In the early 19th century, a quotation was attributed to Oliver Wendell Holmes (father of Justice Holmes): “If all the drugs were thrown into the ocean, it would be all worse for the fishes and all the better for the mankind.” Although we have made significant progress in medical research since then, many more drugs could still be thrown into the ocean.

Polypharmacy is a practice that adversely affects the geriatric population, and physicians need to be aware of its prevalence. Evidence of potentially excessive use of antipsychotic medications in nursing homes, first reported in the 1970s and 1980s, led Congress in 1987 to pass the Omnibus Budget Reconciliation Act (OBRA). There have been many studies addressing the development and prevalence of polypharmacy. Chronic and multiple diseases increase with age, which leads to the use of multiple medications. Currently, the elderly constitute about 12.5% of the U.S. population, but they consume approximately 25% of all prescription drugs administered each year. According to the Agency for Health Care Policy and Research, this figure was 15% in 1987. Even though it is very difficult to measure accurately, it is estimated that older North Americans take an average of 4.5 medications at any given time; this includes both prescribed and non-prescribed medications. The figures released by the Health Care Financing Administration for prescription drug expenditures from 1970 onwards have been staggering. Historical estimates over the past three decades and for 2001 are shown in Figure 1.

Often, the frequencies of adverse drug reactions are correlated with the age of the patient. Recent observations have shown that age is not the major determinant of adverse drug effects; instead, it is the number of drugs administered that is directly related to the risk of adverse drug-related events.

Webster’s dictionary defines polypharmacy as “the practice of administering many different medicines concurrently for the same disease.” The World Health Organization (WHO), a consortium of 350 national organizations and 250 state health, mental health, substance abuse, and environmental agencies, released what is known as the “Healthy People 2010” document, which is the prevention agenda for the U.S. and the world. The Healthy People 2010 document defined polypharmacy as “the taking of multiple prescriptions and over the counter drugs that may have adverse interactions.” In the Netherlands, polypharmacy is defined as the long-term (more than 240 days in a year) simultaneous use of two or more drugs. They further subdivide polypharmacy into “major” and “minor” classes: minor if two to four drugs are used, and major when five or more drugs are used.

In the U.S., polypharmacy has been defined variously by different authors as the simultaneous use of two to more than 10 drugs. One definition of polypharmacy is based on the effects and clinical indications of a given drug regimen, irrespective of the number of drugs used; in other words, it is the inappropriate use of a medication. For example, a patient with diabetes mellitus, hypertension, coronary artery disease, and hyperlipidemia can be safely treated with an angiotensin-converting enzyme (ACE) inhibitor, aspirin, a beta-blocker, a lipid-lowering agent, and insulin. Although this patient is taking five different medications, this is not considered polypharmacy because the drugs are well accepted for the treatment of the above illnesses and they are associated with improved survival.

When the same patient is also given vitamin C, an iron supplement, and calcium supplements without known indications, that is considered polypharmacy.

Epidemiology

Every year over nine million adverse drug events (ADEs) occur in older Americans. The undesired side effects are seven times more common in older patients than in younger adults. Another concern is that nearly one-fourth of all nursing home

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admissions result from the inability of older adults to take their medications properly.

One study found that 50% of the elderly who were using three or more drugs eventually received additional treatment in the following two years, supporting the evidence of increasing polypharmacy over time. Another recent study showed that polypharmacy develops primarily in elderly patients who already use several medications or who are known to have cardiovascular diseases, diabetes, or stomach symptoms. The categories of drugs most frequently prescribed for both hospitalized and non-hospitalized elderly patients are cardiovascular and diuretic agents; 30% of all deaths in the U.S. are caused by heart disease.

PHARMACOLOGY OF AGING

Pharmacokinetic Changes In the Elderly

As a person ages, there are certain changes in the body that occur and alter the effects of medications:

**Absorption:** This is affected minimally. The rate of absorption becomes slightly slow, leading to a delayed time of onset of action and mildly decreased peak serum concentration. For example, absorption of ketoconazole and ferrous sulphate are decreased because of a reduction in gastric acidity.

