Chapter 5

# Medications and the Elderly

# Contents



Tables



Figures

Chapter 5

# Medications and the Elderly

## Introduction

Drug treatment is an important medical technology that is especially important to the elderly population. Medications are widely used by older Americans, and Federal policy directly affects the availability of drugs for general use. The safety of using medications, availability of information about drugs, and new technologies that might improve how drugs are delivered and used are covered in the following chapter.

Congress has demonstrated an interest in issues related to use of medications by older Americans. A joint hearing was held in June 1983 by the Senate Special Committee on Aging and the Subcommittee on Health and Long-Term Care of the House Select Committee on Aging entitled "Drug Use and Misuse: A Growing Concern for Older Americans" (70). That hearing covered many of the issues raised in this chapter.

A number of other medical technologies from this report have been excluded because they are covered in other OTA reports. One area deserves special mention—that of medical devices. There is a vast potential for medical devices that improve function and enhance independence among disabled elderly individuals. Some of these devices are reviewed in the section on ***Long-Term Care*** in chapter 7. others have been assessed in recent OTA reports, such as ***Technology and Handicapped People,*** as noted below, or are currently the subject of other OTA projects. Devices specifically relevant to urinary incontinence and hearing impairments are reviewed in case studies on those subjects to be published separately. Among the current OTA assessments that cover relevant technologies, such as diagnostic and therapeutic procedures, are:

- ***Federal Policies and the Medical Devices Industry*** (october 1984),
- ***Medical Technology and the Costs of the Medicare Program*** (July 1984),
- ***Postmarketing Surveillance of Prescription Drugs*** (November 1982),
- ***Medical Technology Under Proposals To Increase Competition in Health Care*** (october 1982),
- ***MEDLARS and Health Information Policy—A Technical Memorandum*** (September 1982), and
- ***Technology and Handicapped People*** (May 1982).

IThe definition of technology used by OTA is "a drug, device, or medical or surgical procedure used in medical care. "

## Use of medications among the elderly

More than four out of five Americans over 65 now suffer from one or more chronic diseases (86 percent–see chs. 7 and 9 and app. A). About 85 percent of the noninstitutionalized elderly and 95 percent of those in hospitals, nursing homes, and other institutions take medications on a regular basis (39). Although those over 65 constitute 11 percent of the population, they use 30 percent of prescription drugs (54,64), more than twice as many as the average user (7,39). An average of 10 different drugs is prescribed for an elderly patient during each hospital stay; the usual number of prescriptions for those in nursing homes is 4 to 7 (54). The average number of prescriptions for those who use drugs and are over 65 rose from 13.4 per year in 1967 to 17.9 in 1977; 90 percent of these prescriptions are for long-term use to treat chronic medical conditions (37).

As disease prevalence rises with age, drug use increases. older individuals take medications for several types of illnesses. They use the everyday drugs used by the general population for colds, acute infections, and headaches. Such chronic diseases as arthritis, hypertension, and cardiovascular disorders, which are especially common in older people, determine the use of another group of drugs that includes diuretics, anti-hypertensives, anti-inflammatory agents, and cardiac drugs (60).

Elderly women suffer disproportionately from drug-related problems. They live longer, are more likely to live alone (almost twice as likely as men), and have lower average incomes and a higher prevalence of disability than men. Each of these factors complicates drug therapy. The oldest women are the most vulnerable to adverse reactions and other untoward consequences of using drugs.

Drug use improves the condition of most elderly patients; drugs are used because they work. Patients are better off because useful drugs are available, and drugs are '(probably the most cost-effective modality of chronic disease management" (36). While the rate of inflation for medical costs ***overall*** during the last decade has been far greater than for the economy as a whole, pharmaceutical prices have risen more slowly than the Consumer Price Index (CPI) (19). Inflation for pharmaceuticals has exceeded the CPI in recent years (fig. 18), but the average inflation over the past decade remains favorable (table 10). Pharmaceutical therapy is not only medically effective but can also produce savings by diminishing morbidity and forestalling the need for more expensive forms of medical treatment. For example, the use of cimetidine ragamet~ for duodenal ulcer disease led to an estimated 26-to 70-percent cost savings for Medicaid in Michigan in the first year of its use, primarily by substituting for surgery in some patients (18). It is not clear that this figure can be extrapolated specifically to the elderly population, because the study included all age groups, but the potential for cost savings over the short term has been demonstrated for the general population in this study. In another example, lithium treatment of manicdepressive illness has saved an estimated $4 billion over the last decade, **according to the director of the National Institute of Mental Health (56).**

**Use of drugs to treat diseases for which there has never previously been effective therapy can, however, increase health care costs, if their cost is higher than previous modes of therapy. Treatments requiring extensive drug therapy may also increase overall costs.**

**Many issues concerning the cost effectiveness of drug therapy, proper indications for drug use, and regulatory practices vis-a--vis the drug industry are not directly relevant to this report, because they do not specifically affect the older population. Although these issues are important for older Americans because they use more drugs, policy changes would not be directed at improving the lot of the elderly per se. The balance of this chapter thus deals with those aspects of drug therapy that do specifically affect the older American population. The issues to be discussed include metabolic and clinical differences between older and younger individuals, drug testing regulations, and patterns of drug use unique to the elderly.**

**Older Americans pay more for prescription medications than does the general population. Those over 65 pay an average of $93 per year for prescriptions, compared to $79 for those .55 to 64 and $27 for those 19 to 24 (27). Cost differences are especially marked in the heaviest users: 3.3 percent of those over 65 pay more than $250 per year for prescription drugs, compared to 2.2 percent of those 55 to 64 and 0.5 percent of those 19 to 24 (27). Some contend that these figures substantially underestimate the economic impact of drug use among the elderly, because such figures do not capture over-the~ounter medications, and do not measure the impact of a substantial minority of elderly patients who have medication bills far in excess of $250 (37). The important topic of reimbursement policy for prescription drugs under Medicare has been omitted because it has been analyzed in detail in a recent report which gives potential costs of changes in Medicare reimbursement policy and cost estimates for a variety of options (65).**

