Assessing A Drug Product For Formulary Inclusion

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How does one decide whether or not a drug should be included in a formulary or designated the drug of first choice for a clinic? There is a systematic way of thinking about formulary decisions that may help clinicians involved in choosing drug products.

In addition to considering existing agents on a formulary, a decision for formulary inclusion should also include assessment of: (1) pharmacology, including side effect profile; (2) pharmacokinetics; (3) patient population; (4) dosage forms; and (5) cost for a given regimen.

Pharmacology

Pharmacology is the science describing how a drug affects animals or humans. It is necessary to look at the pharmacology of a drug because that determines the agent's therapeutic uniqueness. For example, all of the beta-adrenergic blockers such as propranolol and atenolol have similar pharmacology in that they block beta-adrenergic receptors and work the same way to lower blood pressure, or prevent angina pectoris. These two agents, however, have different pharmacology in that propranolol blocks beta receptors of both vascular and bronchial smooth muscle, while atenolol is more selective for cardiac beta receptors. One can avoid duplication of therapeutic entities by studying their pharmacology.

Pharmacology also contributes to the side effect profile of a drug. Within given therapeutic class, agents may vary in side effect profile. This is more often seen between agents with different pharmacology. For example, propranolol may cause more bronchospasm in a susceptible individual than atenolol. Some antihistimines may cause more sedation than others. An antibiotic may have a lower incidence of allergenicity than one with a similar microbiologic profile.

Pharmacokinetics

Pharmacokinetics is the study of how the body affects the fate of drugs. One looks at pharmacokinetics because agents may vary in the number of doses per day, or how quickly one could expect a therapeutic response. For example, in the treatment of an acute asthma attack or for a patient who wheezes only during field work, one would choose an inhaled selective beta-2 agonist such as metaproterenol or albuterol because of fast onset of action. For a patient who suffers chronically from asthma or bronchitis, one would choose a slow-release theophylline product. These products can often be given twice a day, but take longer for the desired bronchodilation. A patient, however, would benefit from the long-lasting effect and a convenient dosing schedule. The number of doses per day impacts patient compliance and may also effect the cost of the regimen.

Patient Population

The patient population impacts on drug selection in a variety of ways. Individuals who are working may have difficulty with a 3- or 4-time per day dosing regimen. Individuals without refrigeration in the home or who are traveling will be unable to store some antibiotic suspensions, such as amoxicillin. Health centers seeing a population with a wide variety of parasitic infections will need a broad selection of antihelmintics. Certain populations respond better to certain

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Folk Medicines and Drug Interactions

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In the distant past, medicines were derived from medicinal plants, or from earth or animal sources. As modern medicine grew up, chemical analysis of plants that were known to be effective provided a source and a model for many modern pharmaceuticals. In the recent past, pharmaceuticals have been derived more and more from chemical synthesis, and the ethnomedical roots of modern chemistry and pharmacology have been forgotten.

Forgetting the past is hazardous, especially when the past and the future so often mix in modern society. In a society as diverse as the United States, there will always be pockets where the future and the past co-exist. Migrant farm labor is one of these pockets. Within the same family, and for the same person, there is evidence that people simultaneously use modern medical services and folk medicines at the same time (Trotter and Chavira 1981).

This article explores the consequences of mixing modern medicine with ethnomedicine. It shows that home remedies are a hidden source of serious drug interactions. The following example points out the potential seriousness of the modern medicine/ethnomedicine interface.

Three years ago a woman in El Paso was diagnosed as having cardiac problems that would respond to digitalis therapy. Her dosage was carefully titrated, and she was sent home with her medication. About two weeks later she was brought into the emergency room and hospitalized for a digitalis overdose. Her medication level was lowered, and she was sent home with her medication. In a couple of weeks she was back in the hospital with an overdose. Her medication level again was lowered, and she was sent home. The third time she arrived at the emergency room with an overdose. Her medication level was again lowered, and she was sent home. The third time she arrived at the emergency room with correct dose and in the prescribed manner. The woman also had a maid from Mexico who cared very much for her and, knowing that she had a heart problem, faithfully assured that she drank three cups of medicinal tea each day — a tea the maid knew was good for the heart. The medicinal tea was foxglove tea, the earliest natural source of digitalis. With the combination of her prescribed medication and a heavy daily dose of foxglove tea, it was no wonder that the woman had overdosed three times.

