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EXPERT OPINION

Should patients in need be given access to experimental drugs?

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Patient access to experimental drugs outside of clinical trials is called compassionate use or expanded access. Compassionate use/expanded access presents a powerful ethical dilemma in that it involves competing claims that both have moral weight: specifically, an individual patient's very understandable desire to try to extend his or her life versus the orderly and efficient functioning of a drug development and clinical trial system that benefits much larger numbers of patients. Patient advocates, the FDA, pharmaceutical trade groups, and state and national legislators in the US are all currently weighing in on patient access to experimental drugs, and new guidelines and rules are being introduced. In this editorial, we discuss the impulse to rescue individual patients facing dire diseases and underscore the ethical questions that such rescue efforts raise.

Keywords: compassionate use, expanded access, experimental drugs, investigational products, right to try

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1. Introduction

Across the US, compassionate use – or to use the FDA's preferred term 'expanded access' – has become a matter of heated public debate. Patient advocates, state and national legislators, pharmaceutical trade groups, and the FDA are weighing in on the practice of allowing patients who are not participating in clinical trials access to medical products that have not yet been approved by the FDA for use or sale. Answering the question "Should patients in need be given access to experimental drugs?" is complicated because it involves competing claims that both have moral weight: an individual patient's very understandable desire to try to extend his or her life versus the orderly and efficient functioning of a drug development and clinical trial system that benefits much larger numbers of patients.

2. Healthcare providers' duties to patients

A healthcare provider has a duty to try to help his or her patient. However, healthcare providers also have a duty not to harm patients, which generally outweighs the duty to try to help. Thus, healthcare providers have to make balancing decisions, trying to avoid doing harm, trying to help, and, more often than not, trying to ensure that any harm inflicted will be outweighed by the expected benefits of the intervention.

Such balancing decisions are even more complicated when they involve the use of experimental drugs. In the US, it is the FDA's mandate to ensure the safety and efficacy of drugs available on the market. By using an unapproved drug, a healthcare provider and patient forego this protection. As such, it would generally be inappropriate to try an experimental drug when an approved one is available. Thus, even if a healthcare provider, patient, or both are convinced that an experimental agent will cure the patient's illness, it may not be used if an approved drug is available. Clinical trials constitute an acceptable exception to this rule.

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In the case where no approved drugs are available, a healthcare provider may, under certain circumstances, ethically try an experimental drug. First, the patient must be informed that the treatment is experimental, the outcome unpredictable and possibly harmful. Second, the patient's participation must be voluntary or, if the patient is unable to voluntarily consent, participation must be approved by the patient's surrogate decision maker.

3. Who are the 'patients in need' of experimental drugs?

No data are available concerning the total number of requests for experimental drugs, who makes these requests, who receives access, or how frequently the use of the experimental agent in a compassionate use context was considered either a success or a failure. With regard to the numbers of patients seeking access to experimental drugs outside of clinical trials, FDA data from 1 October 2013 to 30 September 2014 show that 1075 patients were granted access on the basis of an undefined emergency need [1]. However, the FDA data do not represent the total number of patient requests: requests declined by either the drug's manufacturer or the patient's physician would not be reported to the FDA. Additionally, the FDA may approve programs, such as expanded access programs (EAPs) through which multiple patients may access an experimental drug. The FDA would record this as one decision.

While most media coverage of compassionate use focuses on terminally ill patients, patients who are not terminally ill but who are suffering with no relief from available treatments (e.g., migraines, Lyme disease) or who face a degenerative process for which no cure exists (e.g., macular degeneration, multiple sclerosis) also seek to try experimental drugs. Their numbers are also unknown.

4. How do patients access experimental drugs?

Ideally, patients who wish to try an experimental drug should do so in a clinical trial. In a trial, outcomes, including adverse events, are monitored, problems identified, and, should the need arise, treatment provided to address side effects or other adverse events. However, for a variety of reasons, not all patients are eligible or willing to participate in a clinical trial.

Some companies offer EAPs through which patients can access an experimental drug. These patients have data collected that are of use to the company but often the amount of data is less than in a clinical trial and there is no possibility of the patient receiving a placebo.

