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Article abstract

The growing demand for novel therapies has raised new ethical dilemmas for society. Vigorous debates have been initiated, especially after the recent *Right to Try Act* in the US, which aims to facilitate access to new agents, even at an early stage of the investigation process. This article explores the concept of patient's autonomy in accessing investigational treatments, and discusses the implications of autonomy for patients, researchers and regulatory authorities. We propose that, in cases of adequate understanding of the anticipated risks and benefits, society should accept patients' autonomy in choosing to try new therapies, even in the absence of firm data. However, basic ethical principles should not be compromised, as the medical community and society as a whole retain the right to properly evaluate the accumulated experience from such cases. These thoughts may contribute to the ongoing discussions on ethical policies in clinical research.



COMMENTAIRE CRITIQUE / CRITICAL COMMENTARY (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

Investigational Therapies and Patients' Autonomy

Trisevgeni Papakonstantinou^a, Theofilos M Kolettis^b

Résumé

La demande croissante de nouvelles thérapies a soulevé de nouveaux dilemmes éthiques pour la société. Des débats vigoureux ont été initiés, notamment après le récent *Right to Try Act* aux États-Unis, qui vise à faciliter l'accès aux nouveaux agents, même à un stade précoce du processus d'expérimentation. Cet article explore le concept d'autonomie du patient dans l'accès aux traitements expérimentaux et discute des implications de l'autonomie pour les patients, les chercheurs et les autorités réglementaires. Nous proposons qu'en cas de compréhension adéquate des risques et des bénéfices anticipés, la société accepte l'autonomie des patients dans le choix d'essayer de nouvelles thérapies, même en l'absence de données probantes. Toutefois, les principes éthiques fondamentaux ne doivent pas être compromis, car la communauté médicale et la société dans son ensemble conservent le droit d'évaluer correctement l'expérience accumulée dans de tels cas. Ces réflexions peuvent contribuer aux discussions en cours sur les politiques éthiques dans la recherche clinique.

Mots-clés

agents expérimentaux, autonomie, patient, éthique kantienne

Abstract

The growing demand for novel therapies has raised new ethical dilemmas for society. Vigorous debates have been initiated, especially after the recent *Right to Try Act* in the US, which aims to facilitate access to new agents, even at an early stage of the investigation process. This article explores the concept of patient's autonomy in accessing investigational treatments, and discusses the implications of autonomy for patients, researchers and regulatory authorities. We propose that, in cases of adequate understanding of the anticipated risks and benefits, society should accept patients' autonomy in choosing to try new therapies, even in the absence of firm data. However, basic ethical principles should not be compromised, as the medical community and society as a whole retain the right to properly evaluate the accumulated experience from such cases. These thoughts may contribute to the ongoing discussions on ethical policies in clinical research.

Keywords

investigational agents, autonomy, patient, Kantian ethics

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INTRODUCTION

The modern era of bioethics is characterized by the establishment of autonomy as a fundamental principle, defined as the person's freedom for self-determination (1). This concept has exerted enormous power on philosophical values and the realm of applied ethics; it implies respecting each person's personal views and concerns on life, or the amount of risk they are willing to undertake to combat disease. Within this frame, patients suffering from serious diseases often seek investigational treatments beyond the standard of care, such as pharmaceutical agents or devices undergoing clinical evaluation. Moreover, patients and their families sometimes wish to circumvent the limitations set by the regulations governing the conduct of clinical trials, demanding access to new therapies, despite their unknown risk-benefit profile.

Contributing to the ongoing debate on patients' rights to access experimental therapies, fuelled by the 2018 American *Right to Try Act* (2), the present article attempts to explore the boundaries of patients' autonomy. We propose that a fine interplay should be sought between the individual freedoms of choice, balanced with the moral obligation to conform to the basic principles of medical science that serve the interests of the society as a whole.

PERSONAL AUTONOMY IN MEDICINE

During the past decade, the liberty to access investigational therapies has emerged as a topic that has stirred vivid public debate. Patients that have exhausted all the available treatments seek additional options in new therapies; they are willing to undertake the risks associated with incomplete information, but several limitations set by official bodies restrict this option. In this context, the role of ethics' committees and other regulatory authorities has been questioned, with some arguing that they are taking an 'overprotective' turn, perhaps in the shadow of ethical violations in recent history.

ETHICS COMMITTEES

The concept of oversight of clinical research by strictly regulated scientific and societal bodies was introduced in the first revision of the *Declaration of Helsinki* (3). Since then, the rights of patients participating in clinical trials have been protected via the meticulous examination of the study protocol by independent bodies, referred to as *review boards* or *ethics*

committees; every investigation involving humans must seek approval by these bodies, appointed at the institutional, national and international levels. The committees consist of stakeholders with diverse expertise, aiming to protect the dignity, rights, safety and well-being of participants in clinical research.

To fulfil their mission, these bodies must be transparent in their functioning and independent of researchers or sponsors; they must take into consideration the social environment in which the research is to be performed, but without compromising internationally accepted standards. Ethics committees seek evidence that all participants are informed about the nature of the trial and that their personhood will be respected at all stages. Driven by the willingness to contribute to the advancement of medicine, patients enter a clinical trial only after adequate understanding of the nature of the trial and after giving their full consent.

SAFETY AND EFFICACY OF EXPERIMENTAL THERAPIES: WHO SETS THE BALANCE?