**Many of the problems of drug use among the elderly are due to altered metabolism, the pres-**

**Figure 18.— Percent Change in Prices From previous Year (based on table 10)**

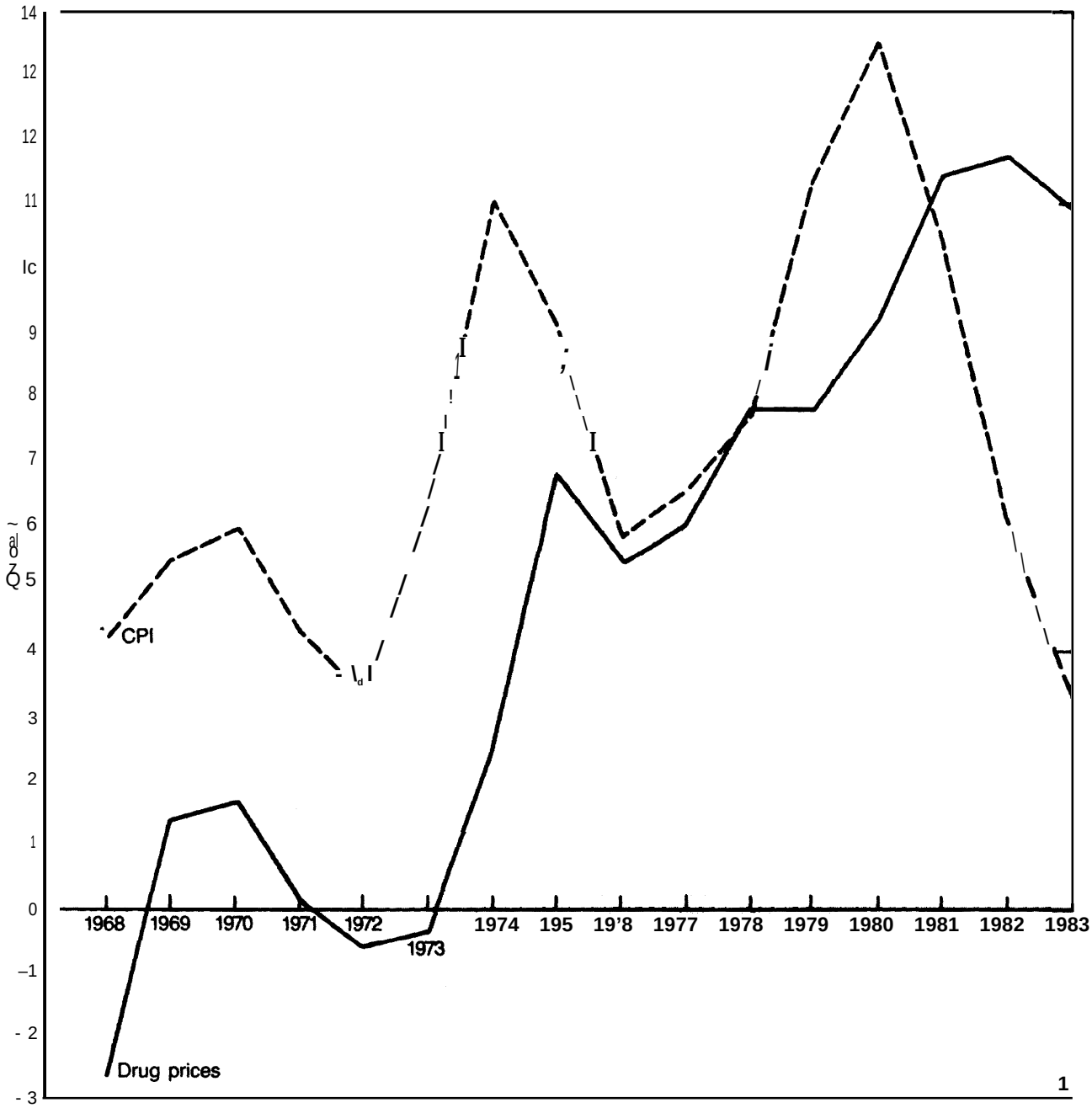

**Table 10.—Comparison of Inflation Factors for Prescription Drugs and Other Goods**

| Year | Prescription Drug Price index | Consumer Price index for ali goods |
|---|---|---|
| 1967 .... | 100.0 | 100.0 |
| 1968 .... | 98.3 | 104.2 |
| 1969 .... | 99.6 | 109.8 |
| 1970 .... | 101.2 | 116.3 |
| 1971 .... | 101.3 | 121.3 |
| 1972 .... | 100.9 | 125.3 |
| 1973 .... | 100.5 | 133.1 |
| 1974 .... | 102.9 | 147.7 |
| 1975 .... | 109.3 | 161.2 |
| 1976 .... | 115.2 | 170.5 |
| 1977 .... | 122.1 | 181.5 |
| 1978 .... | 131.6 | 195.4 |
| 1979 .... | 141.8 | 217.4 |
| 1960 .... | 154.8 | 246.8 |
| 1981 .... | 172.5 | 272.4 |
| 1962 .... | 192.7 | 289.1 |
| 1983 .... | 213.8 | 298.4 |

SOURCE: Bureau of Labor Statistics, cited by Palumbo, 1984 (55).

ence of multiple diseases, the use of multiple drugs, and increased susceptibility to side effects.

## *Biologic differences in drug effects and metabolism in older people*

Drugs are tested for side effects and therapeutic effectiveness in the general population, yet are used most often by the elderly, in whom they may act in a manner not always detected in studies of the general population. Recent studies of pharmacokinetics-the study of how drugs are distributed and metabolized in the body—and pharmacodynamics—the study of how drugs act—show significant differences between older and younger populations. These differences are based on fundamental biological age-related changes that affect the body's ability to process, store, and excrete drugs (table 11).

Biological differences between older and younger patients are analogous to the differences between adults and infants. It has been said that just as it took many years to recognize that infants are not simply "smaller" adults and must be treated differently, it is not yet universally recognized that the elderly require different treatment than younger adults (33).

**Table 11.—Age=Related Changes Altering Drug Metabolism and Sensitivity**

1. **Body composition**
   - A. Decreased lean body mass
   - B. increased proportion body fat
   - C. Decreased total body water
   - D. Decreased blood albumin (small change)

L. **Heart and blood vessels**
   - A. Decreased heart response to stress
   - B. Increased size of heart
   - C. Diminished vessel elasticity
   - D. increased total vascular resistance to blood flow
   - E. Decreased oxygen delivery to selected organs
     - Kidneys
     - Liver, brain, and muscles (small change)

. **Kidneys**
   - A. Decrease in number of blood filtering units (nephrons)
   - B. Decreased blood flow through kidneys
   - C. Decreased filtering and clearance rate of blood components
   - D. Decreased ability to adapt to maximum loads

*Iv.* **Digestive organs**
   - A. Slowed stomach emptying
   - B. Diminished acid secretion
   - C. Decreased peristalsis
   - D. Decreased absorption (small change)

*v.* **Liver**
   - A. Altered drug metabolism (slowed oxidation, especially in men, conjugation relatively unaltered)
   - B. Diminished blood flow (small change)

VI. **Nervous system**
   - A. Decreased threshold for depressant medications
   - B. Decreased coordination and short-term memory (small change, unless another disorder is also present)
   - C. Diminished blood flow to brain and nerves (slight, in absence of vascular disease)
   - D. Slowed velocity of conducting impulses in nerves
   - E. Slowed reflexes

Vii. **Lungs**
   - A. Decreased lung elasticity
   - B. Decreased effective surface area for oxygen exchange
   - C. Decreased effective breathing volume
   - D. Decreased rate of expelling air
   - E. Decreased clearance of irritants (ciliary movement)

Viii. **Endocrine organs**
   - A. Decreased sex hormones (in general, with a few exceptions)
   - B. Decreased response to sugars
   - C. Many other alterations, too numerous to list, including stress hormones, regulators of metabolic rate, and body volume regulation

SOURCE: Lamy, 1982 (33), as modified by OTA with the assistance of J. Rowe,

## *Altered metabolism and tissue sensitivity*

Older adults have significantly altered drug reaction and metabolism (7)20,33)36)38)43). They also have a higher percentage of fatty tissue com-

**pared to lean body mass, which causes increased effective concentrations of water-soluble drugs and prolonged retention of fat-soluble drugs. Hepatic metabolism of drugs, particularly oxidative processing in older males, is altered with age, which may lead to reduction of the required dose of drugs so processed. Decreased kidney function with age leads to prolonged retention of drugs in the body, often lowering the dose of a drug required to achieve useful concentrations, or necessitating an increase in the time between doses. Decreased blood albumin causes increased effective plasma concentrations of many drugs.**

**Tissue sensitivity to drugs may also increase or decrease with age, depending on the tissue, the patient, and the drug. Many of these changes lead to a need for reduced doses of drugs. The clinical effect of many benzodiaepine drugs (common sedative agents) in older patients, for example, is more intense than in younger patients with similar blood concentrations (47).**

**Prescription sleeping pills provide striking examples of how altered biological characteristics can necessitate adapting the treatment to the older patient. Common sleeping pills, also called minor tranquilizers or hypnotics, are fat-soluble chemicals that are retained longer in older patients: flurazepam (Dalmane®, a hypnotic agent) stays in an elderly patient for an average of 1 week (64), and the effective half-life of diazepam (Valium@, a related anti-anxiety agent) averages 90 hours in those over 80, compared to 20 hours in those under the age of 20 (23). These prolonged retention times have led geriatric pharmacologists to urge the prescription of shorter acting drugs at lower doses.[2] Although it is twice the recommended geriatric dose, the usual 5 mg dose of Valium (dizepam) is one of the most commonly prescribed drugs for those over 65 in a private prescription service (29), and more than 13 million prescriptions for Dalmane® (flurazepam) were given to the elderly last year (64). Such figures do not indicate that the drugs are not useful, but do suggest that prescription patterns are not** optimally tailored for the needs of the older population.

[2]The use of very short-acting hypnotic agents is also problematic, in that patients may awaken from '(rebound insomnia" if the drug is metabolized and cleared rapidly. Resolution of proper practice in prescribing hypnotic agents thus awaits further inquiry.

