Securing the Benefits of Medical Innovation for Seniors: The Role of Prescription Drugs and Drug Coverage

U.S. Department of Health and Human Services
Office of the Assistant Secretary for Planning and Evaluation
July, 2002

EXECUTIVE SUMMARY

Americans are living longer and healthier lives. By the year 2030, the number of Americans over the age of 65 is projected to double to 70 million. The life expectancy of the average American is increasing, and the rates of mortality, morbidity, and disability among Americans over age 65 have steadily decreased. In the past, aging has been associated with the development of chronic medical conditions, such as cancer, arthritis, diabetes, and heart disease, which limit participation in daily activities and reduce the quality of life. However, recent advances in the prevention and treatment of chronic diseases have radically altered the quality of life for older Americans.

Innovations in medical science, especially pharmaceuticals, have shifted the focus of medicine from highly invasive treatments and surgeries with potentially serious risks to less-invasive therapies focused on prevention and health maintenance. This shift has allowed many older Americans to remain healthy and independent, avoiding long hospital or nursing home stays. As a result, the Baby Boom and subsequent generations of seniors will likely live longer, healthier, and more productive lives.

The future of medical innovations appears to be even more promising. Many scientists believe that we are on the verge of another round of significant breakthroughs in medical research and development due to the recent mapping of the human genome. The rapidly evolving field of genetic medicine will provide researchers with many new targets for future drug development, as well as provide doctors with information about how to more effectively treat chronic medical conditions. In fact, as a result of pharmacogenomics, physicians may be able to select drugs that are ideally suited for individual patients based on their genetic makeup.

However, the development of valuable new treatments is often costly and time consuming. Consequently, continued investment in research and development is critical to ensure that new treatments are available to enrich the lives of tomorrow's seniors. Both public and private sector efforts are required to maintain a full 'pipeline' of medical innovations.

The United States plays a vital role in the global development of new pharmaceutical treatments, leading the world in spending for research and development of new drugs and biologics and in the introduction and sale of major innovative new drug products. The U.S. leadership in medical innovation and in the availability of valuable new treatments is directly related to the U.S. reliance on competitive approaches in health insurance coverage to encourage medical innovations and reduce costs. For non-elderly Americans, private health insurance plans in the United States use competitive tools like volume purchasing and disease management programs to reduce drug costs. In contrast, many countries rely on direct government controls to keep costs down. These countries seek to reduce drug spending by using the government's authority to delay or deny regulatory approvals or insurance coverage for new medicines, or to restrict coverage significantly for approved drugs (see appendix). These countries can do so because, in contrast to the United States, most health care is delivered through health insurance plans where the government can restrict coverage and availability of therapies.

For example, patients in some countries face restrictions on access to newer drugs (bisphosphonates) that are more effective and have fewer side effects compared to alternatives

(e.g., hormone replacement therapies) in treating older women and others at risk of osteoporosis. Osteoporosis is associated with a significant risk of serious fractures, including hip fractures. In some countries, individuals must have conclusive evidence of low bone density, the hallmark of osteoporosis, or must actually have experienced an osteoporotic fracture before reimbursement for these newer agents is permitted.

As another example, several countries deny reimbursement for a new treatment of asthma—Singulair® (montelukast). This treatment provides for good control of asthma, reducing the need for steroid therapy. Although steroids are a standard treatment for asthma, they may induce significant side effects in individuals who require their long-term use.

This report demonstrates the potentially serious consequences to medical innovation and overall health posed by attempts to contain drug expenditures by implementing government controls that are inevitably arbitrary and out of touch with the diversity of patient needs and circumstances. If applied broadly in the United States, government-controlled restrictions on the coverage of new drugs could put the future of medical innovation at risk and may retard advances in treatment and in the development and introduction of new products. Moreover, government controls may reduce or delay access to specific drugs for seniors. Even when a drug is available, government controls often increase the likelihood that older, lower cost products will be prescribed rather than newer, more innovative products, which may have fewer side effects or other features that improve patient compliance and hence, the effectiveness of medical treatment.

In contrast to many other countries, the U.S. market is relatively free of government-controlled programs to contain medical costs. Although participation in many federal and state buying programs may require certain types of controls—such as rebates and coverage limits—these programs represent only a small fraction of the market.

