Therapeutic Substitution and Formulary Systems

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The practice of therapeutic drug substitution has become common throughout the United States, often without the awareness of many physicians. It occurs to some extent in more than 52% of the nation's acute care hospitals and more than 30% of health maintenance organizations (HMOs) (1, 2). Therapeutic substitution entails dispensing a drug different in chemical structure from the one originally prescribed. The substitute must be from the same therapeutic class (therapeutic alternate) and have the same pharmacodynamic and pharmacokinetic properties (for example, cefazolin for cefotaxime; cimetidine for ranitidine).

Therapeutic substitution originates in an institution's formulary system. Arising from the need for rational drug therapy within the context of increasing medical care costs, the formulary system is devised and approved by an institution's medical staff for the objective evaluation, selection, and use of drugs. An effective formulary system permits a high quality of care while providing economic advantages. This is achieved in part through the development and enforcement of policies preventing the administration of drug therapies likely to lead to suboptimal, hazardous, or unnecessarily costly health outcomes. In addition, the selection of cost-effective formulary drugs that meet the needs of the institution can help offset the 69% rise in producers' prescription drug prices that has occurred since 1982 (3).

The medical staff oversees the formulary system through its Pharmacy and Therapeutics Committee. The Committee, in addition to serving in an advisory capacity, monitors the procurement, prescription, dispensation, and administration of formulary and nonformulary drug products. These relationships and responsibilities have been adopted as requirements for hospitals accredited by the Joint Commission on Accreditation of Healthcare Organizations (4). The Pharmacy and Therapeutics Committee also serves to fulfill the educational needs of medical staff members and other professionals regarding drugs and drug use. This may include the planning and establishment of innovative programs to assist institutional prescribers in providing optimal drug therapy (5, 6).

This paper describes the current practice of therapeutic substitution, its potential benefits and hazards, and the role of the formulary system standards in safeguarding patient welfare in this context.

Therapeutic Substitution

Most licensed and accredited medical institutions have a formulary system. Because contemporary formulary systems and certain third-party payers encourage prescribing drugs by their generic name, medical staff often authorize institutional staff to dispense and administer available drugs to fulfill prescriptions or drug orders. Consequently, preparations may be dispensed and administered that differ either by brand name or chemical composition from that prescribed. *Generic substitution* involves interchanges among nonproprietary and proprietary drugs having the same chemical composition. *Therapeutic substitution* is the selection of a chemically different drug that is considered to be a therapeutic alternative with a comparable therapeutic effect. Therapeutic substitution is more complex than generic substitution. Whereas drugs in a therapeutic class share similar pharmacologic and therapeutic properties, their differences are manifest when administered across a wide range of patients with differing physiologic and pathophysiologic status (7). These differences may involve the mode and extent of action, adverse effects, and potential interactions with other drugs. For these reasons, therapeutic substitution has not been broadly applied to each therapeutic class, but rather to those classes having little diversity among drug candidates or having large disparity in drug prices (for example, oral vitamins, cephalosporins, topical antifungals, oral antacids, laxatives, and antihistamines) (2, 8).

Considerations in Therapeutic Alternate Selection

Therapeutic substitution, as with any drug use policy, entails risks and challenges. These challenges include identifying and selecting appropriate therapeutic alternatives on the proper occasion; obtaining prescriber consent before making a therapeutic interchange; adequately monitoring the effects of therapeutic substitution on patient welfare; handling toxic reactions and drug interactions; and identifying true savings after considering the costs of system implementation, system administration, adverse events, and drug administration.

Identifying and selecting appropriate therapeutic alternatives under appropriate conditions requires considerable training and expertise. In selecting a therapeutic alternative, primary consideration is given to mechanisms of action, therapeutic indications, and achievement of the appropriate therapeutic response. Other specific differences between the drugs must also be taken into account. These differences include the method by which the drug is metabolized; dosage

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ranges, side effects, allergies, and toxicities (frequency and type, prevention, risks and benefits), and other special precautions (contraindications, comparisons with existing therapy, drug-drug interactions) (9-11). Failure to account for these differences can lead to serious toxicity, as in the case of substituting a drug that is metabolized by the debrisoquine pathway in a debrisoquine pathway-deficient patient (12, 13). Further, determinations of therapeutic equivalence often depend on clinical studies that are of limited size and thus fail to pick up idiosyncratic drug reactions, that underrepresent certain racial or age groups, or that exclude patients with underlying conditions that make them more prone to adverse reactions (14, 15). Therapeutic ineffectiveness and adverse effects among the elderly are numerous (16-19).

Position 1

Therapeutic substitution is appropriate only in hospitals with an effectively functioning formulary system and Pharmacy and Therapeutics Committee.

Rationale

Some drugs can be substituted safely for others, but therapeutic substitution can be safely practiced only under carefully controlled conditions. In doing so, risk to the patient is minimized while costs are reduced. Physicians should recognize that on many occasions and in some institutions, therapeutic alternatives should not be used. The key determinants regarding the appropriateness of therapeutic substitution is the effectiveness of the institution's formulary system and its Pharmacy and Therapeutics Committee.