**Distribution:** The total body water volume and lean body mass decrease with age, leading to increases in the half-life and serum concentration of water-soluble agents like morphine and alcohol. Total body fat increases with age from 18% in young males to 33% in elderly males, and from 33% in young females to 45% in elderly females, leading to an increase in the half-life of lipotropic drugs like diazepam.

**Hepatic metabolism:** Blood flow to the liver decreases with age, and oxidative metabolism through the cytochrome P-450 system also slows down; hence drugs like warfarin, diazepam, naproxen, and phenytoin have an increased half-life in the elderly population. Rates of acetylation and conjugation do not decline with age. Because metabolic activity of the liver decreases, pro-drugs like morphine and levodopa are less effective.

**Renal excretion:** The glomerular filtration rate (GFR), which can be easily calculated by using the Cockcroft and Gault formula (Figure 2), declines with age; hence, drugs like insulin, digoxin, and gentamicin, which are excreted by the kidney, have a longer half-life.

Pharmacodynamic Changes In the Elderly

Pharmacodynamic changes are caused by changes seen at the various receptor levels. For example, the total number of beta-receptors decreases; hence, the response to beta-blockers and beta-agonist medications is blunted in the elderly.

In short, when prescribing medications for the elderly, physicians should always remember to “start low and go slow,” observe for toxicity, and use as few agents as possible. The effect of aging on various drug actions is presented in Table 1, which shows how drugs that are commonly prescribed for the elderly are described with their normal action and change in the effect as a result of pharmacokinetic and pharmacodynamic changes with age.

ADEs and Drug Interactions

Patient compliance is dependent on many factors: the cost of medicine, the adverse effects of medicine, remembering to take one’s medications, and the complexity of the schedule of administration of the drugs. It has been shown that, in general, an increased number of drugs per day leads to a decrease in patient compliance. The major ADEs that result from polypharmacy are listed in Table 2.

ADEs are a major concern for physicians treating the elderly, because there are some drugs that can exert ADEs in

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**Table 1 | Effects Of Aging On Drug Actions**

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
<th>Effect</th>
<th>Effect in the Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates</td>
<td>Morphine</td>
<td>Analgesic effect</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Pentazocine</td>
<td>Analgesic effect</td>
<td>High</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Warfarin</td>
<td>Prothrombin time</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
<td>Activated partial thromboplastin time</td>
<td>No Change</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Albuterol</td>
<td>Bronchodilation</td>
<td>Low</td>
</tr>
<tr>
<td>Cardiac agents</td>
<td>Diltiazem</td>
<td>Antihypertensive effect</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td>Antihypertensive effect</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>Antihypertensive effect</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>Antihypertensive effect</td>
<td>High</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Bumetamide</td>
<td>Chronotropic effect</td>
<td>Low</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Bumetamide</td>
<td>Urine flow and sodium excretion</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>Urine flow</td>
<td>Low</td>
</tr>
<tr>
<td>Hypoglycemic agents</td>
<td>Tolbutamide</td>
<td>Acute hypoglycemic effect</td>
<td>Low</td>
</tr>
<tr>
<td>Psychoactive agents</td>
<td>Diazepam</td>
<td>Sedation</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Midazolam</td>
<td>Sedation</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Temazepam</td>
<td>Sedation</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>Acute Sedation</td>
<td>Low</td>
</tr>
</tbody>
</table>

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**Cockcroft and Gault formula:** Creatine clearance = \((140 - \text{Age}) \times \text{Weight in kg} / 72 \times \text{Serum creatine} \)

Multiply by 0.85 for women

Figure 2. Calculating GFR
elderly patients even when drug levels are normal. For example,
digoxin can cause arrhythmia at the normal therapeutic drug
level. Some medications can also cause dementia (e.g., psy-
chotropics, indomethacin, methyldopa, insulin).16 Some ADEs
mimic geriatric syndromes; falls, for example, can be caused by
the administration of benzodiazepines, antidepressants, and
neuroleptics. Urinary incontinence caused by diuretics and
dedatives is also common. Constipation can also be attributed to
various drugs like iron supplements and calcium channel block-
ers. Another aspect of the condition is that once an adverse
effect is identified, the patient is given another agent to treat it,
eventually worsening polypharmacy.2