To ensure continued progress in the fight to treat and prevent diseases, especially the chronic illnesses of older age for which we may be on the verge of unprecedented breakthroughs, the American health care system should not resort to government controlled drug coverage decisions. Other steps can and should be taken to reduce the costs of drugs, such as investing in biomedical research on less costly and more effective treatments, protecting the intellectual property rights of American companies worldwide, improving the efficiency of the regulatory process for new treatments, and increasing the availability and effectiveness of competitive approaches to limit the cost of new treatments. These steps will help keep drugs available and affordable without reducing access to valuable new treatments and discouraging innovation just at the time when the potential for innovation is greatest.

INTRODUCTION

Americans are living longer and healthier lives.

- By the year 2030, the percentage of Americans over the age of 65 will grow dramatically, doubling in number to 70 million (almost 20% of the U.S. population).

- Since 1900, the life expectancy of the average American has increased 29 years. (CDC 2002)

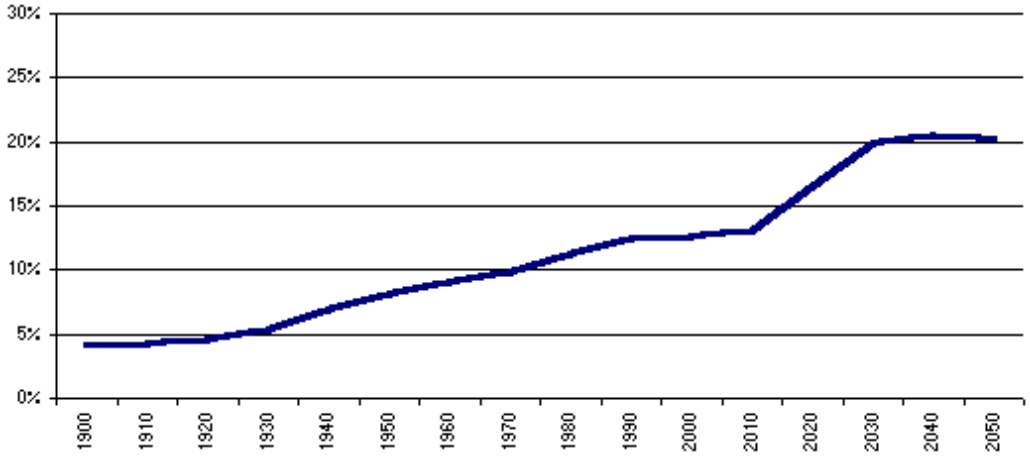
- Over the past century, and especially in the 1980s and 1990s, the rates of mortality, morbidity, and disability among Americans over age 65 have steadily decreased. (CDC 2001; Freedman 2002)

- A recent report by the Centers for Disease Control and Prevention (CDC) notes that between 1979-81 and 1995-97, death rates declined six percent in women and 19 percent in men ages 65 to 74, and eight percent in women and 16 percent in men ages 75 to 84.

- The world's population is aging, too. In the next 50 years, the median age of the world's population will increase 10 years. (United Nations 2002)

- Many of the gains in longevity and quality of life are directly related to advances in medical science and technology, including pharmaceuticals. One new study found that half the drugs prescribed or administered in office visits in 1999 were not prescribed or administered at all in 1985. (Burt 2002)