Outside of clinical trials and EAPs, there are provisions made for emergency use of experimental drugs for individual patients. In these situations the focus is solely on saving the patient, not on gathering data for drug development. Indeed, given the fact that these patients are often in extremis, drug companies often wish to isolate such data from that derived from clinical trials. In the US, emergency use of an experimental drug requires advance approval by the manufacturer of the experimental drug, the FDA, and the institutional review board (IRB) of the facility where the attempt will be conducted [2]. The manufacturer has no obligation to make an experimental drug available and may say no without legal repercussion. According to the agency's records, the FDA approves the vast majority of requests [3]. No data are available concerning IRBs' treatment of requests.

5. Brief historical overview

Patients have demanded access to experimental drugs outside of clinical trials especially since the AIDS epidemic [4,5]. Indeed, programs to allow patients such access gained the moniker of 'compassionate use' for the reason that they were understood as a compassionate reaction to the fact that people were dying from a generally untreatable disease (AIDS) faster than scientific protocols of the day were able to offer solutions or even grounds for much hope of a cure. Taking their cue from AIDS activists, cancer activists began pressuring pharmaceutical companies to make experimental drugs available to those who were unable or unwilling to participate in clinical trials. These activists scored a number of victories in which companies set up compassionate use programs [6-8].

In 2001, 21-year-old cancer patient Abigail Burroughs, who had run out of conventional treatment options, was informed of two investigational drugs that might be of use to her: Imclone System's C225 (Erbitux) and Astra Zeneca's Iressa. Abigail, her family, and her supporters lobbied the companies to make these drugs available; however, Abigail died in mid-2001. Her family founded the Abigail Alliance, an organization devoted to "helping create wider access to developmental cancer drugs and other drugs for serious life-threatening illnesses" [9]. The Abigail Alliance sued the FDA leading, in 2007, to a federal court of appeals ruling that affirmed FDA's authority and found no right to access an investigational drug [10].

6. Current reforms

In the US, trade groups, patient advocates, state and national legislators, and the FDA are all weighing in on the practice of allowing patients who are not participating in clinical trials access to medical products that have not yet been approved for use or sale. In 2014, the Biotechnology Industry Organization (BIO) released a statement in which it promised that its Bioethics Committee would "continue to work on developing a better path forward for all parties involved in" compassionate use cases [11]. Likewise, the Pharmaceutical Research and Manufacturers of America (PhRMA) released a policy to take effect on 1 June 2015 proclaiming its commitment "to continuing its work with patients, patient advocacy groups, regulatory authorities, healthcare practitioners, academia and

policymakers, to help ensure that there are appropriate and targeted regulatory approaches to accelerate the development and availability of innovative new medicines for patients" [12].

At present, 17 states have passed the so-called 'Right to Try' laws, and many others are considering similar legislation. These laws claim to facilitate terminally-ill patients' ability to access experimental drugs by removing the requirement for FDA and IRB approval. These laws are controversial on many grounds, including both the inability of states to legislate about federal matters and whether these laws accomplish anything other than the creation of false hope [13,14].

There are many questions about the laws themselves [15-18]. They contain no language requiring manufacturers to provide products: thus, a patient's 'right' to access pertains only to freedom from interference from the FDA. Furthermore, these laws require only that experimental products have completed Phase I safety testing: thus, they offer no promise that the treatments will be effective or truly safe in an ill patient. To date, no patient has received access to a drug via right to try legislation that was not already available under the pre-existing expanded access policies. Despite these flaws, right to try bills are popular, gaining the support of legislators, the media, and many patient advocacy groups.

On the federal level, US Congressman Michael McCaul (R-Texas) introduced H.R. 5805, the Andrea Sloan Compassionate Use Reform and Enhancement (CURE) Act, which would reform certain aspects of compassionate use [19]. Among other reforms, this act would require the manufacturers of certain types of drugs to make their compassionate use policies publicly accessible; it would require the government to collect and analyze certain information concerning which patients requested and received compassionate use; and it would create an expert body to evaluate compassionate use.

Finally, within the FDA there have been changes with regard to compassionate use. In February 2015, the agency announced that an internal working group had revised the paperwork necessary to request compassionate use. Right to try advocates claimed that it took physicians approximately 100 h to complete the paperwork, ignoring reports of many cases in which the timeline from request to decision was made in hours [20]. After the paperwork revision, the FDA announced that the new form ought to be able to be completed in 45 min [20,21].