The examples of drug interactions in this paper will come from Mexican American folk medicine. This was chosen because Mexican Americans are not only the largest single cultural group in the three U.S. migrant streams, but also are the heaviest users of medicinal teas. (Trotter 1981a, 1981b, 1982, 1983, 1985a, 1985b). They are not the only users of herbal remedies. With the increasing movement toward self help and the increased use of natural products, especially herbal teas, the problems identified in this article could be found for other served by migrant or community health centers. At present, more is known about Mexican American ethnopharmacology, than ethnomedicine for other cultural groups.

Drug interactions can be defined as the alteration of the diagnostic, preventative or therapeutic action of a drug by another exogenous interactant chemical (American Pharmaceutical Association 1976). The current risk of drug interactions is eight percent, or eight in every 100 prescriptions (Martin 1978).

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There are eight basic mechanisms of drug interaction:

1. An exogenous chemical can have a direct effect on the medication prescribed, altering its basic chemistry;

2. An exogenous chemical may modify gastrointestinal absorption, causing the normal dosage estimate to be incorrect because the medication is absorbed either much more slowly or more rapidly than under normal circumstances;

3. An interacting chemical may modify dermatomucosal absorption;

4. An interacting chemical may alter the distribution of the medication within the patient;

5. An exogenous chemical may modify or interfere with the medication's action at the receptor site;

6. The modification of the biotransformation of the medication is a related type of drug interaction;

7. A common drug interaction is for the interfering chemical to alter normal excretion rates for the medication; and,

8. The chemical can disturb the water and/or electrolyte balance of the patient, again interfering with the predicted action of the drug (cf. Goth 1984; Martin 1978).

About three years ago I began to suspect that *remedios caseros* (home remedies) used in Mexican American households might have a more substantial biochemistry than assumed by many health practitioners. A colleague and I began to search for an empirical basis for the use of medicinal teas. We found (Trotter and Logan 1986) that the most commonly used home remedies all had significant biochemical components. Ten examples of the most common remedies are shown in Table 1.

All drug interactions between the estimated 500 home remedies used in Mexican American communities and the hundreds of prescription drugs that are available are not known. Table 1 helps point out some of the potential problems that may exist as a hidden menace.

An example of direct interference on the action of a drug from this commonly-used group is *nopal*. *Nopal* is frequently used for individuals who have diabetes. According to Ibañez (1979), the *nopal* leaf has been shown to contain glucose-6-phosphate isomerase, which effectively lowers blood sugar levels in vivo. Therefore, it may produce drug interactions by interfering with the predicted action of prescribed anti-diabetic drugs administered to diabetic patients. Clinics might consider this as one reason behind some of the complications encountered with diabetic patients.

Modification of gastrointestinal absorption is one of the most commonly encountered problems of drug interaction. It can be caused by alteration of: motility in the gastrointestinal tract, bacterial flora, the gastrointestinal physical environment (alteration of pH, complexation, dissolution, diffusion, osmotic pressure, salt formation, or sequestration), the mucosa, or of the transport mechanisms across the columnar cells.

Drugs that alter gastrointestinal absorption include: acidifying agents, antacids, antidiarrheal medications, cathartics, citric acid, fats and oils, purgatives, bismuth salts, and sodium bicarbonate. Since over-the-counter (OTC) drugs are used as folk medicines along with plant remedies, numerous interactions may occur because of home medication, yet these are frequently overlooked as a source of drug interaction (Lamy 1982). OTC remedies commonly used in migrant households are aspirin, Rolaids, Tums, Alka-Seltzer, and *bismuto* (a bismuth compound purchased in Mexico). All of these can change absorption. In addition, the anti-diarrheal actions of several of the plants, such as *manzanilla* may affect absorption.

At present, there is very little evidence that folk medicines effect dermatomucosal absorption. However, some topical medications may effect systemic medications, so this type of interaction is possible. For example, marijuana is a remedy for arthritis in parts of the southwest. The plant is steeped in rubbing alcohol for several days. When the alcohol turns green from the chlorophyl, the plant is thrown away and the medication is applied topically to the joints. Since the active ingredient in marijuana (THC) is absorbed through the skin, this has the potential for causing drug interactions, as does the application of liniments and other compounds to alleviate aches and pains (Lamy 1982).