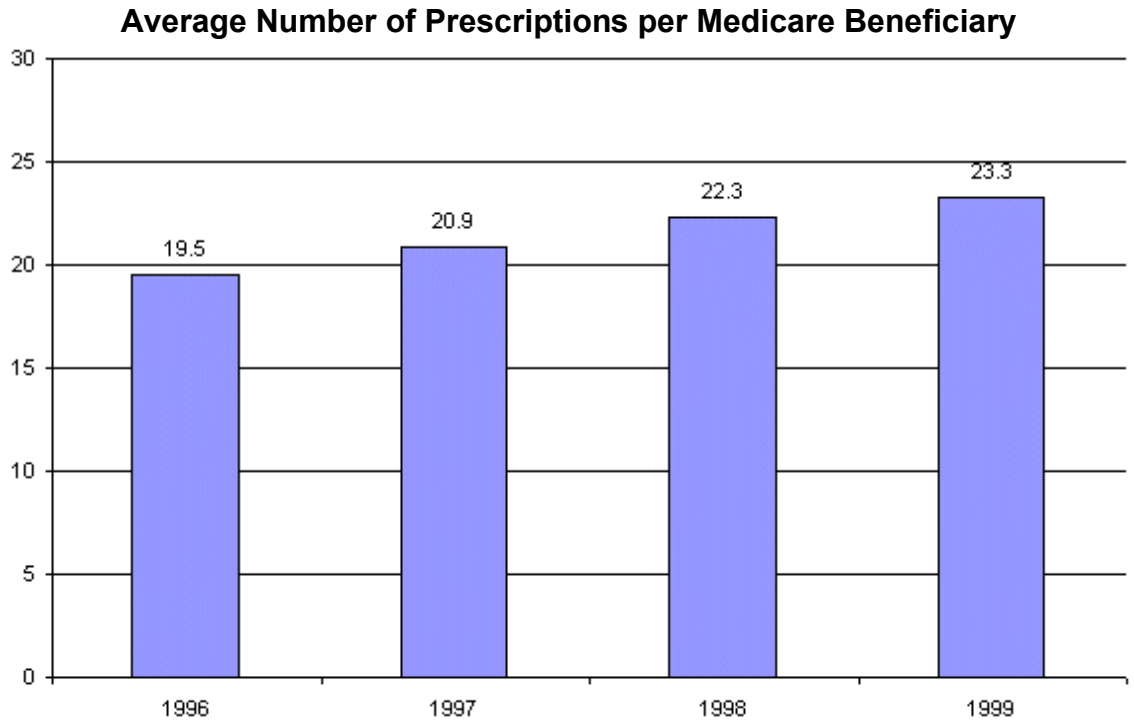
Percentage of the U.S. Population Age 65 and Older, 1900 to 2050



Note: These data refer to the resident population. Data for the years 2000 to 2050 are middle-series projections of the population.
Source: U.S. Census Bureau, Decennial Census Data and Population Projections

In the past, aging has been associated with the development of chronic medical conditions, such as cancer, arthritis, diabetes, and heart disease, which limit participation in daily activities and reduce the quality of life. However, recent advances in the prevention and treatment of chronic diseases have radically altered the quality of life for older Americans. As a result, the Baby Boom and subsequent generations of seniors will likely live longer, healthier, and more productive lives.

The CDC cites decreases in deaths from cardiovascular disease, atherosclerosis, cancer, and hypertension as key contributors to the overall decline in mortality. (CDC, NCHS March 2001) Other studies have found that the levels of physical and cognitive disability among older Americans declined during the 1990s, suggesting that seniors are healthier, and more productive and independent than they were just a decade ago. (Federal Interagency Forum on Aging-Related Statistics 2002; Freedman 2002, 2000, 1998)



Note: The MCBS is believed to under-report the number of prescriptions received by Medicare beneficiaries.
Source: 1999 Medicare Current Beneficiary Survey (MCBS), non-institutionalized population only.

Medical innovations are critical to seniors' quality of life.

Health experts point to advances in disease treatment and prevention as key factors in improving the health of older Americans.

- In recent years, new drugs, medical procedures, screening tools, and prevention strategies have improved the treatment of chronic diseases, which affect 80 percent of all seniors. (CDC, NCCDPHP 1999)

- Prescription drug use has dramatically increased in seniors, indicating that many are taking advantage of new medicines to improve their health and quality of life.

Over the past century, medical innovations, including new drugs, have altered not only the health status of Americans, but also the basic pattern of life in America and around the world:

- Antibiotics and vaccines have drastically reduced the burden of infectious disease in America.