Drug interactions can be divided into drug–drug and
drug–herb interactions. When multiple drug therapies are pre-
scribed, it becomes an important consideration for patients and
physicians. There are a number of examples of drugs that were
removed from the North American market because of cardiotox-
ic interactions:17 terfenadine, when given with ketoconazole or
grapefruit juice, was found to cause prolongation of the QT inter-
val and torsades de pointes arrhythmia;17,18 cisapride was taken
off the market because of its arrhythmogenicity; cervivastatin was
implicated for causing rhabdomyolysis and death in 31 patients
when given alone or in combination with gemfibrozil; troglita-
one and trovafloxacin have been withdrawn because of their
lethal hepatotoxicity. Phenylpropanolamine (PPA) which was
commonly used as one of the important ingredients in various
cold preparations, was recently withdrawn because of an
increased incidence of stroke.

**Table 2 Disadvantages Of Polypharmacy**

| 1. Decreased patient compliance |
| 2. Increased incidence of adverse drug effects |
| 3. Increased incidence of depression (e.g., beta-blockers) |
| 4. Diminished cognition in combination with CNS depressants |
| 5. Worsening of urinary incontinence |
| 6. Increased incidence of falls |
| 7. Difficulty in maintaining drug levels |
| 8. Increased risk for prescribing errors |
| 9. Increased dispensing time for caregivers |
| 10. Increased total medical expenses |
| 11. Increased incidence of nursing home placements and hospitalization |

ADEs, and drug interactions. Based on the data given, it is clear
that even though herbal and nutrient agents appear to be very
safe, they can cause side effects.

Complementary and alternative medicine consists of herbal
therapies, acupuncture, chiropractic treatment, massage, and
other non-conventional therapies. Sales of dietary supplements
have grown from $8.8 billion in 1994 to $15.7 billion in the year
2000.20 These types of therapies have steadily increased since the
1950s, and they are expected to increase even further as insur-
ance coverage for these treatments expands in the future. These
therapies, at least in part, are being used to prevent illness and to
maintain robust health. According to one study, 67.6% of Ameri-
cans have used complementary or alternative medicine therapy at
least one time in their lives.21 Even though the Dietary Supple-
ment Health and Education Act of 1994 states that herbal reme-
dies are “dietary supplements” and are not required to undergo
pre-market testing for safety and efficacy, they are known to
cause adverse effects and drug–drug interactions. A simple exam-
ple is grapefruit juice, which inhibits CYP3A4 isoenzyme in liver
and gut wall, and so it might increase plasma levels of calcium
channel blockers and lead to hypotension.

**ADEs are a major concern for physicians treating
the elderly, because there are some drugs that
can exert ADEs in elderly patients even when
drug levels are normal.**

Chan Su, also known as Secretio bufonis, is used in traditional
Chinese medicine as an anti-inflammatory, analgesic and card-
diotonic agent; however it should be avoided in pregnancy and
should never be used on the eyes. Chan Su also causes displac-
ment of digoxin from protein binding sites in vitro. Danshen is
another traditional Chinese medication. It is used for the treat-
ment of joint pain, angina, furuncles, and menorrhagia. When
used with warfarin, it causes prolongation of prothrombin time
and prolonged bleeding.

Garlic is used to treat hypertension, hyperlipidemia, bronchi-
tis, inflammatory respiratory conditions, and gastrointestinal ail-
ments. When garlic is taken with anticoagulants, however, the
risk of bleeding increases because of platelet function inhibition.

Ginkgo, short for Ginkgo biloba, is used mainly in the
treatment of Alzheimer’s disease, impaired memory, vertigo,
tinnitus, and intermittent claudication. An adverse effect of
Ginko use is bleeding, so caution must be taken when using
Ginkgo with anticoagulants.