7. Societal considerations

Although healthcare providers are obligated to focus on the well being of their patients, they also have a vested interest in the development of new drugs that will benefit not only current patients but also new generations of patients. Deciding whether to allow patients who may benefit from experimental drugs to access them must be done cautiously in order to not slow the approval of new drugs. A negative outcome in a compassionate use context may result in the abandonment of an experimental drug, in the requirement of additional testing of the drug, or in the financial crippling of the company developing the drug. While the FDA has repeatedly stated that adverse events in compassionate use contexts will not be held against a drug when it comes up for approval, pharmaceutical companies are skeptical of this claim, making them reluctant to provide access to their experimental drugs. Successful outcomes in compassionate use also pose a risk to drug development in that patients may opt to try to get access to a drug through compassionate use rather than by enrolling in clinical trials.

All agree that patients seeking an experimental drug need to have made an informed, voluntary decision. But, many patients suffer from the therapeutic misconception, the mistaken belief that research is curative or at least helpful, when the very opposite is sometimes true. Unless a neutral party like an IRB or ethics committee is involved in reviewing consent procedures, it is hard to see how true consent will be achieved.

8. Expert opinion

When a tragic story about a desperate patient makes headlines, the American public looks to castigate some entity to for failing to rescue the individual. The two most common scapegoats are the FDA and drug companies. Americans are keen to rescue those who find themselves in dire straits, and they have supported social media campaigns intended to pressure drug companies into granting access to experimental drugs. Yet this kind of support for patients is situational, often strong when the 'innocent victim' is a child but weaker when the patient is older, not photogenic, perceived as morally flawed, or seen as contributing to their own illness [22].

While pharmaceutical companies insist that the FDA plays a vital role in both drug development and patient protection, right to try laws are premised on the idea of removing the FDA from compassionate use decisions. At the same time, when a company articulates the needs of future patients as a rationale for focusing company resources (time, money, and manpower) on moving an experimental drug toward FDA approval rather than running a compassionate use program, this argument is given short shrift and often dismissed as self-serving or callous by a skeptical media and disbelieving public [23].

Americans believe in rescue, whether that means providing for emergency department care for everyone or seeking to free miners trapped in a mine collapse, a child trapped in a well, or a hiker stuck on a mountaintop. If rescue, even when costly and against long odds, is an important moral value of our society, then society must ensure that access to rescue is fair, transparent, and affordable by those in need. At the moment, access to investigational products is available only to the lucky few who know about it, can draw attention to their plight, navigate the process of requesting it, and who are given access by drug companies, either by the company's own decision or

as a result of pressure brought by an advocacy campaign or powerful person. But who is truly deserving, what right they have to obtain experimental drugs, how this access will be paid for and monitored, who will be accountable for vetting the merit of such requests, and how to balance the claims of current and present patients against future patients remain unresolved despite the enactment of right to try laws and other efforts to reform compassionate use.

Given a lack of either societal or professional consensus about how best to handle the allocation dilemma at the heart of compassionate use, procedural protections become very important. Providers must seek to inform their patients about the availability of experimental treatments to the best of their ability, making clear that both benefit and harm could result. Legislators and others involved in rule-making must look at right to try and other policies and ensure that they protect potentially vulnerable patients from therapeutic misconception, overly eager researchers, and con artists looking to exploit the desperate for personal profit. All stakeholders must also devote themselves to addressing the special issues raised by populations such as those unable to make their own decisions on account of age or disability. Common sense protections may include requiring second opinions of experimental recommendations, while policies that would maximize equity may address such issues as granting non-terminally ill patients the same access to experimental medications as terminally ill patients.

Compassionate use decisions will be made on an array of factors such as disease entity; anticipated outcome with and without the experimental agent; degree to which the experimental agent has been tested [24]; and the cost and/or availability of the experimental agent. At present, it seems impossible to formulate an ethical one-size fits all policy. The best path forward is to devote attention to concerns about fair access, mitigating costs, ensuring informed consent, vetting proposed remedies and those offering them, and broadening access without destroying the current regulatory system which guarantees the safety and efficacy of drugs and interventions for all now and in the future.