An effective formulary system provides detailed methods and criteria for the selection and objective evaluation of available pharmaceuticals (10, 11); policies for the dissemination, maintenance, and comprehensive review of formulary drugs (20-23); protocols for the procurement, storage, distribution, and safe use of formulary and nonformulary drug products (24, 25); active surveillance mechanisms to regularly monitor compliance with these standards and to intercede where indicated (26-33); and enough specially qualified medical staff, pharmacists, and other professionals to carry out these activities.

Several characteristics distinguish the effective Pharmacy and Therapeutics Committee. These include the members' level of competence in clinical pharmacology; specialty and departmental representation; shared participation of each member in all decisions; thorough personal and staff preparation for knowledgeable deliberation; and vigilance in monitoring staff compliance with formulary system policies and procedures (21, 33). The effective Pharmacy and Therapeutics Committee that develops protocols for therapeutic interchange will ensure ongoing communication among prescribers, pharmacists, and others to select the safest, most effective, and most cost-effective drug therapy and drug products for patients.

Position 2

Therapeutic substitution jeopardizes patient management when immediate prior consent is not obtained from the authorized prescriber and when documentation of substitutions is untimely or improper. Such practices must not be permitted.

Rationale

When a therapeutic alternative is identified, it is necessary to consider the individual patient's concurrent therapy, laboratory and physical examination findings, and medical history. Comprehensive training is required to properly assimilate patient status indicators and to direct patient care. Although physicians rely on other medical and health care professionals for their expertise and guidance in providing patient care, physicians are ultimately responsible for the consequences of patient treatment. This necessitates immediate prior authorization from the prescribing physician before the administration of a therapeutic alternate. Approved counter prescriptions must be placed in the patient's chart for the prescribing physician's signature.

In one study, physicians in hospitals were aware of each instance of therapeutic substitution 17% of the time that it occurred. Medication administration records reflected the actual drug dispensed on each occasion 26% of the time (8). Automatic therapeutic substitution that fails to allow the prescribing physician to review the appropriateness of a therapeutic interchange bypasses safeguards associated with formulary systems and, therefore, introduces unnecessary risks to patients.

Position 3

The practice of therapeutic substitution may be acceptable in ambulatory settings that meet standards comparable to those of institutional settings.

Rationale

The challenges associated with therapeutic substitution and the limited mechanisms to monitor its practice and effects when done outside the institutional setting make its practice unsafe in most ambulatory settings. Presently, Illinois and Wisconsin explicitly prohibit therapeutic substitution outside of acute care settings. Other states vary in their restrictions on therapeutic substitution in nonacute care settings. The finding that immediate prior notification of therapeutic substitutions is not provided to physicians in most instances is disturbing (2). Although HMOs and other managed care practice plans are capable of having effectively functioning Pharmacy and Therapeutics Committees and formulary systems, their review by ambulatory care accreditation agencies is typically tangential (34, 35).

Further, the advantages of integrated and interactive computerized data bases that are used in collecting and displaying the requisite patient information (for example, concurrent therapy, previous drug reactions, medical history) are often lacking at the community pharmacy level (36). Likewise, many physicians in the community may lack access to expert consultative services regarding appropriate therapeutic alternatives, dose

levels, and other pharmacokinetic properties and interactions. Diffusion of therapeutic substitution from the institutional setting to the community hampers the physician's ability to regularly monitor therapeutic effectiveness and to intervene immediately during instances of adverse reaction or therapeutic failure (37). Although no reports of adverse outcomes associated with therapeutic substitution done on an ambulatory basis have been published, the American College of Physicians believes that even when therapeutic substitution is done with physician supervision under strict protocols, therapeutic inequivalence may be high for those already stabilized on a drug, for patients taking several medicines, for children, and for patients with a compromised capacity to absorb, metabolize, or eliminate drugs. Thus, it is prudent that the practice of therapeutic substitution in the ambulatory setting be restricted. Therapeutic substitution may be practiced in the ambulatory setting only when standards comparable to those of institutional settings are met.

Position 4

Effective therapeutics require physicians to be well educated in therapeutics and to instruct patients about the proper use and effects of prescribed medication.

Rationale

The American College of Physicians fully supports rational therapeutics and has called for improved education in medical schools, residency training, and continuing medical education courses (38). The interest in and benefits of such an education is well documented (39, 40). The value of other innovative therapeutic programs such as that described by Avorn and colleagues (27) and others (41-43) also greatly contribute to enhancing the prescribing patterns of physicians. When physicians couple this background with time spent with their patients discussing the use and effects of prescribed medication, opportunities develop for treating patients safely, rapidly, and more effectively while reducing costs (44). Therapeutic substitution should only be considered within this context.

Conclusions

The practice of therapeutic substitution is on the rise in the United States. Its practice, as with any drug use policy, entails both risks and opportunities. Therapeutic substitution is appropriate only when done in hospitals with an effectively functioning formulary system and Pharmacy and Therapeutics Committee. It may be acceptable in ambulatory settings when standards and safeguards comparable to those of institutional settings are satisfied. Providing a therapeutic alternate without receiving immediate prior consent from the authorized prescriber jeopardizes patient management and should not be permitted. The proper use of prescription drugs is an integral part of patient care management. Effective drug therapy requires physicians to be well educated in therapeutics and to instruct their patients concerning the proper use and effects of prescribed medicine.

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