Alteration in the distribution of drugs usually comes about by either an alteration in the normal drug transport mechanisms or by a change in the drug binding at plasma protein binding sites. Some

TABLE 1

CHEMICAL CONSTITUENTS AND KNOWN BIOACTIVITY OF 10 MEXICAN AMERICAN HOME REMEDIES

Remedy	Chemistry	Known Bioactivity
Ajo (garlic)	Allyl Disulfide, Allyl Propyl Disulfide, Allicin, Allicetoin 1 and 2, Allinase	Antibacterial, Fungistatic, Hypoglycemic, Hypocholesterolemic, Anthelmintic, Expectorant
Albacar (Sweet Basil)	Estragol, Lineol, Linalool, Eugenol, Tannins, Basil Camphor, D-a-pinene, Cineole, Methylchavicol	Sedative, Stomachic, Antispasmodic, Carminative, Galactagogue
Borraja (Borrage)	Mucilage, Tannins, Volatile Oils, Mineral Acids	Emollient, Demuclent, Diuretic, Sudorific
Comino (Cumin)	Demaldehyde, Terpenes, Cuminaldehyde, Cuminic Alcohol, Pinenes A and B, Pentosan, P-cymene	Stimulant, Abortifacient, Carminative
Golondrina (Swallow Wort)	Germanicol, B-amyrin, Pulcherrol, Kaempferol	CNS Depressant, Hypotensive, Antimicrobial, Antiseptic
Manzanilla (Chamomille)	Volatile Oil, Inositol Bitter Glycoside, Anthemic Acid	Antiseptic, Sedative, Anti-inflammatory, Antispasmodic, Carminative
Hojas de Mesquite (Mesquite Leaves)	Serotonin, Luteolin, Guercetin, Tryptamine, Prosopine	Diuretic, Laxative, Antimicrobial
Miel y Limón (Honey and Lemon)	Ascorbic Acid, Pectin Hesperidin, Citral, Citronellal, D-limonene, Phellandrene Sesquiterpine, Inhibine, Galangine	Diuretic, Carminative Antiseptic, Bacteriostatic
Nopal (Prickly Pear Cactus)	Glucose-6-phosphate Isomerase	Hypoglycemic
Ruda (Rue)	Ketones, Tannins, Rutin, Rhammo Glycoside Coumarin, Bergaptin, Xantotoxin, Alkaloids, Ascorbic Acid, Furocoumarins	Emmenagogue, Abortifacient, Anthelmintic, Diaphoretic, Antiseptic, Stomachic

drugs that displace other drugs from plasma protein binding sites include aspirin, barbiturates, oral hypoglycemics, and tranquilizers (D'Arcy et. al. 1982). So even aspirin used as a folk medicine is definitely a problem unless its use is known. It is possible that *golondrina*, as a central nervous system depressant, has an effect, as well as *albacar*, which acts as a sedative. More work is needed to determine whether or not these remedies have such an effect, but it could be helpful to inquire if they are being taken.

Two mechanisms for potential drug interaction cannot be explored adequately, because of a lack of necessary information. These are the interactions that are due to modifications of drug action at receptor sites and modification of the biotransformation of the drug (enzyme induction or inhibition).

The mechanism for drug interaction that may be the most seriously affected by folk remedies is the alteration of excretion. The urinary excretion of other drugs may be altered by alcohol, ascorbic acid, diuretics, fatty acids, fruit juices, and sodium bicarbonate. A very high proportion of remedies studied so far either have an effect on urinary excretion or on fecal excretion. Several remedies listed in Table 1 are diuretics, such as *borraja, hojas de mesquite,* and *miel y limón.* Others are laxatives, such as *hojas de mesquite,* or another common remedy, *rosa de castilla* (rose petals). Alka-Seltzer and regular sodium bicarbonate are used to settle the stomach (one of the most common home treated illnesses for migrants), and the action of both may effect excretion rates for pharmaceuticals. Another type of excretion is sweating. Excessive sweating brought on by the use of *ruda* or another common remedy, *toronjil* (balm), both of which are diaphoretics, may cause a problem.

