Risks and Benefits of Innovative Off-Label Applications
Caitlin E. Weber


FDA-approved therapies occasionally prove insufficient to treat certain diseases or specific patient populations. In such cases, physicians often turn to drugs or devices that have been approved for use in other settings. Such off-label applications of therapy carry a number of potential risks and uncertain benefits, given the lack of evidence and oversight supporting their use. This article examines some of the major ethical challenges associated with off-label innovation in the context of the controversial off-label use of drug-eluting stents, along with the somewhat more promising use of recombinant activated clotting factor VIIa (rFVIIa) in pediatric patients, a group that poses unique challenges when it comes to innovation.

Ethical Challenges in Off-Label Therapies
In her discussion of the ethical issues associated with off-label device use, Rebecca Dresser draws attention to the complex interaction between law and medical ethics that arises when regulatory practices and the drive for innovation come into conflict with one another [1]. She approaches this issue through a discussion of drug-eluting coronary stents (DES), FDA-approved devices for the management of certain forms of coronary artery disease, specifically small, newly diagnosed blockages.

Since the approval of DES in 2003, it has been increasingly used off-label for high-risk diseases, such as large blockages or small blockages in patients with comorbidities. These indications are quite different from the relatively low-risk conditions for which the device was approved. In 2007, a number of negative case reports led an FDA advisory panel to issue a tentative warning concerning off-label use of DES, citing adverse effects including “increased risk of thrombosis, death, or myocardial infarction compared with on-label use” [1]. A recent study by Carlsson et al. that analyzed outcomes of over 30,000 Swedish patients who received a stent in the past 7 years supported the panel’s conclusions by demonstrating a statistically significant higher risk of myocardial infarction associated with the off-label use of the device when compared with on-label use [2].

Despite studies such as Carlsson et al.’s, Dresser points out that insufficient evidence concerning off-label applications continues to be a significant barrier to safe off-label
use of DES in patients with arterial blockages. She estimates that more than half of all patients receiving DES today are receiving them off-label, suggesting a very real need for better regulation and oversight. Although several professional groups, including the American Medical Association and the American Academy of Pediatrics, have issued general recommendations concerning off-label therapies, most choices fall to individual physicians who must balance their patients’ medical needs with the limited data supporting most off-label uses [1].

Dresser describes a number of significant challenges to obtaining the data necessary to remedy the lack of evidence supporting off-label DES use. Even when a drug or a device has not been FDA-approved for a specific application, manufacturers are often permitted to discuss off-label uses with physicians [3]. Furthermore, with off-label use already so common, there is little financial incentive for product manufacturers to fund the clinical trials needed to test efficacy and safety, making such research costly and impractical. An additional confounding factor lies in the immense difficulty of conducting research in certain patient populations: most clinical research is done with adults and as a result there are fewer therapies explicitly approved for use in children and older adults, necessitating more off-label applications for these patients due to insufficient on-label options [1].

The willingness of individual physicians to implement off-label therapies without sound clinical evidence varies widely. When physicians do use these treatments, the process of gaining informed consent becomes exceedingly problematic. Dresser observes that there is no legal obligation on the part of the physician to inform patients of the off-label status of a therapy. As a result, many patients could be receiving devices such as stents without understanding the nature (or in some cases, lack) of clinical evidence supporting the physician’s choice of treatment—a practice in clear conflict with the fundamental principle of respect for persons underlying all ethically sound medical decision-making.

**Pediatric Medicine and the Need for Innovation**

Off-label therapies occupy a unique position within the context of current medical innovation. New applications of old therapies have paved the way to important medical advances, as evidenced by the numerous drugs designed for the treatment of one condition and later shown to be beneficial in the treatment of another. Surgical innovation has followed a similar pattern, from early surgeons’ developing novel ways to tie a knot to the introduction of robotic surgery in recent years [4]. In order to move from research toward innovation, new ideas must be applied directly to patients, a practice with some unavoidable degree of risk. For most devices and drugs, this transition is carefully regulated through the three phases of clinical trials and FDA approval, but, in the field of pediatrics, the difficulty of conducting the required trials with children has necessitated a different approach.

The responsibility to respect the patient’s right to autonomy becomes more complicated when treating young patients who lack the ability to make informed and rational medical decisions on their own behalf. As Riskin et al. acknowledge, this
has required physicians to favor “the best interests of the child” over “respect for autonomy” (a standard component of caring for adult patients) when insuring the ethical treatment of children too young to provide informed consent [5]. Generally, parental permission and child assent determine these “best interests.” While this approach may be sufficient for some medical decisions, such as choosing between various on-label therapeutic options, it seems inadequate when discussing enrollment in a randomized controlled trial. While a 12-year-old may understand that a trial is experimental or even wish to be enrolled in one out of altruistic motives, not all do, and it becomes difficult to justify more innovative approaches in patients who are unable to comprehend the nature of the intervention. Apart from the ethical questions raised by research using young children, clinical trials can be extremely expensive and cost often becomes a prohibitive feature [5].

With such insufficient research concerning the use of certain drugs and devices in children, doctors treating sick children may be forced to choose between an off-label use of a therapy proven to be effective in adults or a potentially less effective on-label option. Krummel explains this dilemma by providing the example of chemotherapeutic drugs, the vast majority of which have not been approved for use in children due to the costs and risks associated with conducting the needed trials for FDA approval [6]. Despite this fact, pediatric cancer patients do receive chemotherapy because the risks of administering even an off-label drug are deemed slight when compared with those of untreated cancer.

**Responsible Applications of Innovative Therapies**

Though Dresser’s concerns about off-label innovation in the use of DES are sound, pediatric medicine requires a different approach. As long as issues like cost, safety, and ethical treatment of the patient drive most research to be conducted in adult populations, physicians will have to rely on technological and medical advances tested in adult patients, carefully applying them to younger children without the prerequisite clinical trials. As Krummel points out, this is not necessarily a bad thing, for “children have benefited enormously from the duality of technology development, in which a technology developed for one population—either adult or pediatric—ends up benefiting both populations” [6].

One notable example of successful off-label innovation is rFVIIa. Originally developed as a hemostatic agent for a specific subset of hemophilia patients, rFVIIa has been used over the past decade to treat conditions for which it has not been FDA-approved. These off-label uses include platelet disorders, disseminated intravascular coagulation, and the management of excessive bleeding during surgery in some patients without coagulation disorders [7, 8]. While there are several scenarios in which prospective randomized trials have demonstrated either no benefit or considerable harm associated with the off-label use of rFVIIa [7], its use in children with excessive bleeding has been associated with significant clinical benefit thus far [8]. These promising results obtained by Young et al. support the conclusion reached by Riskin and his colleagues that pediatric medicine occasionally demands that risks be taken with off-label treatments in order to provide clinical benefit. While the
success of such innovation can vary greatly depending on the specific off-label application being considered, the large number of articles and case studies published on this topic has made it possible to identify those patients who will receive the greatest benefit from off-label use of rFVIIa [7].

While all off-label applications require a great deal more evidence, oversight, and post-market surveillance than on-label use [1], and carry potential risks, they should not be dismissed altogether. Further research assessing the safety of therapies such as rFVIIa and DES is important if their approved on-label uses are to be expanded to encompass current and consistently successful off-label uses. Likewise, any potential off-label use should be carefully considered in light of all available evidence, as well as a respect for the rights of the research subject and patient.

References
3. Dresser, S64.

Caitlin E. Weber is a second-year medical student at Albany Medical College in New York. She graduated with a bachelor’s degree in English and biology from the College of William and Mary.