Impact of Formularies on Clinical Innovation

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It is important to consider, in light of how innovation has so often occurred, whether today's managed care environment is conducive to continued psychopharmacologic innovation. The initial step in the development of a new area in psychopharmacology has historically relied in large part on individual clinicians who pursued unconventional methods of treatment. When a set of guidelines such as a formulary (a list of drugs eligible for reimbursement compiled by a managed care organization) becomes restrictive, it decreases clinician innovation. In addition to this long-term threat to innovation, studies have found greater restrictiveness in formularies to be associated with higher health care utilization. Thus, restricted formularies that are based on a naive interpretation of "therapeutic equivalence" may slow the advance of medical science without even achieving the only goal that could possibly justify such restrictions—cost control. If innovation is to flourish, formularies must be flexible and advisory, not restrictive. Preserving the climate for innovation in health care requires the management culture to focus on the long-term impact of policies on quality and innovation as well as on the overall health cost in the system. *(J Clin Psychiatry 2003;64[suppl 17]:11–14)*

While it is common to discuss the impact of various methods of managed care on the quality of health care as measured by clinical outcomes, the impact of managed care on pharmacologic innovation at the clinical level is rarely, if ever, discussed. However, it is important to consider, in light of how innovation has historically occurred, whether innovation can continue to thrive in today's managed care environment.

The introduction of health benefits by employers (as a way around government-imposed wage freezes), coupled with the IRS decision not to tax these wage equivalents as income, had the unintended consequence of separating both patients and health care providers from the actual costs of the health care decisions they were making. This effectively removed any incentive to be cost conscious. As the percentage of health care cost paid out-of-pocket by employees (i.e., patients) steadily declined, total health care utilization and costs increased, reflecting a nearly perfect inverse relationship. Given the lack of meaningful incentives for health care decision-makers (both doctors and patients) to be cost conscious, it was entirely predictable that health care costs would continue to escalate. It was this rapid escalation that triggered the hurried institution of top-down controls in the form of managed care, prior to the development of any meaningful knowledge base as to the impact of such systems on quality and innovation.

Managed care as defined by the Institute of Medicine is "a set of techniques used by or on behalf of purchasers of health benefits to manage health care costs by influencing patient care decision-making through case-by-case assessment of the appropriateness of care prior to its provision."[1] The core objectives of managed care organizations, then, are to reduce health benefits' purchase prices, patients' need for services, variation in treatment patterns, and, ultimately, the costs of production. Any of these goals is only problematic if it interferes with the fundamental purposes of health care—delivering quality care with the best possible outcomes and serving as a seedbed for medical innovation.

While the issues we are discussing are relevant to all health care sectors, managed care organizations have been especially vigilant in limiting mental health benefits. Given data[2] that indicate patients with untreated or

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undertreated mental disorders incur general medical expenditures at a rate far greater than average, mental health care restrictions may well represent some of the most glaring examples of penny-wise and pound-foolish policy.

PSYCHOPHARMACOLOGIC INNOVATION

New areas of psychopharmacology have opened up in large part as a result of individual clinicians pursuing unconventional methods of treatment. The research community then becomes engaged and, by applying sound scientific methodology, is able to separate the wheat from the chaff.

Clinicians have frequently noted unintended drug effects in the treatment of one disorder that they then employed in an "off-label" manner in the treatment of another disorder. Almost all physicians prescribe some drugs off label,[3] and such use is especially prevalent in specialty practice.[4–6] The use of lithium to treat mania originated in such a serendipitous manner; indeed, it was lithium that sparked the psychopharmacology revolution—a revolution that has resulted in an entire array of effective agents in psychiatry. In another example, the antipsychotic effects of chlorpromazine were first noted during the use of a closely related compound as an antihistamine. As a result, chlorpromazine was tested, with great success, in patients with mania and schizophrenia. Before the monoamine oxidase inhibitor iproniazid was the first modern antidepressant, it was used in the treatment of tuberculosis, where a noted side effect was elevated mood. Imipramine was developed as an antipsychotic but, due to unexpected mood elevation in schizophrenic patients taking the drug, it found widespread clinical use as an effective antidepressant. The anticonvulsant carbamazepine became an accepted treatment for bipolar disorder after improved mood was noted among epileptic patients taking the drug. In instances such as these, clinicians rather than researchers were responsible for discovering innovative uses for existing drugs.

Off-Label Usage

A drug's particular indication approved by the U.S. Food and Drug Administration (FDA) does not necessarily imply that all the evidence about that drug's efficacy is limited to the approved indication. The FDA considers only the data that are submitted to the agency by the manufacturer of the drug. Submission of data is a financially driven decision influenced by patent law and limited by the costs of the large clinical trials that are required for FDA approval. A drug that has already been approved by the FDA for one indication is unlikely, for economic reasons, to be submitted for approval for a second indication unless substantial patent life remains, allowing the company to recoup the additional research costs required to achieve the second indication (Table 1).

Table 1. Some FDA-Approved Indications and Common Off-Label Uses

Drug	FDA Indication	Common Use
Carbamazepine	Epilepsy Trigeminal neuralgia	Bipolar disorder
Lithium	Mania	Prophylaxis of bipolar II disorder
	Prophylaxis of bipolar I disorder	Recurrent unipolar depression
Imipramine	Major depression	Panic disorder
Amitriptyline	Major depression	Headache
Fluoxetine	Major depression	Obsessive-compulsive disorder

Abbreviation: FDA = U.S. Food and Drug Administration.