## *Characteristics of drug use*

**Those over 65 use more drugs than any other age group (36,43). Many chronic disorders such as arthritis or hypertension are treated with more than one drug. Many older people have multiple chronic diseases, each of which may be treated by drugs. There are more than 43,000 pharmaceutical products on the market, containing 1,900 separate chemical entities (39). The scant attention given to use of drugs peculiar to the elderly in medical practice is due in part to the fact that much drug information (e.g., information in the Physician's Desk Reference) is based on Food and Drug Administration (FDA) requirements for drug certification. At present, FDA drug approval does not require special attention to effects on elderly patients. (See "Drug Testing" below.)**

## *Side effects and adverse drug interactions*

The elderly have a higher incidence of drug side effects and drug interactions (2,20,33,38). The threshold of toxic blood concentration is lower among the elderly for many drugs, leading to increased probability of overdose. The presence of multiple chronic diseases and their treatment with multiple drugs lead to a higher incidence of adverse drug reactions and adverse drug ***interactions (36,43,58).*** This may be due not only to altered pharmacokinetics, but also to possibly increased susceptibility to adverse effects of drug usage resulting from altered inherent susceptibility among older people.

A recent study of adverse drug reactions and interactions, which showed that they accounted for 3 percent of all hospital admissions, found this figure to be much higher for the elderly–12 to 17 percent of hospital admissions for those 70 to 90. Of those suffering adverse drug reactions, 40 percent are over age 60 (cited in 54). Conclusions from the studies that have been performed cannot be generalized to the total American elderly population because they have been small and local. Generation of aggregate data on hospital ad-

missions due to drug reactions is one benefit that may accrue from increased use of computerized medical information systems, and may permit more accurate policy determinations.

Adverse effects are especially common for drugs used to treat cardiovascular and psychiatric diseases and so are used especially heavily by the elderly. Adverse drug reactions among the elderly have been roughly estimated to cost $3 billion per year (cited in 54).

Some assert that side effects-of drugs may be more common among ambulatory patients than among hospital patients (33). Reporting of adverse effects is less reliable for ambulatory patients, and drug errors are more common outside the hospital. Increased home care may exacerbate the problem of adverse drug effects and noncompliance with prescription instructions.

A different type of problem in geriatric drug use is the frequency of drug interactions. Drug interactions can occur between the drug and the patient (due to individual susceptibility), between the drug and numerous diseases (metabolism of drugs for one disorder altered by another disorder), between the drug and drugs for other disorders, and between the drug and a patient's diet.

Interactions between drugs and diet can cause problems in several ways (34). Drugs can affect dietary intake; certain antacids, used to quell stomach complaints, also lead to decreased absorption of phosphate, vitamin $B_1$ (thiamine), and iron (needed to make red blood cells) (42). Laxatives, often used to prevent constipation, can prevent the absorption of fat-soluble vitamins involved in blood coagulation and bone metabolism (see section on *Nutrition* inch. 4). Dietary habits can also influence the efficacy of drugs; diets high in yeast, liver, fish, whole grains, and certain vegetables can inhibit the effectiveness of drugs for Parkinson disease. Diets high in vitamin K, such as spinach, cheese, and liver, can reduce the efficacy of some drugs used to prevent blood clot formation (42). Foods high in the chemical tyramine, found in cheese, wine, and chocolate, can cause dangerous elevation of blood pressure for those taking some types of antidepressant medications. Such problems are not unique to older patient populations, but each of these drug groups is used more by elderly individuals (42).

Although many drug interactions cannot be avoided, the increase of "polypharmacy," the simultaneous use of multiple drugs, highlights current deficiencies in the use, retrieval, and storage of medical information. The problem of predicting and reporting drug interactions is an example; one computer analysis of drug prescriptions showed the potential for harmful drug interactions to be far in excess of those clinically reported (8). Present methods of monitoring adverse drug effects raise questions of whether untoward reactions are markedly underreported or whether the computer model is incorrect; both explanations may be partially valid.

Technology can be useful in identifying drug interactions. A recent study that used a computerized prescription information service found that using the computer did not reduce the number of prescriptions with potential problems, but did shorten the time period needed to recognize and begin dealing with the problem (30). The application of sophisticated "artificial intelligence" to medical monitoring, in which computer programs, such as the RX program developed at Stanford University, (9,10) continuously investigate the patient record data base of a hospital or region, looking for possible medical effects from the use of a particular drug or group of drugs, is likely to be a major improvement. Such data analysis depends, however, on gaining access to statistics on the incidence of drug side effects in the population. Innovations arising from increased use of information technologies, such as "smart cards" or improved patient-centered information systems may enhance the ability to identify drug reactions and interactions. The present system, which relies largely on user, manufacturer, or physician reporting, requires that someone notice a causal relationship, and is especially unreliable when there is a long time lag between the start of drug administration and the development of an adverse effect (8,67). Development of effective methods of monitoring drug use in actual clinical practice may prove important in development of drugs for the elderly population. (See *Drug Testing* below.)

Photo credit *Giant Food,* Inc

Pharmacists use the computer to spot potentially harmful drug use that can occur when people unknowingly mix medications.

## *Patient compliance with drug prescriptions*

**Elderly patients often fail to use drugs exactly as prescribed; 59 percent of patients in a recent survey showed some "error" in drug use (54). The most common error is omission (39), The probability of error rises among women, patients who live alone, those over 75, and those who use a great number of drugs or must take drugs frequently (54). Deviance from prescription instructions is also more likely among those who have numerous diseases, who have poor vision or hearing (17), and whose socioeconomic status is low. Diminished mobility (difficulty in getting to the pharmacy to fill prescriptions) and inattention from medical care providers may also contribute to noncompliance (39).**

Compliance with drug prescriptions is probably not affected by aging per se, but may be diminished by social and biological factors that become more common with age. If nothing else, the greater number of medications taken by older people increases the probability of deviating from instructions for at least one prescription,

The treatment of chronic diseases with drugs taken over long periods clearly requires persistent patient and family participation and the strong motivation of both patients and providers; these factors may not be receiving sufficient attention at present in the medical community (39). Difficulties in communication between physicians and patients may be intensified by older people's difficulty in hearing, understanding, or remembering instructions on drug use (17).

Some noncompliance is deliberate. The tremendous variation in reported rates of deliberate noncompliance ranges from 7 to 43 percent (69); one study found that 70 percent of "errors" were intentional (12). yet the high rates of deviation from prescription instructions do not always portend ill outcomes. Compliance rates vary tremendously, depending on drug type (69), and may at times be due to a judgment of appropriate treatment by the patient. Another study showed the most common reason for not taking medications to be thepatient's perception that he or she did not "like or need" them, which accounted for far more deliberate disuse than cost or presence of side effects (69). These two reasons accounted for 71.6 percent of patient-reported failure to follow a prescription. To the extent that patients can accurately determine their own needs for medication, such "noncompliance" may be intelligent. For example, some inappropriate prescriptions for excessive doses of hypnotic/anti+mxiety drugs, such as Valium® and Dalmane®, may be partially corrected by patients taking fewer pills than directed. Noncompliance with prescriptions, however, is not generally laudable. Misuse of drugs, whether deliberate or unintentional, can lead to serious adverse effects, and, as noted above, to preventable hospitalizations.

"Child-proof" containers may be difficult to open (15,39,41,44), and can thus cause compliance problems. New packaging for over-the-counter medications, instituted in reaction to the deliberate alteration of Tylenol® capsules, may also make opening difficult for older people. However, such protective packaging can also be a blessing in preventing accidental or poorly conceived ingestion of drugs by patients with poor mental function (41), patients whose arthritis affects their hands are particularly likely to have difficulty opening child-proof containers, and should have easy -to-open containers ordered by their physicians.