Ginseng is known to enhance energy and reduce stress. It is
also used for anxiety, cachexia, loss of appetite, impotency,
and insomnia. Ginseng contains germanium, however, which
can cause nephrotoxicity and might cause resistance to loop
diuretics. It interacts with warfarin; coadministration reduces
the effect of warfarin. Ginseng also interacts with an MAO
inhibitor (phenelzine), causing headache, tremors, and mania.
Licorice is used to treat bronchitis, cough, gastritis, constipation, and epilepsy. However, licorice can cause hypokalemia, fluid retention, and hypertension. Furthermore, coadministration with corticosteroids aggravates their combined ADEs. Women show greater sensitivity to its effects than men do.

St. John’s Wort (SJW) is commonly used for the treatment of depression. It is also ingested for the treatment of conditions such as bronchitis, asthma, gastritis, gall bladder disease, gout, and rheumatoid arthritis. SJW activates hepatic cytochrome P-450 enzyme, thereby reducing the plasma concentrations of simultaneously administered expensive drugs like protease inhibitors and cyclosporine. It thus results in increased treatment costs. SJW decreases prothrombin time when used with warfarin; it might also cause a decrease in theophylline levels. When given with any of the SSRI antidepressants, it can lead to the sometimes fatal “serotonin syndrome.” Agitation, hyperthermia, diaphoresis, tachycardia, and neuromuscular disturbances, including rigidity, characterize this syndrome, which occurs as a result of dangerously high levels of serotonin in the brain.

The increased number of drug prescriptions can lead to prescription errors and the inappropriate dispensing of drugs. It has been shown that removing one pill from a drug regimen reduces one minute of dispensing time for the caregiver—time that can be utilized in other medical activities. Polypharmacy also contributes to an increase in total medical expenses. Therefore, it should be recognized early and all efforts should be made to reverse it.

Management

The most devastating effects of polypharmacy are seen in the elderly; frequently, they are found to be iatrogenic. Some factors that are responsible for inappropriate medication use in the elderly are given in Table 4. As we age, the number of chronic conditions increases and we continue to consume more and more medications. Use of OTC medications and nutrients and alternative drug consumption also increase. Patients’ histories of smoking, alcoholism, and illicit drug use should also be taken into account and patients should be properly educated about the dangers of these habits, which are aggravating factors for almost all illnesses (e.g., use of alcohol in a hypertensive patient leads to uncontrolled hypertension). In situations where multiple physicians manage one patient, there is usually a greater risk of polypharmacy and non-compliance.

One aspect of the problem is inappropriate prescription writing without proper periodic review of the patient’s medications. Table 5 describes guidelines for the appropriate prescription of drugs. When prescribing, special attention should be paid to keeping the regimen as simple as possible. Physicians should aim for a once-a-day regimen, because this helps patients remember their daily drug schedule, which results in greater compliance. The adverse effects of medications should always be kept in mind and patients should be informed about the possible ADEs. The cost of drugs should always be taken into account, and patients should be made aware of this.

With the rapidly rising costs of operating medical facilities, especially skilled nursing homes, economics has become a

<table>
<thead>
<tr>
<th>Herb</th>
<th>Action</th>
<th>Adverse effect</th>
<th>Drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan Su</td>
<td>Anti-inflammatory</td>
<td>Eye irritation</td>
<td>Increases unbound digoxin</td>
</tr>
<tr>
<td></td>
<td>Analgesic</td>
<td>Teratogenesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiotonic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danshen</td>
<td>Analgesic</td>
<td>Increased INR when used</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tx of menorrhagia,</td>
<td>with coumadin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>post-partum bleeding,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>angina and furunculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic</td>
<td>Anti-hypertensive</td>
<td>Increased risk of bleeding</td>
<td>Increased risk of bleeding with anticoagulants</td>
</tr>
<tr>
<td></td>
<td>Hypolipidemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tx of bronchitis and gastritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Tx of memory loss,</td>
<td>Increased bleeding</td>
<td>Increased INR with warfarin</td>
</tr>
<tr>
<td></td>
<td>Alzheimer’s disease, vertigo, tinnitus, and intermittent claudication</td>
<td></td>
<td>Hypertension with thiazide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits efficacy of insulin</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Stress reducer</td>
<td>Nephrotoxicity</td>
<td>Causes resistance to loop diuretics</td>
</tr>
<tr>
<td></td>
<td>Tx of anxiety, insomnia, impotence, loss of appetite</td>
<td></td>
<td>Reduces effect of warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Causes headache, tremors with MAO inhibitors</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Tx of bronchitis, cough, gastritis, constipation</td>
<td></td>
<td>Increases plasma level of calcium channel blockers</td>
</tr>
<tr>
<td>Licorice</td>
<td></td>
<td>Hypokalemia</td>
<td>Potentiates effect of corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Anti-inflammatory agent</td>
<td>Decreases protease inhibitor activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tx of depression, anxiety</td>
<td>Decreases cyclosporin and theophylline levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases prothrombin time with warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Causes serotonin syndrome with SSRIs</td>
<td></td>
</tr>
</tbody>
</table>

