Published in final edited form as:

Ann Intern Med. 2011 June 21; 154(12): 833–301. doi:10.7326/0003-4819-154-12-201106210-00012.

ENHANCING PRESCRIPTION DRUG INNOVATION AND ADOPTION

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Abstract

The adoption and use of a new drug would ideally be guided by its Innovation and cost-effectiveness. The adoption and use of a new drug would ideally be guided by its innovation and cost-effectiveness. However, information about the relative efficacy and safety of a drug is typically incomplete even well after market entry, and various other forces create a market place in which most new drugs are little better than their older counterparts. Five proposed mechanisms are considered for promoting innovation and reducing the use of therapies ultimately found to offer poor value or have unacceptable risks. These changes range from increasing the evidence required for U.S. Food and Drug Administration approval to modifying the structure of drug reimbursement. Despite the challenges of policy implementation, the United States has a long history of successfully improving the societal value and safe use of prescription medicines.

New drugs have the potential for transformative innovation. Improvements in outcomes and adverse-effect profiles, as well as simpler regimens that improve convenience and adherence, all reflect important increases in the clinical utility of new products (1). These innovations and the cost-effectiveness of a drug would ideally guide its adoption and use. However, information about the relative efficacy and safety is only learned well after market

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entry. To complicate matters, other factors independently contribute to prescription use. Drug advertising may imply clinical benefit so persuasively that a casual reader might fail to notice the absence of the statement that really matters: “this drug has been shown to be better than its alternatives” (2). Providers and patients may infer greater quality with newer products because of a belief in the “engine of innovation,” a perception that branding indicates greater quality, and the use of price as a heuristic, as in “you get what you pay for” (3,4). These drivers of diffusion help to explain a current marketplace where most new drugs are little better than their older counterparts (5–7).

These observations are not new, but solutions to these challenges have been particularly elusive in the United States. As a result, newly released and branded therapies continue to be adopted into clinical practice without evidence of their comparative effectiveness or superior safety. Rofecoxib, ezetimibe, dexfenfluramine, troglitazone, and sibutramine provide just a few recent examples. Growing interest in comparative effectiveness research and rapidly increasing health care expenditures make propitious the reconsideration of calls to improve pharmaceutical regulation and reimbursement in the United States (8–11).

Increasing the threshold of evidence required for FDA approval

Although the Food and Drug Administration (FDA) regulates drug approval, not drug prescribing, the approval process has a critical impact on the ultimate use of prescription therapies. More rational adoption of new treatments could be achieved by increasing the quantity and quality of evidence required for FDA approval. The FDA should be empowered to require sponsors to perform active comparator clinical trials in which new treatments are compared with an existing standard of care (and placebo, where feasible) to ensure the relative efficacy and tolerability of the new treatment. The FDA could collaborate with independent consultants to define the most clinically relevant comparator and margins of non-inferiority for these trials (12). The availability of comparative efficacy and safety information at the time of drug approval would reduce the approval of inferior treatments. Moreover, the data generated by these trials would help to clarify the role of new treatments prior to the development of usage patterns that are difficult to change and which potentially expose millions of patients to harm (13). This requirement would also increase the systematic generation of evidence at the time of Agency review, augmenting federally-funded comparative effectiveness research.

The FDA should continue emphasizing patient-oriented and global clinical outcomes during drug approval, such as critical health events and health-related quality of life. In most cases, the use of surrogate outcomes such as blood pressure or inherently incomplete endpoints such as tumor response (14) to define the primary indications of a drug’s label is inadequate. Unfortunately, these endpoints can yield findings suggestive of efficacy or safety when no such benefit in direct outcomes exists (15,16). Among many examples, a recent cautionary one is torcetrapib’s increased risk of major adverse cardiac events despite its ability to raise High Density Lipoprotein cholesterol levels by 72% (17). Better detection of toxicities should focus on defining anticipated adverse events (e.g., cardiac valvular dysfunction in weight loss trials), inclusion of clinically vulnerable subpopulations such as elderly patients with comorbidities, and increasing statistical power through larger sample sizes (18).

Finally, more therapies should be evaluated in “real-world” settings whose heterogeneous populations more closely reflect those encountered in clinical practice, including pragmatic clinical trials and observational analyses augmenting safety and efficacy data from clinical trials (19).

There are several barriers to implementing these changes. Requiring active comparator trials and minimizing the use of surrogate outcomes will increase the sample sizes, duration, complexity, and costs of clinical trials. On the other hand, such changes may also increase the signal detection of potential safety concerns. Raising the threshold for approval may also increase the likelihood that companies will abandon drugs after nearly all drug development costs have been expended. There are legitimate concerns that these barriers would reduce industry research and development, suggesting the importance of greater use of marketplace incentives to promote drug innovation. Raising the evidentiary threshold required for approval need not prevent the development of valuable new therapies; it is noteworthy that the 1962 requirement for drug makers to establish evidence of effectiveness in controlled trials has been associated with increased rather than decreased innovation (20,21).