Correct administration of drugs is especially difficult in patients afflicted with dementia and psychiatric illness, for whom expectation of patient-initiated accuracy of drug administration is a vain hope. For these patients, the involvement of other family members is essential (41). The use of medication "boxes," with drugs arranged for time of day **and date by a family member or health professional can help; as can the use of charts with examples of the appropriate pill taped to the proper column. Prescription labels in lay language in large type on containers of different colored pills can also help avoid mistakes .There is great opportunity here also for technological innovation. New products relying on "smart" electronics to keep track of proper times for dispensing particular drugs are under development. One simple device in a relatively inexpensive bottle cap sounds an alarm when it is time to take the medication (Med-Tymer, Boston Medical Research, 1983). Other systems under development could dispense multiple medications on different schedules and notify patients when it is time to take a particu-**

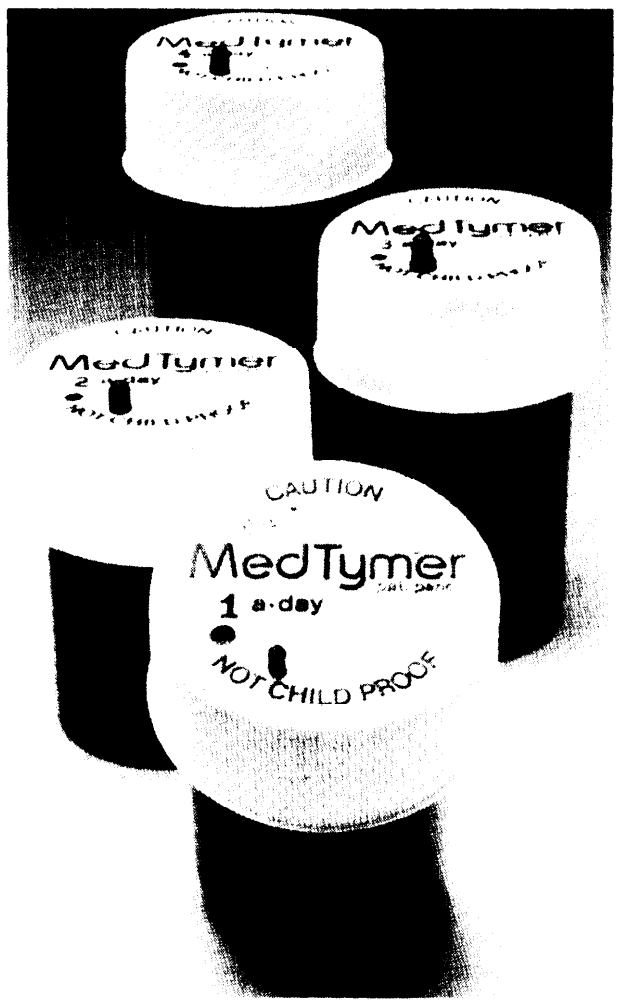


*Photo credit: Boston Medical Research, Inc.*

**lar pill. This would be helpful to all patients requiring multiple medications, and would be particularly welcome for patients with diminished mental function (although others would have to fill the prescriptions and program the mechanisms).**

## *Issues specific to drugs affecting mental function*

### DEMENTIA CAUSED BY DRUGS AND DEPRESSION

**Depression may cause or complicate dementia (loss of higher mental functions) in 8 to 23 percent of patients who receive a diagnosis of irreversible dementia. This is partly due to inaccurate diagnosis, and partly to an increased prevalence of depression among demented patients (4 I). Further, drugs used to treat other diseases can cause dementia. Many drugs that block the effect of acetylcholine,[3] either as a primary effect or as an unwanted side effect, are used in the treatment of Parkinson disease, insomnia, hypertension (46), colds (32), depression, and psychosis (14). The rare syndrome of "atropine psychosis)" a severe form of mental reaction to certain anti-cholinergic drugs characterized by psychotic symptoms, may tempt a physician to treat the psychosis with drugs that can further worsen the patient's symptoms (14). Much more common, however, is mild confusion induced by over-the-counter or prescription drugs that have mild or moderate anticholinergic actions.**

**Drug-induced dementia is even more common as a cause of reversible dementia than depression (25). Drugs are thus the most common cause of this syndrome, which carries the awkward title of "pseudodementia" (20). Sedatives and hypnotic drugs often diminish intellectual function in patients at all ages, and are especially likely to do so among older people.**

**Drugs given to correct other conditions, such as heart disease or hypertension, can also cause loss of mental functions by altering blood flow** to the **brain or by directly acting on brain cells. These effects are rare in younger age groups, but increase with age.**

[3]Acetylcholine is a molecule used to communicate between nerve cells, and is implicated in memory processes. Loss of brain cells that use it is found in some diseases, such as Alzheimer disease, that lead to dementia. Blocking of acetylcholine, with drugs called anticholinergic drugs, might, therefore, lead to exacerbation of dementia and increase in confusion in susceptible patients,

### DRUGS USED FOR MANAGEMENT EASE, RATHER THAN PATIENT BENEFIT

There is some evidence that psychopharmaceuticals are used to make nursing home patients easier to manage, rather than to improve their medical condition. One study found that a small minority of physicians (1.3 percent) with large nursing home practices prescribed a large proportion (37 percent) of the anti-psychotic medications dispensed in the nursing homes sampled; the 14 percent of physicians who had 10 or more nursing home patients prescribed 81 percent of the anti-psychotic drugs (57). The prevalence of anti-psychotic drug use in this study varied widely—more than three-hundredfold—among nursing homes. Usage increased with nursing home size, and was inversely related to the ratio of nursing home staff to patient (57), suggesting that anti-psychotic medications may be used as a substitute for personnel in some institutions,

## *Need for increased education of health care providers*

**One way to** improve the manner in which drugs are used is to educate the physicians who prescribe them. Such education includes not only instilling knowledge about proper use of drugs, but also increasing awareness among practitioners about the special biological and physiological characteristics of older patients. studies suggest that physicians may base more of their prescription decisions on drug advertisements than on scientifically verified studies (3). In response to this finding, a group seeking to promote appropriate prescription habits has borrowed the techniques used by pharmaceutical companies to promote the use of their drugs—using trained personnel to personally visit physicians to educate them about common prescription errors [4). Such methods are experimental, and some have questioned the appropriateness of this approach (45), but there is wide agreement on the need to improve physicians' awareness of the importance of the vicissitudes of drug therapy among older patients.

Recent data show that the use of physician advisors can be especially effective in changing physicians' prescribing habits (59). A large recent study found efforts to change physician habits to be cost effective in saving funds for Medicaid. Costs of educational materials and personnel for educating physicians were $93 per physician per year, compared with $205 saved from Medicaid funds. The program was especially effective for those physicians who were the heaviest prescribers, and was received well by the physicians involved (61).

## *Use of over-the-counter (OTC) drugs*

Many elderly people use OTC drugs: 70 percent of those 65 and over use some OTC medication regularly (64). Physicians are often unaware that their patients are taking OTC agents, either because patients do not inform them, or because they fail to ask (13). The most common drug in this class is aspirin, which is often used to treat the pain and inflammation associated with arthritis (13,35). Aspirin is one of the cheapest and most effective remedies for arthritis, but is also associated with ear and vision toxicity, loss of control of body heat, confusion, nausea, diarrhea, and gastrointestinal bleeding (13). Some patients, who also have asthma and nasal polyps, can have life-threatening reactions to aspirin. Yet aspirin is ubiquitous; more than 200 products contain it, and some of them are not clearly labeled (13).

Another common side effect of OTC medications is confusion. Many nonprescription drugs contain agents that block the effects of acetylcholine. Many nonprescription sleeping pills and anti-cold remedies contain agents that can induce confusion.

The special biological and sociological characteristics of older populations may indicate a need for caution in converting drugs from prescription to over-the-counter status. For those drugs that are used primarily by older people, special attention to the incidence of side effects in the older subpopulation may be in order when deciding to make medications available to all consumers.

## *patient information on drugs*

The need for active patient participation in treatment of chronic diseases requires improved methods of teaching patients about their treatments. In a recent FDA survey, 58 percent of patients received information on how to take their medication, but 75 percent received no information regarding potential side effects (48). Physicians in a recent survey believed that their patients were either very well (32 percent) or adequately (56 percent) informed about their medications (40), yet other studies show patients are often ignorant of important facts about their therapy (48). Patients rarely ask physicians about their drugs, but instead ask nurses, clerks, family, or friends (50). The transfer of information to patients is worse for older patients than for the general population, and especially poor for one group-old and less educated women (49).

Poorly informed patients are unable to make rational decisions, and may experience unnecessary drug interactions. Lack of information from health professionals leaves patients vulnerable to the advice of uninformed or ill-informed acquaintances and family members. Some of the problems in communication may stem from the reluctance of patients to ask physicians for information: in the FDA survey, only 2 percent of the patients asked their physicians about their medications (48). Heightened sensitivity to the need for adequate patient education among health providers could improve the efficacy of treatment; greater assertiveness on the part of patients could diminish anxiety and aid in the treatment process by improving patient awareness of potential adverse reactions and contraindications.

