Should Evidence-Based Proof of Efficacy as Defined for a Specific Therapeutic Agent be Extrapolated to Encompass a Therapeutic Class of Agents?

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Our task as clinicians would be simple if all we had to do was to follow the logical sequence of identifying a biological target, finding a drug or treatment specifically affecting that target, testing the efficacy of the drug or treatment in appropriately designed clinical trials, and then prescribing only those drugs or treatments with proven efficacy and an acceptable safety profile. Drugs that affect a given biological target could be considered as a “class,” with those that show “efficacy” in clinical trials considered as therapeutic alternatives within that class. Unfortunately, the real world is not that simple. Defining precisely what we mean by class effect and efficacy becomes increasingly problematic, for example, as we have recently witnessed with calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, HMG CoA reductase inhibitors, glycoprotein IIb/IIIa antagonists, low-molecular-weight heparins, and direct thrombin antagonists. If we identify a drug that demonstrates efficacy, are the benefits of that drug generalizable to all drugs with similar biological targets? If benefits are present in one clinical circumstance, are those benefits generalizable to all circumstances in which that class of drugs can be applied? In the modern cost-conscious arena, can we substitute less expensive, mechanistically similar agents that may not have the same weight of clinical evidence support or even the same degree of clinical benefit? When is it acceptable to generalize to a class effect, or should we adhere strictly to evidence-based therapy with individual compounds? These issues can be viewed from both scientific and clinical perspectives.

Scientific Perspectives

Definition of Biological Target

As our scientific knowledge grows, our traditional grouping of drugs has become, to a large extent, obsolete. For example, there are 9 different calcium channel blockers that are approved for clinical use in the United States, which can be divided into 5 general groups on the basis of chemical structure. However, voltage-sensitive calcium channels have been classified into L, N, and T subtypes on the basis of their conductances and sensitivities to voltage. Only the L-type channel is sensitive to the dihydropyridines. Any attempt to lump all calcium channel blockers into a single class is an oversimplification and obscures important observations with therapeutic consequences. Although short-acting dihydropyridines can be harmful in the setting of myocardial ischemia when β-blockade is inadequate, such concerns do not appear to be present for the phenylalkylamines and benzothiazepines.

The anticipated advances in genomics and proteomics underscore the need to be open-minded in our characterization of biological targets. Old concepts are unlikely to serve us well as the complex interplay of receptor structure–function–drug interaction is better understood. Analogous to the Heisenberg Uncertainty Principle, as our level of under-
standing moves to the cellular and molecular levels, our ability to identify a specific therapeutic “target” becomes less and less precise.

Variations Within a Class
Even if we can agree on a biological target and identify a group of agents that affect it, variations in drug structure, metabolism, and interactions may confound the simple notion of a class effect. For example, statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A and share the common mechanism of lowering LDL cholesterol. However, statins vary in structure. Some are fungal derivatives, and others are synthetic compounds. The percentage absorption of an oral dose, amount of protein binding, degree of renal excretion, hydrophilicity, and potency on a weight basis varies among the individual agents. Specific side effects and interactions may be much more prominent with specific agents—for example, cerivastatin, which recently was withdrawn from the market.

Indirect trial-versus-trial comparisons are fraught with hazard and potentially misleading because of fundamental philosophies. The percentage absorption of an oral dose, amount of protein binding, degree of renal excretion, hydrophilicity, and potency on a weight basis varies among the individual agents. Specific side effects and interactions may be much more prominent with specific agents—for example, cerivastatin, which recently was withdrawn from the market. Atorvastatin, simvastatin, and lovastatin are metabolized through the cytochrome P450 3A4 pathway, whereas fluvastatin is metabolized through the 2C9 pathway. Thus, those statins that are metabolized through the 3A4 pathway are subject to drug interactions with anti-infective, antifungal, and antiviral agents; antidepressants; and the phenylalkylamine and benzothiazepine type of calcium channel antagonists. A stable therapeutic response to a statin in a given patient may be affected by the initiation or discontinuation of another drug that is responsible for an interaction at the 3A4 pathway level.

Thus, within a class of therapeutic agents there can be substantial individual variation in the response, side effects, and drug interactions of the individual compounds.

Assessment of Relative Efficacy in Clinical Trials
Indirect trial-versus-trial comparisons are fraught with hazard and potentially misleading because of fundamental “apples-to-oranges” comparisons secondary to differences between trials in patient populations, inclusion criteria, management algorithms, and end-point definitions. Therapeutic decision-making and guideline development now often rely on meta-analyses to handle the vast amount of clinical information available from clinical trials in cardiovascular medicine. Despite the establishment of standards for reporting meta-analyses, there are also limitations that need to be acknowledged. Without access to original source data, reliably identifying adverse events can be very difficult. Statistical testing for heterogeneity of treatment effects across drugs in a class is not a particularly sensitive analysis and is only as statistically robust as the power of the original smaller studies. Thus, a nonsignificant heterogeneity test does not necessarily exclude the presence of important variations in the response to different drugs. Pooling agents within a class can also be problematic if there are potential differences among the agents. For example, when pooled as a class, low-molecular-weight heparins are superior to placebo but similar in efficacy to unfractionated heparin for management of patients with unstable angina/non–ST-elevation myocardial infarction. If the low-molecular-weight heparins are not pooled, it appears that enoxaparin is superior to unfractionated heparin, whereas dalteparin and nadroparin are not.

Head-to-head comparisons of drugs within a class are rarely performed, given the unwillingness of industry sponsors to take on the risk of failing to show their drug is noninferior to another agent in the same class. Moreover, even if head-to-head data exist, they are generally underpowered to look at individual end points such as mortality. Statistical techniques for estimating the comparative therapeutic efficacy of “competing” compounds using indirect methods have been proposed. However, the many classes of drugs used in cardiovascular medicine have not been rigorously evaluated using such techniques, and we are therefore far from a robust database of statistical evidence comparing drugs.