As seen in Table 1, several of the folk remedies contain special alcohols. Alcohol is also frequently used as a recreational drug. It is not known if these folk remedies have a high enough concentration of alcohol to cause drug interactions altering excretion. The concentration level may be so low that they are not a problem. Nevertheless, it is probably useful to ask if these remedies, e.g. *albacar* or *comino,* are being taken at home.

The disturbance of water and electrolyte balance in the patient is the final type of chemical reaction that may affect other drugs. One of the common causes for this type of problem is an alteration of pH, where an acidic or basic drug is prevented from passing across cell membranes. At this time, it is impossible to determine with any level of confidence whether or not this type of drug interaction could be caused by home remedies, but it appears that it could be possible, given the chemistry of some of the remedies listed in Table 1.

This preliminary exploration of a very new field shows that all of the available evidence points to the probability that home remedies cause some, and possibly all, of the common types of drug interactions found among prescription and over-the-counter medications.

When a new medication is prescribed for an individual who comes from a cultural background where medicinal teas are frequently used, some exploration of this use should be made for that particular individual. Ask the patient if they are taking any teas or other remedies. If you ask what medications they are taking, usually they will reply with only the types of prescription medications they take. If you ask if they use folk medicine, you will probably receive a negative response even if they take folk remedies. (This is due to the negative responses about folk medicine some health professionals have expressed in the past.) Asking about teas seems to be neutral, especially if you seem to know about teas. You could ask, "Are you taking *te de manzanilla* or *te de yerbabuena* (spearmint), or any other teas?" This is a reasonably non-threatening way to begin to explore the use of folk medicines.

Even though it is not necessary to ask about herbal teas on all occasions, there are some circumstances when the question should definitely be asked. As a general guideline, you should become suspicious when you see the classical signs of drug interactions. Some of the indicators are: an inappropriate drug level for the dosage prescribed, an inappropriate time interval between predicted drug levels and clinical manifestations, and unexpected side effects for a particular drug level. At first it is important to: have a good working knowledge of drugs frequently prescribed in your clinic and their common interactions, have very good documentation of the patient's current medications and medical history, and develop the suspicion that the problem is not caused by interactions between the drugs that the patient is using and their medical condition. At that point, it would be a good procedure to begin exploring the patient's use of common or uncommon herbal teas and remedies.

If you have either examples of home-remedy-based drug interactions, or come across them in the future, it would be very useful if you would send these examples to the author or to the National Migrant Referral Project, Austin, Texas. We hope that in the future this area can be thoroughly explored so that migrant health centers can be provided additional material that will allow them to identify or to avoid possible drug interactions with home remedies.

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therapeutic classes than others. An example is the growing evidence that Black hypertensive patients respond uniformly well to diuretic therapy and often less well to beta-adrenergic blockers.

Dosage Forms

A drug available in a variety of dosage forms is useful. It is more important to be certain that within a therapeutic class, one has all the dosage forms needed. For example, beta-2 agonists such as metaproterenol or albuterol are necessary for intermittent asthma. These are available both in tablets and as inhalers for people old enough to use them. However, a syrup form of one product should also be available for smaller children.

Drugs available only in capsule form should be approved at the lowest strength likely to be needed since capsules cannot be broken. Scored tablets should be acquired at a higher strength. It is usually not necessary to have all strengths of a drug product, as this contributes to higher acquisition costs. Duplication of agents within a therapeutic class should be avoided. By assessing an agent's pharmacology, pharmacokinetics, side effects, and dosage forms objectively, one can avoid duplication.

Cost for a Given Regimen

In general, for cost containment, a generic equivalent should be used except where bioavailability is a known problem. (For this information, use the U.S. Food and Drug Administration, *Approved Drug Products with Therapeutic Equivalents Evaluations*, not a pharmaceutical sales representative's word.) Combination drug products may at first appear advantageous, but invariably are more expensive than separate entities as these are usually available generically. Combination products also make individual adjustment of the various components difficult.

Multiple daily dosing is often more expensive than one-a-day doses. Total cost for a month of a chronic medication should always be calculated and compared to an existing agent, if there is one. Remember that product literature often bases comparable cost on a **starting** regimen, and that actual patient requirements may be considerably higher.

By choosing unique therapeutic agents in response to the needs of a unique patient population, clinicians serving migrant farmworkers can optimize patient care, contribute to rational drug use, and practice cost-effective medicine. A descriptive algorithm of the decision-making process follows.

Algorithm for Formulary Decision Making