The recently formed National Council for Patient Information and Education (NCPIE) is addressing the need for increased involvement of patients in their treatment by encouraging patients to ask questions of their physicians. Current NCPIE strategy is to sponsor television and mass media advertisements (52). Other patient-information activities include community programs at the Albany College of Pharmacy, the University of Maryland, and the University of Michigan,

and in Los Angeles, San Francisco, and Osceola, FL (39). Many other communities not noted in national publications are also known to have developed special patient education programs for the elderly.

Accompanying certain prescription drugs with information for patients became an area of Federal concern in 1981, when the FDA mandated the inclusion of information with prescriptions for cimetidine, clofibrate, propoxyphene, and seven other drugs. This requirement was reversed by Executive Order 12291 shortly after the start of the Reagan Administration in February 1981, although inserts are still required for several medications such as isoproterenol inhalants and contraceptives.

The delay in implementation of Executive Order 12291 coincided with the start of the voluntary American Medical Association's Patient Medication Information program, in which physicians are to distribute patient information on drugs to their patients at the physician's expense. A recent survey showed that 22 percent of physicians who prescribe medications were participating in the program; 50 percent of physicians did not know about the program, and a small minority of older male physicians disagreed with AMA policy in distributing patient-information leaflets (31).

Another program of patient education undertaken by the American Association of Retired Persons (AARP) has been especially effective. "Medication Information Leaflets for Seniors" accompany each prescription emanating from several mail prescription services available to AARP's 14 million members, who order more than 5 million prescriptions per year. The inserts, in leaflet form, explain the reason for taking the drug, how to administer it, what information the physician needs to properly prescribe it, contraindications and potential interactions with food and other drugs, and potential side effects. An early survey of recipients showed that although 24 percent of people either did not notice them or did not receive them; of those who did, 90 percent found the leaflets useful, 95 percent read them, and 76 percent kept them for possible future reference. Fears that providing patients with information about their prescription would increase anxiety were allayed by finding that 40 percent of those responding "felt better" about their medications, and 56 percent "felt no different" after receiving the leaflets (21,53). The package inserts were more extensively used for anti-hypertensive medications than for anti-arthritic agents or minor tranquilizers (51). The AARP drug leaflet is currently being comprehensively evaluated to determine its effect on patient attitudes, perceptions, and behavior (6).

Patient package inserts may be especially helpful to older patients. A large and extensive Rand Corp. study of patient package inserts sponsored by the FDA found that older patients read them more often, resulting in a small but detectable increase in patient knowledge about medications (26). Patient package inserts can thus be useful, although questions remain about patients' judgments of risk. Patients remember less about side effects than other aspects of the leaflets (26) and some patients have difficulty in accurately assessing the relative seriousness of risks (28).

Patient education need not be restricted to leaflets included with the drug. Several pharmacies have taught classes, trained educators, arranged for educational programs, or written leaflets for their older patrons. Computer networks, as noted in chapter 6, may also encourage information networks on topics related to health. National and local press also serve an important function in highlighting new developments relevant to drug use.

# Congressional issues and options

## Background

DRUG TESTING

The FDA's drug approval process begins with laboratory discovery of a drug's action. Once a potentially useful new chemical activity has been discovered, tests of efficacy and toxicity are performed on animals. At this point, the manufacturer applies to the FDA for certification of the New Chemical Entity (NCE) to be tested in humans as an Investigational New Drug (IND). The agent is then tested for safety in a small number of relatively healthy volunteer patients, and long-term toxicity is measured in animals. This is called Phase I testing.

If preliminary tests are successful, phase II trials—larger clinical trials—are undertaken in a small number of patients (100 to 300) to establish dosage range and efficacy, and as a further measure of safety. Phase III is usually the final stage of testing and involves carefully controlled trials and field testing in larger numbers of patients (500 to 3)000). Although the FDA can request further testing, the agency cannot require it. Adverse effects may be detected by the clinical trials; the probability of detecting a harmful effect depends on the number of patients tested, the frequency of the reaction, and the duration of the study (67).

Elderly patients, who consume a large proportion of most types of drugs (7,38), are not specifically mandated for inclusion as patients during clinical trials performed for FDA approval. The trend in recent years has been to include more older patients in clinical trials (63), but there are no specific guidelines or regulations for assuring that clinical trials take account of the special drug needs of the older population.

There are several reasons that inclusion of greater proportions of older patients might complicate clinical trials. volunteers and patients used in early trials must be relatively healthy to assure safety of the testing procedure. Although a more representative patient mix could be incorporated into later testing, elderly patients are likely to have several diseases, making it difficult to ascertain whether a new sign or symptom is in fact due to drug use rather than to a new disease or a new manifestation of an existing condition. And many older patients take other drugs, making it difficult to identify the particular drug that might be causing a problem. The high prevalence of disease among the elderly increases the "noise" level in drug reaction data, compounding the difficulty of detecting problems. In order to compensate for this factor, more patients must be included in tests; this pushes up development costs and makes analysis more difficult.

problems in current methods of drug testing have been underscored by recent episodes of adverse reactions to antidiabetic drugs, and nonsteroidal anti-inflammatory agents for treating arthritis. The problem for these agents was lack of testing in populations similar to those that used the drugs in routine practice, although this was not necessarily due specifically to a dearth of older patients in the test groups. Both classes of drugs are used more often in the elderly, however, and representatives of each of these drug classes were recently removed voluntarily from the market by their manufacturers in the United States because of newly discovered adverse effects that were not found in premarket testing. Such problems might be minimized in the future by increased attention to premarket testing in representative populations, which in many cases will involve inclusion of older individuals.

It is important to note that testing of drugs in patients over 65, if it is to be realistic, must be done in populations that have numbers and types of illnesses, average ages, and sex and racial balance similar to those groups that would actually use the drugs in practice (71).

The most difficult aspect of testing drugs in elderly populations is assuring safety, The pharmacokinetic and pharmacodynamic differences between the elderly and younger cohorts are more likely to lead to overdose than to underdose, and the increased incidence of side effects among older populations adds to this risk. Modification of current regulations regarding drug testing in the elderly could focus on issues of safety, In connec -

**tion with this, the FDA has recently proposed guidelines for testing of drugs in older populations. The guidelines stress including older patients in late (Phase III) clinical trials and analyzing clinical trial data with attention to effects of aging (62). The proposed guidelines focus on the most dramatic known differences between older and younger population groups, and do not emphasize questions of bioavailability, dosage forms, or tissue sensitivity of new agents specific to older patients (67). One potential problem with establishing adequate guidelines is likely to be determination that a truly representative population of older patients has been tested (71). Identification of drug interactions is especially difficult, but also important in older patient populations because of the larger average number of agents that such patients take simultaneously. In addition, it may prove difficult to test the safety of the *long-term* drug use in older patients who often take drugs for chronic conditions over months or years. Long-term administration of drugs for older patients may expose adverse effects that appear only after cumulative use that would have been absent in tests for premarket approval. The FDA will continue to seek advice on how to establish guidelines that satisfy both public demand for safety and industrial concern over increased costs of drug development and increased regulation (63).**

## COSTS OF DRUG DEVELOPMENT

The cost of clinical testing is the largest single hurdle between drug discovery and routine clinical use (16). A 1978 report estimates that development of a new drug costs an average of $54 million per drug marketed, which includes the cost of testing drugs that never reach the market (22). A more recent estimate is $70 million.

The costs of new drug development vary widely, depending on the nature of the drug. Antibiotics cost less than $20 million to develop, because efficacy is easy to demonstrate, and animal models of infectious disease are readily available. Psychopharmaceuticals, in contrast, cost more than three times as much to develop—approximately $70 million each—largely because of costs of clinical testing and the absence of applicable animal models of drug action (11,19).

