Formularies, costs, and quality of care

Limiting formularies is not harmful to patients

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Drug formularies have existed since the 1940s. The formulary in any health system is not a static list of drugs; it is not a “light switch” or a “yes” and “no” system. The formulary is part of a system for quality drug therapy within that system. The formulary in hospitals and large systems is established by the Pharmacy and Therapeutics Committee (or similar body) by a medical staff committee establishing policies for the effective, safe, and cost-effective use of drugs. Overall, a formulary should meet the needs of individual patients based on the best available evidence. The formulary is part of quality improvement and education programs within a health system.

Drugs coming into the marketplace need to be evaluated prior to becoming part of the formulary. A detailed review of new drugs should be completed in a timely manner based primarily upon efficacy, safety, and cost. In addition, the review should also be a comparison to other drugs within a class. In my experience of formulary development, newer agents should always be approached cautiously unless there are no other options.

The review of a drug under consideration for formulary addition should be based on randomized controlled trials since these give the strongest evidence about a drug. When drugs are marketed, they are often compared to a placebo to establish efficacy of a drug. That is appropriate for determining whether a drug is better than no therapy, but misses the point of comparing to similar agents in a therapeutic class. Comparative studies are crucial to making the best formulary decisions and typically are not funded by pharmaceutical companies. The SANAD^{1,2} is one comparative study of antiepileptic drugs (AEDs). Valproate was more effective for generalized seizures and lamotrigine for partial seizures, but all drugs were effective. The most effective drugs should be the first ones used to manage seizures. Other agents can be used if there are clear failures or toxicity. It is also evident from these studies that all AEDs produce adverse effects in a large fraction of patients.^{1,2} Quality of life (QOL)—not well studied with AEDs—is also part of the equation in deciding whether 2 therapies are equal. One article shows no practical difference between carbamazepine and lamotrigine in elderly patients.³ Another trial related the QOL to having fewer seizures at the onset of the

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study and throughout the trial. Patients having greater seizure frequency were found to have lower QOL at any point in the study. The finding of a baseline difference of having a better QOL when there were fewer seizures was not expected.⁴

The second component of the formulary review is establishing whether a drug is safe to take. What is difficult to assess from a formulary perspective is long-term safety since most clinical trials to get a drug marketed are performed in small groups of a more homogenous group of patients for less than 1 year. Compared to the hundreds of thousands or millions of patients prescribed a drug in practice, a few hundred to a few thousand might be enrolled in clinical trials that have exclusions for enrollment. For example, felbamate was approved by the Food and Drug Administration (FDA) in 1993. Less than 1 year after approval, the drug was markedly limited because aplastic anemia was reported after a total of 150,000 patients had been given the drug. Vigabatrin was approved by the FDA in 2009 based upon less than 500 patients. Vigabatrin had been used in other countries for years prior to approval in the United States. It was known the drug can cause irreversible vision loss and a safety mechanism was established for the use of this AED. In the management of Parkinson disease, tolcapone was marketed as effective and safe in 1998 and was later found to cause fatal hepatitis. More than 20 drugs have been taken off the market since 2000 due to findings of lack of effectiveness or serious toxicity. The unknown long-term safety of new drugs should be a critical decision point regarding formulary addition. When there is a vigorous attempt to use new drugs because they are new and similar to another drug that is on a formulary, it is reasonable to develop criteria for use. This mechanism can allow prospective development of a rational approach to using a new drug (e.g., the new drug would be used when another agent is not effective or not tolerated). In formulary systems there is some type of approval mechanism. The practice guidelines need to be reviewed and updated as new evidence becomes available.

When 2 drugs are very similar in efficacy and safety, cost should be the deciding factor. Although many physicians see cost as the only issue impacting addition of a drug to a formulary, in my view this is the last major item to consider. Many new drugs being marketed are more “me too” than “unique chemical entities.” Some of the newer products are older drugs made into long-acting forms or racemic modifications promoted as a new drug. The comparison of costs should be based on the overall cost of care and not just drug acquisition cost. If a drug requires laboratory monitoring that adds to the cost of care, that should be part of the information used in making a formulary recommendation. Very few of the AEDs require no monitoring. The cost of treating recurrent seizures should be considered also for AEDs.

The use of generic drugs is part of the cost and quality controversy. There are very limited data to determine whether the use of generic drugs instead of brand name drugs is different. Labiner et al.⁵ found in a retrospective study more resource utilization when generic AEDs were used. Besag⁶ pointed out that correlation is not causation in his editorial of this study. In a similarly designed study, no increase in resource use and outcome was reported by Kesselheim et al. when generic drugs were used.⁷ These studies suffer from being retrospective and do not account for persistence and adherence to medications as a possible reason for increased seizure frequency and subsequent health care expenditures. Generic drugs have lower costs than brand name drugs. These are not small differences. For example, the cost of taking gabapentin 600 mg 3 times daily may cost about \$4,500 per year for the branded product and about \$475 per year for a generic (about 9.6 times greater for the branded product). Divalproex ER 500 mg twice daily costs about \$430 per year and the brand name product costs about \$2,500 per year (about 6 times greater for the brand name product).

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Another issue that should be considered in formulary decision-making includes sound-alike names such as levetiracetam/levofloxacin or levocarnitine and carbamazepine/oxcarbazepine. Drug–drug interactions that complicate therapy with other concurrent drugs need consideration. Something as simple as decimal point errors would also be a consideration for making drugs available generally. It is possible a formulary decision would be to avoid these potential errors. A checklist of these kinds of issues has been developed.⁸

Formularies can improve the quality of care by carefully evaluating medications for their appropriateness, safety, and cost-effectiveness. I do not see formularies as harmful to patients. For AEDs, the issues of having a formulary are not different than in other drug classes. Whenever high-quality evidence suggests one therapy produces a better outcome, formulary decisions should reflect that evidence.

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