For example, imipramine was approved by the FDA for use as an antidepressant. Over time, imipramine proved effective in the treatment of panic disorder as well, but because patent protection had expired, imipramine was not submitted for approval by the FDA in the treatment of panic disorder. Indeed, prior to the selective serotonin reuptake inhibitors, the only FDA-approved drug for panic disorder was alprazolam, based on considerably fewer studies than were available for imipramine. The antidepressant amitriptyline is widely used for the treatment of headache, but amitriptyline will never be approved for this indication because it would be economically untenable for any company to undertake the research that would be required to support a new indication for a generic drug.

THE IMPACT OF RESTRICTED FORMULARIES

Practice guidelines were originally developed within the health care community itself to inform both practitioners and patients about the opinions of experts regarding specific treatment decisions. Paradoxically, those providers who treat the most seriously ill patients and the trailblazers who specialize in new techniques are more likely than the average clinician to find their clinical practice falling outside of standard practice guidelines. Further, the lengthy period of time that usually passes between expert consensus and publication means that some guidelines are out-of-date by the time they become readily available. The more specific a practice guideline is, the more unlikely that it will stay current for long.

In some managed care systems, guidelines (which frequently limit drug uses to FDA-approved indications) have come to resemble recipes governing physician choice. A set of guidelines such as a formulary (a list of drugs eligible for reimbursement) will be employed by a third party—that is, someone outside the clinical situation with no knowledge of the individual patient or physician—and for this reason, they tend to become very specific and uniform. Such formularies are a disincentive

for the tailoring of treatment to individual patients as well as a disincentive for innovation.[7]

Some critics have said that the managed care movement does less to manage care than it does to manage costs. Managed care does in fact manage and in some cases restrict access to care, which is hardly surprising given the Institute of Medicine's definition of managed care quoted above. In the Managed Care Outcomes Project, Horn et al.[8] conducted a longitudinal prospective study examining the relationship between health maintenance organization cost-containment strategies and utilization and total cost of health care for a number of medical (nonpsychiatric) illnesses. At each study site, the formulary was scored for its level of restrictiveness. Horn's findings were, to say the least, unexpected by the managed care industry: for each of the 5 illness categories, the tighter the restrictiveness of the formulary, the higher the overall cost of care. What drove the increased cost was the association between formulary restrictiveness and utilization of care. This result should not be surprising, given that pharmacy costs (totaling about 10%–12% of health care expenditures) are dwarfed by costs such as physician visits and days spent in the hospital.[9] While the formularies that Horn and colleagues[8] studied generally did not result in absolute exclusion from use of unlisted drugs, listed drugs were prescribed much more frequently than unlisted drugs. Across the 5 sites studied, the rate of physician compliance with formularies was 95%, but this figure may be misleading. All study sites required prior authorization, by physician request, for reimbursement of nonformulary drugs. Thus, prescribing unlisted drugs may have seemed infeasible in the many instances where the patient was in the office and a prompt decision was required.

Restricted formularies were associated with even higher resource utilization among elderly patients than nonelderly patients.[10] While sicker patients in each illness category unsurprisingly used more health care resources than their healthier counterparts, the relationship between formulary restrictiveness and increased total costs was consistent across all levels of severity.

The premise underlying restrictive formularies is that when 2 drugs are "therapeutically equivalent," the cheaper drug should be used. If for each and every patient a generic drug is truly therapeutically equivalent to a more expensive brand name in the same drug class, then, clearly, using a generic drug makes sense. However, there are problems with the current interpretation of therapeutic equivalence—between generic and patented drugs as well as between patented drugs in the same class. As Greene et al.[11] have pointed out, assertions of therapeutic equivalence may not be supported by the experimental methods used, which tend to be less stringent than methods used to determine significant superiority of one drug over another. In terms of hypothesis testing, proof of true equivalence would require an exceedingly large sample size in order to establish with certainty that no difference existed between compared drugs (that is, to avoid a type II, or false negative, error). In a review of 88 published clinical studies that concluded therapeutic equivalence,[11] more than three quarters did not specify that the research was intended to show equivalence, did not set a quantitative boundary for the degree of equivalence, did not use a sample size adequately powered to detect a meaningful difference between drugs, or did not use an appropriate statistical test. In approximately two thirds of the studies examined, equivalence between drugs was declared after a "failed" test for superiority. Statistics maintains that absence of evidence is not necessarily evidence of absence. Freiman et al.[12] found that, of the studies he investigated, 70% of those that reported no difference between 2 drugs had a greater than 10% chance of failing to find a 50% difference in efficacy. Further, crossover studies consistently show that nonresponse to one drug does not necessarily predict nonresponse to another drug (in the same general class) previously deemed to be "therapeutically equivalent" based on group comparisons.[13] That is, group comparisons of drugs with similar response rates can easily miss differences among individual responses or subgroups. Restricted formularies based on uncritical assumptions about therapeutic equivalence may lead to inferior care and therefore inefficient cost control, as when, for example, a patient completes a failed trial of a formulary drug when another drug in the same class would have been initially effective.

CONCLUSION

Innovation in medicine often starts with an individual clinician trying something unconventional. Such novel therapeutic observations have triggered fresh insights into disease mechanisms. If pharmacologic innovation is to flourish, formularies must be flexible. Flexibility is compromised when adherence to guidelines is influenced by financial or other incentives, or when it is practically difficult for a clinician to deviate from a restricted formulary. Managed care need not be inherently antithetical to innovation. However, preserving the climate for innovation in the management of health care requires that the management culture focus on long-term, rather than short-term, improvements in cost effectiveness. Further, treatment guidelines including formularies should be presented to clinicians and patients as advisory, not requisite. If the revolution in pharmacotherapy is to continue, there must be incentives for clinician investment in innovation, and in taking on the most severely ill patients.

Drug names: alprazolam (Xanax), amitriptyline (Elavil, Endep, and others), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others).

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