**These high development costs have led to calls for reducing the cost of clinical trials. It is important to rationalize the conflicts between patient safety and expeditious approval. Additional costs could lead to a reduction in the rate of introduction of new and useful drugs, but loosening safety requirements might be costly in patient health and welfare. Increased drug testing in the elderly might increase the costs of clinical trials, and thus of drug development. Such cost increases could range from adding tests of pharmacokinetics in older people, as suggested by the proposed FDA guidelines, which would require only a few added tests, to extensive epidemiological surveys, pharmacodynamic studies, and tests of potential drug interactions that would cost substantially more.**

**Increased use of postmarketing surveillance could contribute to establishing drug safety and efficacy, and have the added benefit of focusing attention on the special problems of the elderly. Drugs could be monitored in actual use, thus identifying currently unknown adverse reactions, and adverse effects detectable by present methods might be found more quickly. Premarket test results could thus be supplemented, and premarket requirements might even be reduced in some instances; representative sampling of the elderly would be assured because monitoring would reflect actual clinical use. Safety would be encouraged by intensive surveillance. There are, however, problems with using postmarketing surveillance to assure safety; current methods of reporting adverse effects, for example, are unreliable (67). This may be crucial because safety is one of the most important reasons for the stringency of FDA clinical trial protocols. There is strong pressure to err on the side of safety, because the agency has limited power to recall drugs once they are approved (19,39,67).**

**Monitoring of actual drug use is an important element of drug regulation in several countries. The international nature of pharmaceutical marketing suggests that monitoring of drug use is an important area for potential international cooperation that could benefit all countries involved. Some other nations already rely more on postmarketing surveillance than does the United States. Some of this increased reliance on postmarketing surveillance is ascribed to the presence**

of central or national medical care delivery systems that increase physician-government contact and allow easier governmental access to patient and physician records (66). Because such mechanisms are not in place in the United States, effective postmarketing surveillance would require establishment of new means of monitoring drug effects in clinical use.

Postmarked surveillance is not, however, solely a means of reducing the need for premarket testing; postmarked surveillance is also a mechanism for assuring safety independently of premarket approval practices. There are strong arguments for retaining current procedures for premarket testing of effectiveness and safety. The stringently controlled clinical trials now required improve the quality of evidence used in making treatment decisions: new drug therapies are instituted only after careful analysis, in contrast to many other treatment modalities. Elimination or reduction of the current premarket approval process could result in proliferation of poorly verified treatments.

ISSUE 1: Should Congress require special testing of drugs in older population groups before approval for marketing?

FDA requires demonstration of safety and efficacy before approving a drug or device for marketing. At present, this does not include explicit mention of testing in older population groups. Several drugs used primarily in older populations have recently been withdrawn from the market because of concern for patient safety, Yet testing of drugs in older patients adds costs because such patients have more complicated medical histories. This complexity determines that more patients must be analyzed to assure sensitivity in demonstrating efficacy or safety.

*Options:*

*1.1: Congress could continue present regulatory requirements.*

Many believe that present mechanisms of approval of drugs and medical devices are adequate for assuring public safety.

1.2: *Congress could encourage inclusion of drug testing among older populations by oversight of FDA .*

This would entail obtaining assurances that interpretation of current legislation would be changed to include emphasis on the needs of the older population. The emphasis on testing drugs could be changed, for example, by requiring pre - market testing of agents intended for use in those conditions identified as highly prevalent among older populations.

1.3: *Congress could* create *new legislation to mandate drug testing among older populations.*

This option would entail defining those conditions for which special testing is needed, and definition of the population to be protected.

Option 1.1 would retain the status quo for drug testing. Options 1.2 and 1.3 would be intended to protect a special population group at risk of developing adverse reactions from drugs, but would do so at increased cost to pharmaceutical and medical device manufacturers, The guidelines proposed by FDA should entail minimal increased cost (62), but more stringent requirements would increase costs further. Increased development costs might lead to fewer new agents being developed, increased risk for investors, and disincentives for established companies to manufacture such products or for companies to newly address the affected markets. Nevertheless, cost savings to other groups, including the Federal Government, might occur if the incidence of adverse side effects could be diminished. Savings would result from preventing disability and lost productivity, as well as from avoiding those health care expenditures due to adverse effects of drugs.

ISSUE 2: Should Congress require increased postmarketing surveillance of drugs already approved?

*Options:*

*2.1: Congress could continue present patterns of postmarketing surveillance.*

2.2: Congress *could* encourage *increased use of* postmarketing surveillance.

This option could include oversight of FDA activities, mandating new requirements for manufacturers and new authorities for FDA. These could be done either independently of or in combination with options discussed under drug testing.

**Mandating increased use of postmarketing surveillance for drugs and medical devices could be effective in monitoring the safety of such products in actual use. This is relevant to the general population, but especially relevant to older patients, in whom the risks of adverse effects, interactions, and complications are higher. Increased use of postmarketing surveillance would entail establishing better mechanisms for reporting adverse reactions, and might require altering FDA legislation to permit FDA to withdraw drugs found to be unsafe in actual use. One potential problem in this area is access to and analysis of drug information in Federal data systems. The Computerized On-line Medicaid Pharmaceutical Analysis and Surveillance System (COMPASS) at FDA, for example, is intended to permit rapid epidemiologic surveys of drug reactions, but has been fraught with technical problems. The National Institute on Aging, with the American Association of Retired Persons and the Andrus Foundation, is supporting research on computer-assisted epidemiologic research on drug effects at Harvard Medical School (6). If Congress chooses to encourage postmarketing surveillance of drug use, more resources for epidemiologic data acquisition and information processing may be required; current university research may help determine the feasibility of monitoring for drug effects on a national scale.**

**Implementation of requirements for postmarketing surveillance would raise development costs for each drug and device, and thus might reduce the incentives for innovation, as also noted in the discussion of drug testing.**

**A more comprehensive discussion of postmarketing surveillance, which focused on the general population rather than the special needs of the older population, appeared in the OTA publication: *Postmarketing Surveillance of Prescription Drugs,* which also included specific legislative options (67).**

ISSUE 3: Should Congress encourage improved patient education regarding use of medications?

***Options:***

***3.1: Congress could refrain from taking action.***

3.2: *Congress could encourage FDA to issue patient package inserts on medications especially prone to misuse among older populations.*

3.3: *Congress could mandate inclusion of patient package inserts on medications determined to be especially prone to misuse by older patients.*

3.4: *Congress could encourage Department of Health and Human Services activities in the area of patient education.*

**This could include public service messages, research support, and developement and dissemination of booklets.**

**Increased patient education on medications is intended to prevent misuse by providing information to consumers. It can be accomplished by voluntary mechanisms, such as those of the NCPIE, AMA, and AARP mentioned above; through executive action, as taken by the Carter Administration and revoked by the Reagan Administration; or by legislative mandate.**

**Those who believe that voluntary programs already under way are sufficient see no role for increased Federal intervention. Federal requirements would increase costs for those affected by such requirements. Mandating patient package inserts for medications, if supplied by the manufacturer, would increase distribution and production costs. Requiring patient education through other means, such as through physicians, pharmacists, or other health professionals, would increase the costs of their services. Increasing production and distribution costs could adversely affect incentives for innovation, as noted under other options. Increasing costs of health care would raise Federal outlays for such services. Conversely, cost savings might also be possible by preventing adverse side effects, interactions, and complications, as well as by reducing the number of hospital admissions for drug-related problems.**

ISSUE 4: Should Congress encourage improved education of health care providers regarding older patients?

The special biological and social characteristics of older patients have been widely noted, yet little attention has been devoted to educating physicians and other health care providers about

these characteristics (5). Increased knowledge of pharmacological differences between older and younger patients is one of many high priorities for educating health professionals about the special needs of the older population (1,24). Professional education has the potential to become one of the most effective methods of preventing future problems in drug use, and might also save some health care costs associated with drug reactions, complications, and interactions. Some educational programs directed at physicians have already been shown directly to reduce Medicaid expenditures for medications, even without taking into account the indirect savings from avoiding adverse reactions (61).

The Federal role in educating health professionals is less prominent than State and local statutes regarding certification of practitioners and proper medical practices. There is, however, a Federal role in supporting training programs for basic and clinical research and through reimbursement policies affecting delivery of health care. The problem of insufficient knowledge and education about gerontology and geriatrics is global, affecting social as well as medical fields. Actions regarding this issue are thus only discussed; congressional options are part of a larger option of general education regarding geriatrics and gerontology in chapter 2 and other chapters of this report.

ISSUE 6: Should Congress require improved labeling of over-the-counter medication?

