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A users' guide to understanding therapeutic substitutions

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Abstract

Therapeutic substitutions are common at the level of ministries of health, clinicians, and pharmacy dispensaries. Guidance in determining whether drugs offer similar risk–benefit profiles is limited. Those making decisions on therapeutic substitutions should be aware of potential biases that make differentiating therapeutic agents difficult. Readers should consider whether the biological mechanisms and doses are similar across agents, whether the evidence is sufficiently valid across agents, and whether the safety and therapeutic effects of each drug are similar. This article uses a problem-based format to address the biological mechanism, validity, and results of a scenario in which therapeutic substitutions may be considered.

Keywords: Therapeutic substitutions; Class effects; Network meta-analysis; Generic substitutions; Statins; Evidence-based medicine

1. Introduction

By its broadest definition, a therapeutic substitution (or therapeutic interchange) occurs when a medication is automatically provided in a manner other than prescribed, whether by changing the dose, formulation, or medication. A guideline by the American College of Clinical Pharmacy provides a comprehensive review on therapeutic substitutions [1]. This guideline recommends that therapeutic substitution policies be limited to institutions and health systems with a functioning formulary, pharmacy and therapeutics committee, that rationale for each substitution policy be readily available to all clinicians, and that the clinical, economic, and humanistic impact be measured.

Determining the suitability of therapeutic substitutions is usually based on an evaluation of the empirical data and pharmacopathophysiologic reasoning. Because of the typical inadequacies of the former and the subjective nature of the latter, a rigorous and reproducible process is required to support the establishment of what are intended to be widely acceptable and valid therapeutic substitution policies.

In this users' guide (see Box 1), we focus on evaluating the suitability of substituting one medication when another is prescribed as a policy affecting a population of patients as opposed to when an individual pharmacist uses their clinical discretion to substitute one medication for another. To justify the substitution policy, the replacement medication needs to demonstrate predictable effectiveness that is equal to that of the originally prescribed medication but is preferred because of one or more distinct advantages including improved tolerability, safety, access, cost, or convenience. Therapeutic substitution differs from generic substitution, which involves the use of a pharmacokinetically equivalent form of the same medication as a generic. A therapeutic substitute need not be from the same pharmacological class and is typically based on evidence in the form of randomized outcome studies. It can differ in its mechanism (pharmacology) and its pharmacokinetics, resulting in clinical differences in its adverse effect and drug interaction profiles, desired and undesired [1].

The ability for health workers to change a prescribed medication without involving the prescribing physician varies

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What is new?

Key findings

- Therapeutic substitutions are the change of a prescribed medication by a person or institution other than the prescribing clinician. Therapeutic substitutions broadly assume similar effectiveness and safety of the substituted drug. However, methods to assess whether the drugs are similar have been lacking. In this review, we suggest questions a user should ask when determining if substitutions are valid.

What this adds to what was known?

- We ask as a series of methodological questions to ascertain the similarity of the drugs, the validity of the evidence and whether the results are clear. We demonstrate that even in common prescribing areas, such as statin therapy, there are potentially important differences at the level of the biological agent, the quality of the evidence, and the clarity of the results.

What is the implication and what should change now?

- This review suggests users should be cautious in assuming therapeutic similarity and seek convincing evidence before a therapeutic substitution can be applied with confidence.

within and across countries. In Canada, for example, 6 of 13 provinces permit generic and therapeutic substitutions [2]. In the United Kingdom, pharmacists are permitted to conduct therapeutic substitutions for within-class agents and across classes for more minor conditions [3]. Much of Europe, as well as New Zealand and Australia, have followed suit [4,5]. In the United States, certain health systems and health management organizations may permit therapeutic substitutions, but this is normally decided upon by private companies rather than a government regulator [6].

Hospitals (health districts and trusts) have had therapeutic substitution policies in place for decades [7], a classic example being the automatic use of oral amoxicillin when oral ampicillin is prescribed. Amoxicillin's advantages are reduced dosing frequency (every 8 instead 6 hours) and reliable absorption regardless of stomach contents. Policy decisions for therapeutic substitutions are generally proposed by a hospital or health district's Drugs and Therapeutics (D&T) committee, composed of hospital physicians, pharmacists, and nurses, and ratified by the Medical Advisory Committee (or its equivalent). Nonetheless, these policies occasionally conjure up acrimony, often based on a judgment-based disagreements or a misunderstanding of the process [8–10].

Box 1 Readers guide questions

The biological agent

- Are the agents biologically similar?

Are the sources of evidence valid?

- What is the geometry of evidence for your evaluation?
- Does evidence exists from large head-to-head evidence?
- If indirect evidence is used, is it sufficiently convincing?
- Are the end points in clinical trials of similar importance that a patient would consider them equal?

What are the results?

- Are there important differences in the number of trials representing different agents?
- Are treatment effects similar across agents?
- Would the addition of sufficiently powered evidence change the results of direct or indirect evidence?
- Are adverse events similar across agents?
- What is the overall quality and limitations of the evidence?

An underlying assumption with therapeutic substitutions—an assumption that may or may not be accurate—is that the replacement drug offers similar therapeutic efficacy and at least as good a safety profile as the prescribed drug. However, the methods for determining whether two drugs exhibit the same therapeutic effectiveness or safety are not well established. To date, considerations regarding the methodological shortcomings of therapeutic substitution have received inadequate consideration [10,11]. Conceptually, determining whether a drug is sufficiently similar to another drug should be based on its evidence profile rather than its name or mechanism of action alone.

Using a series of methodological questions developed by methodological and clinical experts (Box 1), we use the clinical example of 3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors (statins) to determine whether therapeutic substitution offers patients a sufficiently similar efficacy–safety profile to justify interchangeable use of different statins. We chose statins as the example because they have been well evaluated in more than 80 randomized clinical trials (RCTs) [12], are one of the most