Therapeutic Substitution

Guilty Until Proven Innocent

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The most savage controversies are about those matters to which there is no good evidence either way.
—Bertrand Russell, "An Outline of Intellectual Rubbish," in *Unpopular Essays* (1950)

The "evidence" is evidence-based medicine, which defines therapeutic efficacy and safety for specific pharmacological interventions. The "weight" or power of evidence in support of treatment is maximum when determined by large, placebo-controlled, randomized trials (Level A), less definite when based on smaller randomized trials and/or clinical registries (Level B), and least reliable when dependent on expert panel consensus (Level C). Clinical practice guidelines (CPGs), such as those jointly sponsored by the American College of Cardiology and American Heart Association, provide an algorithm by which evidenced-based medicine may be applied to clinical practice. Considerable public and private industry resources are routinely expended to devise and execute randomized controlled trials that demonstrate the efficacy and safety of a specific therapeutic agent or strategy. Pharmacotherapeutic agents have traditionally been grouped into classes on the basis of a demonstrated affinity for a single biological target. However, individual members of a therapeutic class may be widely disparate in pharmacokinetic and pharmacodynamic response, side effect profile, and propensity for drug–drug interactions. For example, in the class of low-molecular-weight heparins, the US Food and Drug Administration has determined that individual agents are structurally and biochemically distinct. Unfortunately, randomized controlled comparisons of specific agents within a therapeutic class rarely are performed, and the clinician is forced to rely on much less definitive (and at times misleading) sources of information, such as indirect trial comparisons, meta-analyses of multiple trials, or statistical pooling of agents in a class. Regrettably, the complexity of clinical science is compounded by economic considerations.

Economic considerations provide the impetus to make both generic and therapeutic substitutions for agents that have established clinical efficacy according to definitive, placebo-controlled, randomized trials. Economic factors have made the choice of specific pharmacotherapeutic agents the purview of hospital pharmacies and health benefit plans, not physicians. This unfortunate situation has understandably spawned "the most savage controversies" as described by Bertrand Russell, from which the "evidence either way" is presented in the current issue of *Circulation* by Drs Ferguson and Antman[1] and Furberg and Psaty.[2] Each of these thought leaders has been intimately involved in constructing and executing multiple clinical trials that have contributed to the evidence base from which current guidelines are derived. The consistency of their expert opinions on this topic allows for potential consensus to be drawn.

The Problem

First, most physicians are resigned to the concept of generic substitution, acknowledging the potential for differences in bioavailability, side effect profile, and patient tolerance. The

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(*Circulation.* 2003;108:2611-2612.)

***Circulation* is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000103637.50536.CC**

treating physician retains discretion in this situation, and after consultation with the patient, may reinstitute the brand-name pharmacotherapeutic agent by simply prescribing "dispense as written." Most health benefit plans will not penalize the patient financially for a brand-name agent when the generic substitution is associated with intolerable side effects or diminished therapeutic efficacy.

Second, the practice of therapeutic substitution is both more challenging and less scientifically sound. Hospital pharmacies may simply take a medication with efficacy documented by large randomized trials (Level A) off the formulary and make it unavailable to the prescribing physician. The pharmacy then dispenses another agent (which may have little or no evidence-based support) from the same general pharmacotherapeutic class instead of the prescribed medicine. Drs Antman and Ferguson succinctly review the argument in support of this practice from the perspective of evidence-based medicine. Their conceptual analogy of therapeutic class effect in this context to the ethics of "innocent until proven guilty" or "guilty until proven innocent" is pertinent. The position adopted by some pharmacies that "in the absence of definitive evidence to the contrary, I will treat all agents within the class similarly" is very disturbing. In the current era of evidence-based medicine, "Get With the Guidelines,"[3] and "Guidelines Applied to Practice,"[4] when does the absence of data drive clinical practice? Although this premise would seem intuitively absurd, practicing clinicians across the United States face it daily.

As the motivation of pharmacies is inevitably procurement cost (not cost-efficacy, which considers offsets due to better outcomes) for these specific agents in question, we are reminded by Abraham Lincoln that "moral principle is a looser bond than pecuniary interest."

Drs Ferguson and Antman propose minimum criteria necessary to define *class effect* and thus to justify the practice of therapeutic substitution. First, there must exist a clearly defined biological target. Next, comparable efficacy must be demonstrated for the therapeutic "substitute" by multiple randomized controlled trials. We would add that "comparable efficacy" does not require randomized comparison, acknowledging the complexities of between-trial comparisons. However, trial construct and study population should be similar, and the efficacy demonstrated should be for the same prescribed indication. Lastly, it is helpful to the class effect doctrine if none of the class members has been demonstrated ineffective for the prescribed indication.

As pointed out by Drs Furberg and Psaty, "extrapolations are not accepted by regulatory agencies" (ie, the US Food and Drug Administration). Why should extrapolations be accepted by hospital or health plan pharmacy and therapeutic committees? In part, this incongruity is spawned by vagueness in the definition of class effect. In fact, as stated by Drs Furberg and Psaty, "the term *class effect* has never been defined scientifically, clinically, or from a regulatory perspective."

A Potential Solution

What remedy exists for the current situation? Extreme caution and concern are expressed in the admonitions of our thought leaders: "therapeutic substitution is a potentially dangerous practice when it moves beyond the realm of evidence base—as it often does"; "prescription of a me-too drug with incomplete documentation and unknown fully effective dosing ought to be restricted."

As we emerge from the era of evidence-based CPG development into the new era of measuring guideline implementation and monitoring adherence, who should be the arbiter of pharmacy practice? Most prescribing physicians already have expressed concerns about the legitimacy of therapeutic substitution, to no avail. Our professional societies allocate considerable resources to construction of CPGs. Furthermore, the Center for Medicare and Medicaid Services plans to implement monitoring of guideline adherence with incremental reimbursement for maintenance of "best-practice" benchmarks. These agencies could and possibly should mandate against the "lack of evidence-based medicine" approach in the current "innocent until proven guilty" strategy used to support the practice of therapeutic substitution. How does one mandate best-practice guideline-driven algorithms for care and not assure access to pharmacotherapeutic agents considered best in class according to randomized trials and guideline recommendations? Indeed, should we educate physicians and grade their performance without placing the same high standards on the facilities in which they practice?

We believe that the practice of therapeutic substitution should be specifically addressed by the same American College of Cardiology/American Heart Association task forces that construct CPGs and by the Center for Medicare and Medicare Services, who will monitor guideline adherence. Efforts to assure that the medicines considered the "best available" on the basis of well-constructed and well-executed randomized controlled trials are indeed available would be in the best interest of our patients.

References

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