Move to a period of conditional FDA approval

Even if the evidentiary threshold for FDA approval is increased, important safety questions will remain after a drug is approved. Conditional FDA approval would help moderate exposure to new drugs that enter the market (9). During a time-limited conditional approval (such as 3 years), restrictions could apply while manufacturers implement formal data-collection plans. These could include limiting professional marketing and prohibiting direct advertising to consumers (10). After this period, full approval would be granted only if the manufacturer generated additional evidence that corroborated the safety of the drug in real-world populations. The type and amount of evidence required for granting full approval would depend on the evidence available at the time of conditional approval, the indication, and the drug itself. At a minimum, detailed surveillance data that documented possible safety concerns and the type and amount of use should be reported, but the FDA might also require trials that addressed specific safety or efficacy questions that were outstanding at the time of conditional approval. During a second review by the FDA, additional safety plans could be based on actual use patterns, and subpopulations with more favorable or unfavorable benefit–harm profiles could be identified. This is especially important because therapies may be widely used for off-label indications with little or no scientific evaluation or regulatory scrutiny (22); drug safety and effectiveness depend on the context of real-world use, which cannot be fully known or anticipated at the time of initial FDA approval. Formalizing the process of conditional approval would also provide an enforceable mechanism for phase 4 trials, which firms often do not complete (23). Although the FDA Amendments Act of 2007 provides the FDA with greater ability to enforce post approval commitments through risk evaluation and mitigation strategies, the effectiveness of these strategies has not yet been established. Conditional approval would formalize the generation and review of real-world safety information by both sponsors and the FDA. This change would stimulate sponsors to consider and evaluate clinical applications of their therapies, because such data would contribute to the viability of a drug on the market. Barriers also exist to creating a period of conditional approval. The likelihood that a drug would become a

blockbuster would decrease, at least until after the conditional approval period. The FDA could require additional trials to be done, which would increase sponsors' costs, or limit the approved patient population after further evaluation, which would further decrease revenue and willingness to invest in developing new drugs. A second formal review for each new drug would increase the burden on the FDA. As with raising the threshold for approval, legislative change would be required. In part because of these barriers, some have proposed extended patent exclusivity for firms as an incentive for demonstrating the long-term safety and efficacy of their products (8). These too have appeal, although such proposals would not provide the regulatory oversight and scientific scrutiny available through conditional approval.

ALTERING INCENTIVES TO ENCOURAGE VALUE-ADDED INNOVATION

Raising the threshold for approval and requiring a period of conditional approval could increase development costs and result in the abandonment of new treatments that might have proven useful. Providing substantial incentives for developing innovative therapies would help ensure that such treatments continue to be developed. Incentives should be structured to refocus industry efforts on developing treatments with clear clinical benefits. The FDA has successfully used patent exclusivity incentives to stimulate both the development of orphan and generic drugs and research into the safety of drugs in pediatric populations. Offering additional patent exclusivity for drugs that are unequivocal therapeutic breakthroughs for common diseases could stimulate industry to develop innovative drugs with substantial public health benefits. In addition, the FDA expedites reviews in some settings, such as with a new drug that seems to offer a substantial therapeutic advance or fill a previously unmet need (24). Innovative drugs (such as the first drug in its class) with especially strong and favorable comparative efficacy and safety data at the time of initial approval could also be granted exemptions from some or all of the restrictions of conditional approval; this would also facilitate the more rapid diffusion of these drugs.

The patent life of a drug is partly consumed by the duration of the FDA review, which has resulted in intense pressure for FDA reviews to be completed quickly. This pressure for the FDA to rapidly approve drugs is at odds with ensuring a thorough review. Several studies have concluded that the acceleration of drug reviews has compromised drug safety, although this remains a controversial area with conflicting evidence (11, 25–28) (Grabowski H, Wang YR. Unpublished data. 2006). New requirements for adequate comparative efficacy and safety assessments, such as those we suggest, would further erode patent life unless the patent laws pertaining to new drugs are changed. Extending the duration of patent life by the duration of the initial FDA review could reduce the tension between the ticking clock of patent protection and drug safety. Although these incentives would probably stimulate innovative drug development, previous regulatory incentives have had unintended consequences. For example, offering market exclusivity or extending patent duration can pass additional costs to patients, which may reduce their access to medicines. In some cases, these incentives will further subsidize blockbuster drugs. Monitoring the effects of the incentives and revising them as appropriate would be essential (11). Defining what constitutes a breakthrough and passing legislation to support this change would be challenging but ultimately fruitful.