The progress of medical science is a difficult path full of disappointments and failures, exemplified by the fact that the vast majority of pharmaceutical molecules, evaluated at the preclinical stage, prove ineffective or harmful. More importantly, only a small fraction of investigational treatments, qualifying for clinical testing, eventually become part of the therapeutic armamentarium (4). New therapies are, therefore, rigorously validated in clinical trials, with their scale constantly rising. Such a trend is dictated by the need for firm scientific evidence for beneficial effects of a new therapy, coupled with the vigilance for patient safety; hence, the examination of the scientific rationale behind the study constitutes an important task of the ethics committees and other regulatory bodies (5). In fact, the reassurance provided to the patient, knowing that well respected authorities have reviewed a specific protocol and will supervise its conduct at all stages, often plays a major role in the decision to participate.

The regulatory authorities assess the balance between the anticipated risks and benefits for the participants, taking into account the characteristics of every specific patient-group, such as the overall prognosis and the availability of alternative therapies. In this regard, a favourable risk-to-benefit ratio is considered an important prerequisite for the approval of a clinical trial by ethics committees (5). However, such policy is open to criticism, because it cannot take into account the wide variation of needs, beliefs and life-stance of each individual patient. Thus, an arbitrarily set risk-benefit balance may eventually restrict the patient's autonomy, in cases where an individual patient is willing to undertake a greater risk than which is considered generally acceptable. Furthermore, the definition of the expected benefit may vary substantially; for example, many patients would opt to live a better, albeit shorter, life, thereby placing symptomatic relief above survival, the latter considered as the 'holy grail' of the clinical end-points in medical research.

DEMAND FOR EARLY ACCESS

The demonstration of safety and efficacy of a new therapy is a slow process, which currently requires an average of 8 years for the conduct and evaluation of clinical trials (6). This time-frame may prove too long for health professionals, who are often eager to adopt new therapies prior to their full assessment. To bridge this gap, regulatory bodies worldwide established various access programs, which have been in effect for decades (7). Through such programs, health authorities grant permission on an individual basis for a therapy, prior to its formal approval for a specific indication. In this process, the patients' interests are invariably served through their treating physicians, who acts on their behalf.

Despite such 'early access' paths, the pressure continues to rise in the new era of widely accessible information, which permits the fast dissemination of medical innovations not only to health professionals, but also to patients and their families. Those suffering from serious diseases tend to rest their hope in new therapies, even without substantial evidence of safety and efficacy. As a result, they often demand easier access, by alleviating or even bypassing the strict requirements for adequate patient safeguards set by the authorities. This pressure has led to legislative changes in several US states between 2014 and 2018, pushing for a uniform system for terminally ill patients seeking new therapies; indeed, the House of Representatives and the Senate formulated the *Right-to-Try Act*, which was signed into law by the US President on May 30, 2018 (2). This *Act* facilitates access to investigational drugs after demonstration of their safety in phase I trials; eligible patients are those with life-threatening illnesses having exhausted approved treatments, deemed unable to participate in clinical trials.

SAFEGUARDS AND OBLIGATIONS

We generally concur that society should respect patient autonomy and respond favourably to requests for easier access to investigational treatments. However, two important requirements have to be met: *First*, there must be evidence for adequate information and understanding of the anticipated risks and benefits. In this regard, information and knowledge are tightly bound with personal autonomy, whereas inadequate understanding prevents mature choices (8). To ascertain the adequacy of information on the treatment in question, the patient's understanding and explicit consent must be meticulously verified by the appropriate bodies. This statement gains particular significance, given the well-described unrealistic optimism, common in oncology patients seeking agents at an early phase of research (9,10). The risk of false hope and misconception increases markedly, if information is derived from unreliable sources, such as social media or blogs (11). It appears that such unrealistic therapeutic optimism may be observed even in persons with generally pessimistic views in their life prior to sickness (12).

The *second* important requirement for patient autonomy is the respect for the highest moral values, by the willingness to conform to the basic principles of medical research, which ultimately serve the 'common good'. It is imperative that indices of safety and efficacy are meticulously examined and weighed, and should be publically available for collective analysis. Every piece of information on safety counts, and any benefit, however small, may be valuable for some patients. Therefore, the medical community and society as a whole have the 'right to know', because only careful scientific evaluation will facilitate the widespread availability of a new treatment, if it proves beneficial, or restrict its use, if it proves harmful.

Science is a slow process that requires patience, a virtue that every researcher learns to embrace, but, understandably, it is tested during illness or suffering. Despite the inherent difficulties, the participants of early access programs remain morally obliged to allow their medical case to be processed in a strict scientific way. Claims for facilitated administration of investigational therapies without concomitant respect for societal needs may be viewed as contradicting autonomy, because the two concepts are tightly intertwined (13).

CONCLUSIONS

The momentum towards earlier access to new therapies will likely continue to rise, raising difficult ethical dilemmas for society. Under the growing demand for medical innovation, every effort should be made to provide medical care in a manner that remains scientifically, clinically and ethically sound. In this regard, indices of safety and efficacy should be accurately monitored and such experience should be recorded and made publically available for analysis. Patient organizations, researchers, health officials, medical doctors and philosophers should participate in this task, by contributing to the ongoing discussions on bioethical matters. This general call is bound to highlight and improve scientific, ethical and societal values.

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