to approval of a new drug. This may pose a problem in the future, considering that the cost of some therapies, such as onco-hematologic treatments, has risen considerably in the recent times⁴⁸. Although cost evaluation and humanization could be apparently unrelated, they are actually closely related. If the costs of new drugs—especially of those with a higher economic impact—are not assessed, there is a risk of underestimating the cost for the clinical benefit obtained or wasting resources, thereby limiting access of other patients to an adequate treatment³⁰. Should healthcare humanization allow failing to treat a patient because all resources were used in another patient receiving a treatment with a high level of uncertainty? Certainly, the answer is *no*. It is essential that regulatory agencies, in collaboration with the pharmaceutical industry, are committed to avoiding this situation. In this line, the Directorate-General for Pharmacy and Health Products took a step forward and incorporated pharmacoeconomic studies in decisions involving Therapeutic Positioning Reports^{49,50}, which fulfils the principle of Justice.

Hospital pharmacists specialized in drug evaluation and positioning analyze new drugs and their potential role in meeting patient needs²³. The technical criteria applied, such as efficacy, quality of life or safety, are intended to assess the extent to which a drug meets the primary needs of patients^{51,52}. Indeed, the most important endpoints to which evaluators give more relevance are called *patient-centered endpoints* or *final endpoints* (i.e. overall survival or quality). Thus, these are the most frequently claimed endpoints in studies assessing patient empowerment and opinion^{15,16}. A good

understanding and interpretation of the methods used in studies (i.e. clinical trial design) is essential to associating the effect of treatments and facilitating therapeutic decision-making. Therefore, drug selection, technical criteria are not used as a goal, but as a means to meet patient needs, thereby fulfilling the four Principles of Bioethics.

As other fields, evidence-based clinical practice has evolved over the years. As a result, the selection and place of drugs in therapeutics should be adapted to continuous advances. However, changes in the terminology of processes should not overrule the know-how accrued from long experience. An example is the recent emergence of studies based on Real World Data⁵³, formerly called retrospective descriptive studies. Although the name of the concept has changed, its limitations persist^{43,54}. A recent study revealed that Real World Data studies conducted with EMA/FDA-approved drugs for the treatment of solid tumors had low quality and lower survival rates, as compared to pivotal clinical trials⁵⁴.

Both, the humanization process and evaluation of new drugs require the involvement of a multidisciplinary team^{55,56}. Efforts should be made to raise awareness on humanization among all healthcare professionals involved in the selection, prescription and administration of drugs. The use of healthcare resources should be aimed at meeting patient preferences and expectations, which are focused on improving survival and quality of life^{15,16}. Therefore, cross-level collaboration between centers where medicines are used and regulatory medicines agencies is essential^{33,37,38}. This way, prior to the authorization and marketing of new molecules, the pharmaceutical industry should be required to provide further data about patient-centered endpoints.

Healthcare humanization has gained considerable relevance in the recent years. This movement has spread across almost all areas of hospital pharmacy, including pharmaceutical care or the dispensing of oncologic medicines to pediatric patients^{57,58}. All these interventions are aimed at meeting patient needs and preferences. As mentioned above, patients primarily want to improve their life expectancy and quality of life^{15,16}. This is also the main goal of drug evaluation. Therefore, humanization is a positive process that should always comply with the Principles of Bioethics (Beneficence, Non-Maleficence, Autonomy and Justice)^{11,25,28}. As described above, these principles are closely related to basic criteria for drug evaluation (efficacy, safety, convenience and cost). Then, where should this new humanization process be directed to? The primary goal of any healthcare humanization process should be certainly aimed at achieving patient benefit.

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Conflicts of interest

Manuel David Gil-Sierra was a member of an advisory board of Janssen Pharmaceutica, and in symposia about onco-hematologic drugs marketed by Janssen Pharmaceutica and Pfizer. The rest of authors declare no conflicts of interest.

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