Tx=Treatment; MAO=Monoamine oxidase; SSRI=Selective Serotonin Reuptake Inhibitor; INR=International Normalization Ratio

Table 3: Interactions Between Common Herbs and Pharmacological Agents
critical issue. The Monsignor Fitzpatrick Skilled Nursing Pavilion, a 115-bed unit in New York, has been running quite efficiently by paying close attention to the issue of polypharmacy. Medications are reviewed upon admission of new residents, and they are reviewed each month on a regular basis. Any resident who takes nine or more medications is carefully monitored. The institutional formulary is adhered to as much as possible without compromising medical care. Cost savings are achieved by using generic medications whenever possible, instead of using brand medications that have been recently introduced into the market, and which are generally untested in the frail elderly. With the implementation of the above principles, during the past two quarters from April to June 2001 and from July to September 2001, the aforementioned nursing home has been able to decrease the average drug utilization from 7.46 to 7.38 drugs per resident, and the use of antipsychotics has decreased from 20.7% to 18.0%.

Because of changes in the body chemistry of elderly patients, some drugs stay active for a longer duration, and their chances of causing toxicity are high. Bearing that in mind, drugs with a wide therapeutic index should be used to minimize toxicity. Particular attention should be given to the continued indication for the use of any drug prescribed. For example, consider a female patient with gastritis who is started on famotidine. If, after one year, she continues to be on the same medication with no existing symptoms of gastritis, then the drug dosage should be reduced, tapered, or stopped as recommended by her physician. All alternative agents should be registered and followed for the length of time that they are used; their ADEs and therapeutic effects should also be monitored.

The use of medications to prevent certain illnesses is not only medico-legally important, it is good medical practice. One example is warfarin, which is prescribed for patients with atrial fibrillation to reduce the risk of possible future cerebrovascular accidents. Its use should be limited to those elderly individuals who are functional, who do not have a gait imbalance, who understand the changing dosing schedule of the drug, and who are ready for monthly blood testing for measurement of international normalizing ratio (INR). Medications like iron supplements should also be administered judiciously, because they might aggravate constipation.

It has been said that “prevention is better than cure.” The early recognition of and timely intervention in reducing the number of drugs used is an important step in decreasing the incidence of polypharmacy. The use of both prescription and non-prescription drugs should be based on specific clinical indications. If a single drug can be used to treat more than one disease, that drug should be preferred. For example, a patient with a history of migraine headache, hypertension, and hyperthyroidism could be treated with beta-blockers.

CONCLUSION
Physicians, nurse practitioners, physician assistants, and other health care providers need to be cognizant of the age-related physiologic changes that are commonly encountered, especially in the frail elderly. To increase awareness in the medical community and among senior citizens, it is both advisable and sensible to continue to hold meetings like the one that resulted in the well-known “Healthy People 2010” document.

With all of the rapid advances in the field of medicine, we have been inundated with newer and more potent medications. This has further complicated the problem of polypharmacy that the medical community first recognized in the early 1970s. Both the cost and the number of medicines in use have steadily increased resulting in a corresponding increase in ADEs. ADEs cannot be completely eliminated, but we can certainly minimize them if we are vigilant.

REFERENCES

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