Changing drug labeling to better inform patients and physicians

Including comparative information in prescription drug labels could also help to reduce the use of ineffective and unsafe therapies, while refocusing drug development. Like food labels, which contain standardized and practical information, drug labeling should include the information that consumers need to be well-informed health care participants (29).

Although the FDA has enacted recent changes in labeling to improve the accessibility and usability of drug information (30), these changes do not go far enough in providing patients with the information they need. Labels do not include simplified summaries of comparative effectiveness studies, distillations of benefits and risks, or descriptions of the evidence evaluating common off-label uses. Including this type of information might temper patients and prescribers' reflexive tendency to equate newness with superior efficacy and safety (31).

Summarizing the evidence regarding use of a drug is an onerous task and the evidence that patients and prescribers need most doesn't exist. Changes such as those we proposed would help to increase the availability of this information. But even with greater evidentiary standards, conditional approval, and realigned incentives, information will remain difficult to synthesize, because data regarding a particular therapy may be vast, provide conflicting evidence, and always changes over time. Such challenges may be especially great for off-label uses, because these applications have not been closely scrutinized by the FDA.

Modifying the structure of drug reimbursement by health care payers

In addition to regulatory changes Independent of regulatory changes, improved reimbursement strategies can also play an important role in reducing wasteful spending on prescription drugs. Some are already in widespread use, such as tiered formularies and other incentive-based designs, prior authorization policies, and other techniques that payers routinely use (32). Despite this, wasteful spending continues under current reimbursement strategies. For example, approximately \$2.8 billion dollars were spent in 2009 on esomeprazole (33), a drug without no clear clinical advantages over generically available proton pump inhibitors. Although the FDA issued a prominent safety advisory in April 2005 about the use of atypical antipsychotics in elderly patients with dementia, more than a year later no state Medicaid formularies had modified their prior authorization policies to steer patients towards one of many safer and less expensive alternatives (34). Such formularies similar did not modify coverage policies regarding rosiglitazone despite prominent safety signals. (N Shah, personal communication, October 4, 2010).

Health care payers must limit the inappropriate use of drugs for which evidence of safety, efficacy, and cost-effectiveness is insufficient. Demonstration of the cost-effectiveness of a new treatment, which accounts for a new treatment's incremental benefits and costs relative to the best available alternative, is a requirement for coverage by national health services in many other industrialized countries. Although such a shift is unlikely in the United States, data-driven approaches to payment decisions are needed to improve health and contain costs. Allowing consumers choices that factor in price differences, particularly if sufficient information to make comparative decisions is available, would likely be an acceptable approach for Americans (35). These activities can be more systematically driven by additional data made available through an altered drug approval process such as the one we

propose. For example, a recent proposal for Medicare (36) describes a dynamic pricing model that includes a tiered reimbursement scheme based on the strength of the available comparative effectiveness evidence.

The biggest challenge in improving reimbursement schemes is minimizing inappropriate use, while allowing patients who truly need treatments to have ready access. For example, administrative data are not designed for clinical purposes; thus often lacks adequate detail to be used for judgments about clinical appropriateness. This lack of detail makes it more difficult to develop value-based insurance designs, which hold promise of linking coverage to evidence and thereby reducing wasteful drug spending. Current prior authorization processes are time consuming and frustrating to providers. The presence of substantial treatment heterogeneity further complicates matters, because a treatment that may be less effective on average may still be more effective among an individual patient. Despite these challenges, the past decade reveals many missed opportunities on the part of payers to better align reimbursement with evidence of safety, efficacy, and cost-effectiveness.

SUMMARY

We describe strategies to promote more rapid adoption of truly innovative drugs, to help inhibit the reflexive adoption of noninnovative products, and to avoid the premature abandonment of older, established therapies (37). These recommendations need not be cumulative, but each could incrementally improve the adoption of prescription drugs.

Policy changes such as those we propose entail many challenges and must be carefully implemented and assessed. Such proposals such as increasing evidentiary standards or moving to a period of conditional approval would require new legislation to pass a divided Congress. Each of the proposals would touch a various stakeholders whose interests do not perfectly align. Improving labeling and payment reform require high quality information about evidence, which may be dynamic and difficult to summarize and link to payment policies even when present. Despite these challenges, there is a long history of successfully improving the safety and value of prescription drugs in the United States to improve the safety and value of prescription drugs (21), and substantial progress to be made.

Acknowledgments

The authors thank Dr. Robert H. Dworkin, Professor of Anesthesiology, Neurology, Oncology, and Psychiatry at the University of Rochester School of Medicine and Dentistry, for his thoughtful comments on an earlier manuscript draft.

Funding

Dr. Alexander is supported by the Agency for Healthcare Research and Quality (K08 HS15699; RO1 HS0189960). Dr. Stafford is supported by the National Heart, Lung and Blood Institute (K24 HL086703). These funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the manuscript for publication.

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