Declaration of interest

AL Caplan and A Bateman-House serve as non-voting, non-paid chair person and deputy chairperson of the compassionate Use Advisory Committee (CompAC), an external, expert panel of internationally recognized medical experts, bioethicists, a patient representative formed by NYU School of Medicine, which advises the Janssen division of Johnson and Johnson about requests for compassionate use of some its investigational medicines. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Bibliography

1. Expanded Access Submissions Receipt Report Oct 1, 2013-Sep 30, 2014. Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/UCM430188.pdf
2. This is not the case in the 17 states that have passed so-called “Right to Try” laws, which will be discussed elsewhere in this editorial
3. For the most recent numbers from the FDA, see Expanded Access Submissions Receipt Report Oct 1, 2013- Sep 30, 2014. Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/UCM430188.pdf
4. Buhles WC. Compassionate use: a story of ethics and science in the development of a new drug. Perspect Biol Med 2011;54(3):304-15
5. Darrow JJ, Sarpatwari A, Avorn J, et al. Practical, legal, and ethical issues in expanded access to investigational drugs. N Engl J Med 2015;372:279-86
6. See, for example, United States, Congress. House, Committee on Government Reform. Compassionate Use of Investigational New Drugs: Is the Current Process Effective?: Hearing before the Committee on Government Reform, House of Representatives 107th Congress, 1st Session, June 20, 2001. U.S. Government Printing Office; DC, USA: 2002
7. Burke MC. Oncology compassionate use, single patient exemptions and expanded access: a discussion of policies and programs. Masters thesis, Massachusetts College of Pharmacy and Health Sciences 2002
8. Bazell R. Her-2: the making of herceptin, a revolutionary treatment for breast cancer. Random House; New York, NY, USA: 1998
9. The Abigail Alliance mission. Available from: www.scotusblog.com/archives/07-444-cb.pdf [Last accessed 28 March 2015]
10. Abigail Alliance v. von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007). Available from: www.scotusblog.com/archives/07-444_ob.pdf
11. Biotechnology Industry Organization. BIO statement on compassionate use 2014. Available from: https://www.bio.org/articles/bio-statement-compassionate-use
12. PhRMA. Principles on conduct of clinical trials communication of clinical trials results. Available from: http://www.phrma.org/sites/default/files/pdf/042009_clinical_trial_principles_final_0.pdf [Last accessed 29 December 2014]
13. Drug and Device Law. On “right to try” legislation. 2014. Available from: http://druganddevicelaw.blogspot.com/2014/10/on-right-to-try-legislation.html
14. Gorski D. “Right to try” laws and dallas buyers’ club: great movie, terrible for patients and terrible policy. Science-Based Medicine

2014. Available from: http://www.sciencebasedmedicine.org/right-to-try-laws-and-dallas-buyers-club-great-movie-terrible-public-policy/

15. Caplan A. Right-to-try laws do nothing to pay for unapproved drugs. Iowa City Press-Citizen 2014. Available from: http://www.press-citizen.com/story/opinion/editorials/2014/08/20/right-try-laws-nothing-pay-unapproved-drugs/14302827/
16. Bateman-House A, Caplan A. Drug-right bills give patients false hope. Philadelphia Inquirer 2014. Available from: http://www.philly.com/philly/opinion/20141116_Drug-right_bills_give_patients_false_hope.html
17. Bateman-House A. Are right to try laws a good idea? National Coalition for Cancer Survivorship 2014. Available from: http://www.canceradvocacy.org/news/guest-post-are-right-to-try-laws-a-good-idea/
18. Wilkens RB. Is 'right to try' the right fit for better access to investigational drugs? IRB Advisor 2015;21-3
19. Congressman Michael McCaul. Available from: http://mccaul.house.gov/sites/mccaul.house.gov/files/Andrea%20Sloan%20CURE%20Act.pdf
20. Lowes R. FDA to simplify "compassionate use" drug applications. Medscape Medical News 2015. Available from: http://www.medscape.com/viewarticle/839292
21. Gaffney A. From 100 Hours to 1: FDA Dramatically Simplifies its Compassionate Use Process, Regulatory Affairs Professionals Society 2015. Available from: http://www.raps.org/Regulatory-Focus/News/2015/02/04/21243/From-100-Hours-to-1-FDA-Dramatically-Simplifies-its-Compassionate-Use-Process/
22. Kroll D. Rescuing Compassionate Use from Social Media and Death Threats 2014. Available from: www.forbes.com
23. Caplan A, Moch K. Rescue me: the challenge of compassionate use in the social media era. Health Affairs 2014. Available from: http://healthaffairs.org/blog/2014/08/27/rescue-me-the-challenge-of-compassionate-use-in-the-social-media-era/
24. Caplan A, Plunkett C, Levin B. Selecting the right tool for the job. Am J Bioeth 2015;15(4):1526-32

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