Clinical Practice Considerations
The Figure shows a theoretical group of drugs that are viewed as a class because they interact with the same biological target. Drugs A, B, and C are all brand-name drugs that have been shown to be statistically superior to placebo for preventing clinical events. Note that Drug A appears to have the largest treatment effect but is the most expensive. A test for heterogeneity is negative, but it is recognized that such tests are not very powerful and could miss true heterogeneity. The US Food and Drug Administration has approved all 3 drugs for use in patients. From a regulatory perspective, no judgment is made about the relative efficacy of A, B, or C—each has individually satisfied the standard that it is effective and safe. Drug D, a chemically related compound, has not been tested in a clinical trial but is the least expensive of the group.
Clinical decision-making that is consistent with evidence-based medicine dictates that physicians should select from among the drugs for which evidence of benefit exists. Even acknowledging all the previously discussed difficulties in defining a class effect, and judging relative efficacy, a clinician might believe that Drug A is the most effective and feel that in the best interest of the patient, Drug A should be prescribed. However, as most practitioners know, the scenario does not end there. Several forces are in conflict that now place filters between the physician’s prescription pad and the patient.

Pharmacy benefit managers have appeared on the scene as fiscal intermediaries that administer pharmacy benefits for employers, health insurers, and health maintenance organizations. A variety of mechanisms are used to drive down medication costs, such as discounted pharmacy pricing for “preferred drugs,” the requirement for prior authorization from a physician before dispensing a medication, and mail-order prescription programs that supply preferred drugs in identical, opaque white containers with similar labels. Generic and therapeutic substitution of drugs is encouraged.

Generic substitution is the act of dispensing a different brand or an unbranded drug product that is the same chemical entity and meets US Food and Drug Administration criteria for bioequivalence (eg, generic lisinopril in place of brand-name Prinivil [Merck & Co.] or Zestril [Zeneca Pharmaceuticals]). Therapeutic substitution is the dispensing of an alternate chemical entity for the original drug prescribed by the physician from the same general therapeutic class (eg, a physician orders enoxaparin, but the hospital pharmacy dispenses dalteparin; a physician writes a prescription for ramipril, and the pharmacy dispenses moexipril). The American Heart Association and the American College of Cardiology have formally and vigorously opposed therapeutic substitution, arguing that it is the province and responsibility of the physician to integrate the medical history, physical status of the patient, and the disease process. Furthermore, therapeutic substitution may result in the patient’s receiving a drug that may not be effective, produces life-threatening toxicity, and interacts adversely with other drugs the patient is receiving. Therapeutic substitution is also opposed by the American Medical Association, World Medical Association, and American Academy of Family Physicians.

In some cases, before therapeutic substitution is made by the pharmacy or pharmacy benefit manager, a physician is contacted and the request is made that the prescription be rewritten for a preferred drug. We have had the experience of attempting to explain our medical reasoning over the phone to an individual who is not medically trained, is ill equipped to understand the subtleties of clinical medicine, and simply states, “The patient will be faced with a larger copay if the switch is not made.” Among the most disturbing of such encounters are those in which a request is made for therapeutic substitution to a drug from the same class that has never been evaluated in a clinical trial (eg, Drug D in the theoretical example above). Such requests cannot be condoned because they are inherently inconsistent with evidence-based medicine.

**Recommendations**

How one views class effect is a lot like “innocent until proven guilty” versus “guilty until proven innocent.” In other words, “in the absence of definitive evidence to the contrary, I will treat all agents within the class similarly,” or “in the absence of definitive evidence of equivalence, I will only use those agents that have demonstrated significant clinical benefit in randomized, controlled clinical trials.” There are minimum criteria that we would consider as necessary to define a class effect of a drug:

- A clearly defined biological target or pathway.
- Comparable efficacy demonstrated for multiple agents within the class (with multiple randomized, controlled clinical trials for each agent).
- Absence of convincing evidence that there is a member of the class that does not have comparable clinical benefit to that of other agents within the class.

There are other factors that should also be weighed by practitioners as they decide for themselves on interchangeability within a given therapeutic class.

- The absolute and relative degree of benefit for each agent.
- The exact clinical circumstances in which benefit has been demonstrated.
- The extent and the depth of the evidence in favor of a particular agent.
- The safety profile and tolerability of agents within a class. (For example: ticlopidine versus clopidogrel among the thienopyridines, with comparable antiplatelet effects but very different safety profiles.)
- The cost of the alternatives, viewed not only in terms of cost per quality life-year saved versus placebo or an established control but also in terms of cost per quality life-year lost in the case of less expensive, but also less effective, alternatives.
- The specific details of the inclusion/exclusion criteria and the exact management protocols used in the individual supporting clinical trials.
- The particular subgroups that show benefit (or lack of benefit) for agents within the class. Do all agents show similar broad (or narrow) clinical benefit?

Whenever possible, physicians should prescribe drugs for which evidence exists from clinical trials, using the doses that were actually studied in randomized, controlled clinical trials. Authors of guidelines should explicitly mention the drugs in a given therapeutic class that have been tested and make definitive recommendations one way or another as to which agents (if any) can be substituted within the class. Therapeutic substitution is a potentially dangerous practice when it
moves beyond the realm of evidence-based medicine—as it often does. Alternative methods for limiting the costs of our ever-advancing standard of care are urgently needed. The oversimplified and inappropriate use of the class effect concept is not fair to healthcare providers or their patients.

References
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