A Hemorrhage of Off-Label Use

For 2 millennia, medicine was guided by the principles of logic. One discerned the cause of a given condition and then applied a treatment that would be expected to correct the underlying disease process. As long as the cause, pathophysiology, and therapeutic mechanism all made sense, it was not thought necessary to look too hard at how well anything worked. This internally consistent approach to health care gave us purgatives, bleeding, mutilative surgeries, and a host of herbal and pharmaceutical treatments that fit perfectly with prevailing views of disease etiology. However, most therapies were ineffective, caused serious side effects, or both. The emergence of modern medicine from its dark ages began in earnest in the middle of the 20th century, when we began to subject treatments to randomized, controlled trials to find out whether they actually did any good. A large proportion did not (1). In 1962, the U.S. Food and Drug Administration (FDA) was first given authority to require the radical criterion of trial-documented efficacy before a drug could be granted marketing approval (2).

Armed with this powerful intellectual tool, medicine has made impressive headway in the past 50 years in separating the therapeutic wheat from the chaff of quackery. Countless lives were saved because we got better at distinguishing treatments that worked from those that did not or that harmed patients (3). New laws and policies backed the scientific superiority of the randomized, controlled trial with regulatory clout that made it the law of the land, at least for drug approval. Yet other factors weighed against this movement. First, physicians crave autonomy, as evidenced by the sometimes slow uptake of recommendations from those trials about what we should and should not do (4). Second, pharmaceutical manufacturers found that substantial profits could be made by selling their products to a population much larger than the limited group of patients for whom high-quality and FDA-reviewed efficacy data actually exist. Off-label marketing campaigns flourished in the 1990s and early 2000s, with several companies promoting drugs for uses for which there was neither FDA approval nor credible evidence of efficacy (5).

Of course, a drug may have reasonable evidence supporting its use in particular clinical situations even if the FDA has not defined these as approved indications, perhaps because a manufacturer has not formally applied for that designation. For example, propranolol was initially approved for tachyarrhythmias, and its use as an antihyperensive and antianginal agent was at first “off-label.” At present, rosuvastatin (Crestor, AstraZeneca, Wilmington, Delaware) is the only statin that is approved by the FDA for some patients with high C-reactive protein and normal low-density lipoprotein cholesterol levels, although many researchers in this area believe that other statins may have similar efficacy for this purpose. Thus, off-label prescribing can run the gamut from adequately data-driven to truly implausible and potentially harmful. The latter case is illustrated by gabapentin (Neurontin, Pfizer, New York, New York), whose manufacturer agreed in 2004 to pay the government $430 million to settle charges of improper off-label marketing. Its promotional campaigns had been so successful that by 2004, an estimated 90% of Neurontin sales were for off-label uses (6), including many indications with little convincing evidence of efficacy. A recent review of off-label prescribing among office-based physicians found that a sobering 73% of off-label prescribing had little or no scientific support (7).

This brings us to the case of recombinant factor VIIa (rFVIIa) (NovoSeven, Novo Nordisk, Bagsværd, Denmark), the recombinant procoagulant originally approved in 1999 solely for the management of patients with hemophilia, especially those who had developed inhibitors to factor VIII. However, not many persons have hemophilia and even fewer have inhibitors to factor VIII; in fact, there is so little hemophilia in the marketplace that rFVIIa was approved as an orphan drug under a legislative program designed to incentivize drug development for patients with rare diseases. That law provides manufacturers with numerous financial benefits, including tax breaks for research and 7 years of guaranteed market exclusivity after approval.

However, in this issue, Logan and colleagues (8) show that use of rFVIIa in hospitalized patients without hemophilia grew more than 140-fold from 2000 to 2008 (8). By the end of that period, its approved indication for hemophilia comprised only 3% of its in-hospital use, with 97% of its use for off-label indications, including cardiovascular surgery, trauma, intracerebral hemorrhage, and other purposes. One explanation may derive from the understandable desire of surgeons and neurologists to protect their patients from excessive bleeding, and such use has the Galenic justification of appearing logical on its face: “The patient is bleeding! Administer a procoagulant!”

It is not yet clear whether improper promotion of the product contributed to this rapid expansion of use. The manufacturer has denied such practices (9), although it is under investigation by the U.S. Department of Defense (10), which was reported to be looking into “financial arrangements between the [army] and Novo Nordisk” related to use of NovoSeven in overseas combat operations (11). There is reason to wonder how the use of an obscure recombinant coagulation factor marketed exclusively to hematologists came to be used so widely by cardiac surgeons, neurologists, and trauma specialists. Further investigation may cast additional light on this question (12).

Is such off-label use nonetheless warranted by solid trial evidence? Yank and coworkers (13) address this topic in this issue. In this study, investigators systematically reviewed the literature on the efficacy and safety of rFVIIa...
used for a variety of unapproved indications. They identified all available reports that addressed this issue and found 64 worthy of review. Only 16 were randomized, controlled trials; the others were observational studies (n = 26) that compared the treatment with another approach or had no comparator group (n = 22). Overall, Yank and coworkers found no evidence that rFVIIa reduced mortality for any off-label use; however, it did increase the risk for thromboembolism. Their findings are compatible with other recent studies (14, 15).

So here we have rapidly increasing use of a treatment that does not benefit patients and increases the risk for dangerous thrombotic events—and which the investigators estimate to cost $10 000 per dose. Allowing physician autonomy to choose medications is appealing, but not when it results in unhelpful, dangerous, and costly decisions.

With such compelling data in place about the runaway use, uselessness, and risk for this expensive treatment, what can be done to reduce it? First, if evidence should emerge that the manufacturer played a role in building a market for the unauthorized and increasingly implausible prescribing of its product, both civil and criminal responses will probably be brought to bear, as has occurred for many other instances of corporate-sponsored drug misuse (16). Second, rFVIIa is used in hospitals, which should be providing organizational oversight to protect patients, as well as the institutions’ own pharmacy budgets. In hospitals where such use continues, existing quality assurance, patient safety, and risk-management groups will surely want to look hard at these practices. Although off-label prescribing by physicians is not illegal, physicians who persist in such use in the face of clear evidence of inutility and harm could be subject to civil action by the affected patients or their heirs.

There is some good news. Both of these studies were made possible by funding from the Agency for Healthcare Research and Quality, which is devoting increasing resources to support such comprehensive assessments of both utilization and of efficacy and safety—the sine qua non of a data-driven health care enterprise (17). The study by Logan and colleagues (8) represents rigorous use of emerging data sets of medication use, and the study by Yank and coworkers (13) is a good example of a solid systematic review, a once-arcane approach that is assuming greater maturity and utility as we begin to think more clearly about the inputs and outcomes of our often out-of-control health care system. These studies provide rigorous, unbiased assessments of both utilization patterns and clinical evidence that can serve as a model for the many other issues of rational therapy decisions that physicians, patients, and policymakers face.

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