Options:

5.1: *Congress could refrain from taking action.*

*5.2: Congress could encourage* action by *FDA to require such labeling through oversight of FDA activity.*

*5.3: Congress could require FDA action by new legislation.*

Improved labeling of over-the-counter medications, especially aspirin and drugs with mental side effects, would allow consumers to avoid agents that contain ingredients to which they know they are sensitive. Special notice of changes in drug ingredients marketed under the same name might be beneficial in some instances. Special labeling might include warnings to specific classes of individuals, such as those subject to aspirin reactions or susceptible to drug-induced dementia. It could also encompass prominent listing of potentially hazardous reactions to ingredients. Such labeling might increase manufacturing and distribution costs, increasing the price of a product needed in high quantities by several groups of patients, especially those afflicted with osteoarthritis. Potential cost increases, however, might be defrayed in part or entirely by reduced incidence of aspirin reactions and side effects resulting from unknowing ingestion of compounds that cause confusion in susceptible patients.

ISSUE 6: Should Congress authorize and fund more randomized clinical trials for drugs and treatments prevalent among older Americans?

*Options:*

*6.1: Congress could refrain from mandating funding of more clinical trials.*

*6.2: Congress could direct the Health Care Financing Administration (HCFA) or the National Institutes of Health (NIH) to support more randomized clinical trials, especially for those conditions requiring multiple agents or for conditions highly preva* - lent in the older population.

*6.3: Congress could encourage or require third-party payers (e.g., health* insurers) to fund some clini*cal trials.*

Older people are susceptible to multiple disorders, and often have conditions that can be treated in a multiplicity of ways. Treatments for such disorders as hypertension, osteoarthritis, and osteoporosis are common in the geriatric population, and yet optimal treatments for these conditions are often not apparent because of the plethora of potentially effective drugs and other treatments. Comparative studies of different treatment combinations are often not available. The large number of non-steroidal anti-inflammatory drugs, for example, have not been directly compared for relative overall efficacy, incidence of adverse side effects, and comparative appropriateness for patient subgroups. Several members of this group of drugs have not been compared with aspirin, the most common drug used for osteoarthritis, Drugs from this class have been

recalled for unanticipated side effects noted in clinical use after approval for marketing, and two additional agents are currently under investigation by the Secretary of Health and Human Services. Clinical use of the different agents is a topic of current medical controversy.

The standard method for dealing with such controversies is the randomized clinical trial, the acceptance of which marks one of the major advances of modern medicine. Careful studies of different treatments can be compared under controlled circumstances to establish the utility of competing regimens, and may also determine the lack of substantial differences between different modalities of treatment (68).

Increased support for such trials, however, is likely to be quite costly. Supporting these trials from the NIH budget might detract from more basic biomedical research. Supporting trials through HCFA has been suggested, but would require a new allocation of resources within HCFA or increased overall funding for the agency. Increased support for trials could also be obtained through partial or full reimbursement by third-party payers.

Savings from such research might be obtained both for the Federal Government and third-party payers through reduced incidence of side effects due to present suboptimal levels of treatment and by preventing unnecessary complications. The magnitude of savings, however, cannot be estimated because there is insufficient knowledge about current therapeutic practices and the potential for improvement in health that might arise from rationalizing treatment.

A more complete discussion of the issues surrounding clinical trials can be found in the OTA Background Paper *The Impact of Randomized Clinical Trials on Health Policy and Medical Practice (68).*

## Chapter 5 references


1. Association of American Medical Colleges, *Undergraduate Medical Education: Preparation for Improved Geriatric Care, A Guideline for Curriculum Assessment* (Washington, DC: AAMC, 1983).
2. Avorn, J., Lamy, P. P., and Vestal, R. E., "Prescribing for the Elderly —Safely," *Patient Care,* June 30, 1982.
3. Avorn, J., Chen, M., and Hartley, R., "Scientific v. Commercial Sources of Influence on the Prescribing Behavior of Physicians, "Am. *J. Med.,* July 1982.
4. Avorn, J., and Soumerai, S. B., "Improving Drug Therapy Decisions Through Educational Outreach," N. *Engl. J. Med.* 308:1457-1463, *1983.*
5. Avorn, J., "Drug Policy in an Aging Society, "*Health Affairs* 2:23-32 (Millwood, VA: project HOPE, 1983).
6. Avorn, J., Harvard Medical School, Boston, MA, personal communications, January and March 1984.
7. Bartus, R., "Biomedical Needs of the Elderly," editorial sent to OTA, May 1983.
8. Block, L. H., "Polymedicine: Known and Unknown Drug Interactions)" *J. Am. Geriat. Soc. Suppl.* 30:s94-s98, *1982,*
9. Blum, R. L., "Discovery, Confirmation, and Incorporation of Causal Relationships From a Large Time-Oriented Clinical Data Base: The RX Project," *Computers* and *Biomed. Res.* 15:164-187, 1982.
10. Blum, R. L., "Discovery and Representative of Causal Relationships From a Large Time-Oriented Clinical Data Base: The RX Project," thesis, Department of Computer Science, Stanford University, Report #STAN-CS-82-900, Stanford, CA, January 1982.
11. Cole, J. O., "Outlook for New Drug Development)" *Physician Handbook on Psychotherapeutic Drug Use in the Aged,* T. Crook and G. Cohen (eds.) (New Canaan, CT: Mark Powley & Associates, Inc., 1981).
12. Cooper, J. K., Love, D. W., and Rattoul, P, R., "Intentional Prescription Non-adherence by the Elderly," *J. Am. Geriat. Soc.* 30:329-333, *1982.*
13. Cupit, C. C., "The Use of Non-prescription Analgesics in an Older Population, " *J. Am. Geriat. Soc.* @@. 30:s76-s80, *1983,*
14. Davis, J. J., "Anti-psychotic Drugs," *Physician's Handbook on Psychotherapeutic Drug Use in the Aged,* T. Crook and G. Cohen (eds.) (New Canaan, CT: Mark Powley & Associates, Inc., 1981).
15. Ehrlich, G. E., "Diagnosis and Management of Rheumatic Diseases in Older Patients," *J. Am. Geriat. Soc. Suppl.* 30:s45-s51, *1982.*
16. Erikson, T., Arthur D. Little, Inc., address at "Re-

search and Development in the Global Pharmaceutical Economy," Institute for Alternative Futures, Apr. 11, 1983.
17. Fedder, D. O., "Managing Medication and Compliance: Physician-Pharmacist-Patient Interactions," *J. Am. Geriat. Soc. Suppl.* 30:s113-s118, *1982.*
18. Geweke, J., and Weisbrod, B. A., "Expenditure Effects of Technological Change: The Case of a New Drug," manuscript from the Department of Economics, University of Wisconsin, Madison, 1982.
19. Grabowski, H. G., and Vernon, J. M., "The Pharmaceutical Industry," *The Government and Technical Process,* R. R. Nelson (cd.) (New York: Pergamon Press, 1982).
20, Greenblatt, D. J., Divoll, M., Abernathy, D. R., and Shader, R. I., '(Physiologic Changes in Old Age: Relation to Altered Drug Disposition," *J. Am. Geriat. Soc. Suppl.* 30:s6-s10, 1982.
21, *Green Sheet, The,* "Weekly Pharmacy Reports," Chevy Chase, MD, Mar. 14, 1983.
22. Hansen, R. W., "The Pharmaceutical Development Process: Estimates of Development Costs and Times and Effects of Proposed Regulatory Changes)" *Issues in Pharmaceutical Economics,* R. I. Chien (cd.) (Lexington, MA: Lexington Books, 1979), pp. 151-181.
23 Hollister, L. E., "General Principles of Psychotherapeutic Drug Use in the Aged," *Physician's Handbook on Psychotherapeutic Drug Use in the Aged,* T. Crook and G. Cohen (eds.) (New Canaan, CT: Mark Powley & Associates, Inc., 1981).
24. Institute of Medicine, *Aging and Medical Education* (Committee chairman: Paul B. Beeson), Publication IOM-78-04 (Washington, DC: National Academy Press, 1978).
25. Jarvik, J., and Reisberg, B., "Drugs Prescribed To Treat Cognitive Dysfunction," *Physician's Handbook on Psychotherapeutic Drug Use in the Aged,* T. Crook and G. Cohen (eds.) (New Canaan, CT: Mark Powley & Associates, Inc., 1981).
26 Kanouse, D. E., Berry, S. H., Hayes-Roth, B,, et al., *Informing Patients About Drugs* (Washington, DC: Rand Corp., 1981).
27. Kasper, J. A., "National Health Care Expenditures Study," *Prescribed Medicines: Use, Expenditures, and Sources of Payment,* Data Review 9, National Center for Health Services Research, U.S. Department of Health and Human Services, Hyattsville, MD, April 1982.
28. Keown, C. F., "Risk Judgments and Intention Measures After Reading About Prescription Drug Side Effects in the Format of a Patient Package Insert)" *Journal of Consumer Affairs,* 17:277-289, *1983.*
29. Knapp, D., Food and Drug Administration, Public Health Service, U.S. Department of Health and Human Services, 1982: "Geriatric use of drugs," "Geriatric use of drug products lacking adequate evidence of effectiveness," and "Geriatric use of drugs with psychiatric effects," papers prepared by FDA, not published because statistical analysis was not conclusive. The points made in this chapter do not depend on such statistical analysis.
30. Koepsell, T. D,, Gurtel, A. L., Diehr, P. H., et al., "The Seattle Evaluation of Computerized Drug Profiles: Effects on Prescribing Practices and Resource Use," *Am. J. Pub. Hlth.,* August 1983.
31. Lampe, K. F., "Physician Interventions," presented at the Drug Information Association workshop on Geriatric Drug Use-Clinical and Social Perspectives, Washington, DC, Feb. 27, 1984.
32. Lamy, P, P., "Drug Prescribing for the Elderly," *Bull. N.Y. Acad. Med.* 57:718-730, *1981.*
33. Lamy, P. P., "Comparative Pharmacokinetic Changes and Drug Therapy in an Older Population," *J. Am. Geriat. Soc. Suppl.* 30:s11-s19, *1982.*
34. Lamy, P. P., 'Effects of Diet and Nutrition on Drug Therapy)" *J.* Am. *Geriat. Soc. Suppl.* 30:s99-s112, 1982.
35. Lamy, P. P., "Over-the-Counter Medication: The Drug Interactions We overlooked," *J. Am. Geriat. Soc. Suppl.* 30:s69-s75, 1982.
36. Lamy, P. P., "Therapeutics and an Older Population: A Pharmacist's Perspective," *J. Am. Geriat. Soc. Suppl.* 30:s3-s5, 1982.
37. Lamy, P. P., response to OTA draft document, March 1984.
38. Lee, P. R., and Lipton, H. L., "Drugs and the Elderly," contract report, University of California at San Francisco, August 1983.
39. Lipton, H. L., and Lee, P. R., "Drugs and the Elderly," Administration on Aging Background Paper, draft, Office of Human Development Services, U.S. Department of Health and Human Services, September 1982,
40. Louis Harris & Associates, "Patient Information and Prescription Drugs: Parallel Surveys of Physicians and Pharmacists," March 1983.
41. Mace, N. L., and Rabins, P. V., *The 36-Hour Day* (Baltimore: Johns Hopkins University Press, 1981).
42. McGandy, R., et al., USDA Human Nutrition Research Center on Aging, Tufts University, "Drug-Nutrient Interactions," *Nutrition and Aging,* contract report for the Office of Technology Assessment, October 1983.
43. McGlone, F. B., "Therapeutics and an Older Population: A Physician's Perspective," *J. Am. Geriat. Soc. Suppl.* 30:s1-s2, 1982.
44. Medical Economics Co., "Medication Mistakes and

Noncompliance," *Practical Guide to Geriatric Medications* (Oradell, NJ: Medical Economics Co. Book Division, 1980), pp. 93-138.
45. Melmon, K. L., and Blaschke, T. F., "The Undereducated Physician's Therapeutic Decisions, " *N. Engl. J. Med.* 308:1473-1474, *1983.*
46. Mendels, J., "Antidepressants," *Physician's Handbook on Psychotherapeutic Drug Use in the Aged,* T. Crook and G. Cohen (eds.) (New Canaan, CT: Mark Powley & Associates, Inc., 1981).
47. Meyer, B. R., "Pharmacodynamic Risk Factors in Geriatric Drug Use," presented at the Drug Information Association workshop on Geriatric Drug Use--Clinical and Social Perspectives, Washington, DC, Feb. 28, 1984.
48. Miller, R. W., "Doctors, Patients Don't Communicate," *FDA Consumer,* DHHS publication No. (FDA) 83-1102, reprinted July/August 1983.
49. Moore, S. R., Kalu, M., and Yavaprabbas, S., "Geriatrics and Gerontology," Drug *Intell. Clin.* Pharm. 17:920-3, 1983.
50. Morris, L. A., Grossman, R., Barkdoll, G. L., Gordon, E., and Soviero, C., "Patient Receipt of Prescription Drug Information, " OPE Study 67, September 1983.
51. Morris, L. A., and Olins, N. J., "Utility of Drug Leaflets for Elderly Consumers," *Am. J. Pub. Hlth., 1984.*
52. National Council for Patient Information and Education, press releases and Task Force Reports, 1983.
53. Olins, N. J., press releases from the American Association of Retired Persons, Alexandria, VA, 1983.
54. Ouslander, J. G., "Drug Therapy in the Elderly," *Annals Int. Med.* 95:711-722, *1981.*
55. Palumbo, F., University of Maryland, Baltimore, personal communication, March 1984.
56. Paroles, H., opening address, "Practical Approaches for Meeting the Mental Health Needs of the Elderly," Project HOPE, Millwood, VA, March 1983, pp. 23-24.
57. Ray, W. A., Federspiel, C. F., and Schaffner, W., "A Study of Anti-psychotic Drug Use in Nursing Homes: Epidemiologic Evidence Suggesting Misuse," *Am. J. Pub. Hlth.* 70:485-491, *1980.*
58. Reidenberg, M. M., "Drug Interactions and the Elderly," *J. Am. Geriat. Soc. Suppl.* 30:s67-s68, *1982.*
59. Schaffer, W., Ray, W. A., Federspiel, C. F., and Miller, W. O., "Improving Antibiotic Prescribing in Office Practice," *J.A.M.A.*, Oct. 7, 1983.
60. Simonson, W., *Medications and the Elderly* (Rockville, MD: Aspen Publications, 1984).
61. Soumerai, S. B., and Avorn, J., '(Benefits and Costs of an Experimental Academically Based 'Detailing' Program To Improve Drug Therapy Decisions of Office-Based Physicians, " October 1983.
62. Temple, R., "Discussion Paper on Testing of Drugs in the Elderly," FDA memorandum, Sept. 30, 1983.
63. Temple, R., "FDA Clinical Guidelines for Geriatric Testing)" presented at the Drug Information Association workshop on Geriatric Drug Use—Clinical and Social Perspectives, Washington, DC, Feb. 28, 1984.
64. Thompson, T. L., Moran, M. G., and Nies, A. S., "Psychotropic Drug Use in the Elderly," N. *Engl. J. Med.* 308:134-138, *194-199, 1983.*
65. Trapnell, G. R., *National Health Insurance Issues: the Cost of a National Prescription Program (New* York: Health Issues, sponsored by Roche Laboratories, 1979).
66. U.S. Congress, General Accounting Office, *FDA Drug Approval—A Lengthy Process That Delays the Availability of Important New Drugs, HRD-80-64,* May 28, 1980.
67. U.S. Congress, Office of Technology Assessment, *Postmarketing Surveillance of Prescription Drugs, OTA-H-189* (Washington, DC: US. Government Printing Office, November 1982).
68. U.S. Congress, Office of Technology Assessment, *The Impact of Randomized Clinical Trials on Health Policy and Medical Practice-A Background Paper, OTA-BP-H-22* (Washington, DC: U.S. Government Printing Office, August 1983).
69. U.S. Department of Health and Human Services, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, *Treatment Research Report: Drug Taking Among the Elderly,* DHHS publication No. (ADM)83-1229, 1982.
70. U.S. Senate, Special Committee on Aging, U.S. House of Representatives, Select Committee on Aging, and the Subcommittee on Health and Long-Term Care, S. Hrg. 98-392, *Drug Use and Misuse: A Growing Concern for Older Americans,* June 28, 1983.
71. Williams, T. F., "Setting the Agenda for Geriatric Drug Research," presented at the Drug Information Association workshop on Geriatric Drug Use—Clinical and Social Perspectives, Washington, DC, Feb. 27, 1984.