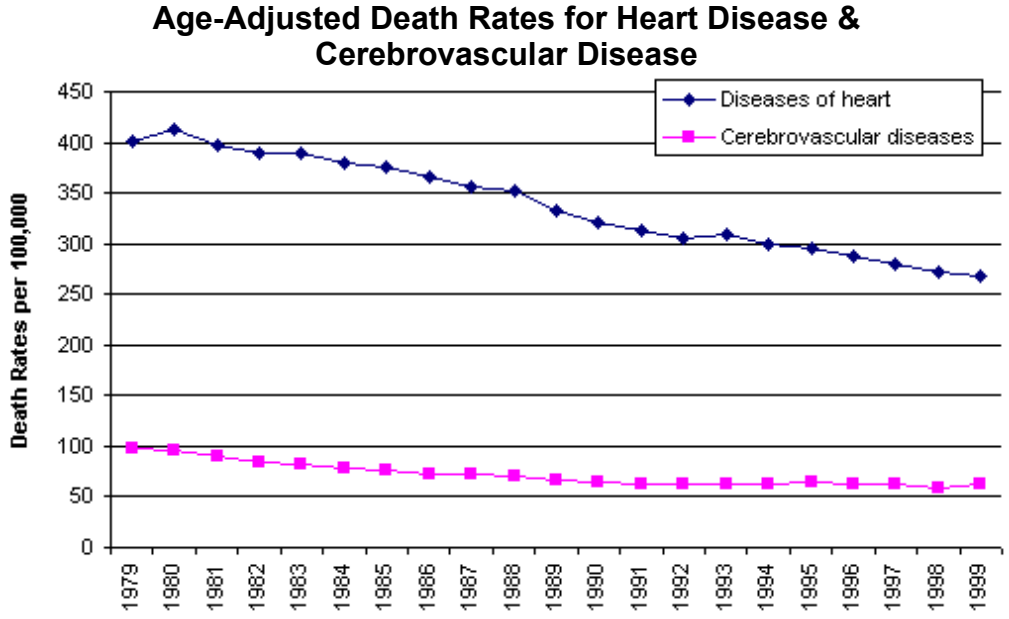
- Readily available insulin transformed type 1 diabetes from a childhood death sentence to a chronic but manageable disease.

- Gastric acid reducing agents, such as H2 blockers, revolutionized the treatment of gastric ulcers by eliminating the need for surgery.

- Effective, tolerable psychiatric medications have made it possible for millions of Americans to lead normal lives, free from the extreme suffering caused by mental illness.

- New technologies (such as coronary angioplasty, pacemakers, and cardiac stents) have enhanced quality of life among those suffering with chronic heart disease.

Often, the benefits from development of new drugs and technologies are additive. For example, a host of medical advances have combined to yield a 35 percent reduction in mortality from coronary heart disease and a 36 percent reduction in mortality from stroke since 1980. (See Chart 3)



Source: Vital Statistics Data, NCHS

In addition to providing cures and preventing more severe and costly effects of diseases, innovations in treatment and medical science, especially pharmaceuticals, have shifted the focus of medicine from highly invasive treatments and surgeries with potentially serious risks to less-invasive practices and therapies focused on prevention and health maintenance. This shift has allowed many older Americans to remain healthy and independent, avoiding long hospital or nursing home stays.

The future of medical innovation looks promising.

- The recent mapping of the human genome may usher in a new era of medical therapeutics.

- Future generations of American seniors stand to benefit from continued vigorous medical innovation.

Many scientists believe that we are on the verge of another significant round of breakthroughs in medical research and development due to the recent mapping of the human genome. The deciphering of the human genome has improved our understanding of health and disease. (Bumol 2001) As scientists learn more about the function of different genes and their protein products, we will gain a more sophisticated knowledge of the cellular and molecular mechanisms of specific diseases. At the same time, new biological techniques and tools will enable scientists to explore both normal and abnormal biological systems with high molecular resolution.

As a result, pharmaceutical research will be able to capitalize on this increased appreciation of the cellular and molecular basis for diseases by identifying new genetic or protein targets for drug development. New products will be designed to interact with specific molecular entities involved in the generation of certain diseases. This targeted approach may reduce disabling or complicating side effects, which limit the usefulness of some current treatments. For example, new cancer treatments are being developed that target specific molecular features of cancer cells not found in normal cells. Hence, these agents will attack cancer cells but not healthy cells, thereby reducing some of the debilitating side effects of more standard cancer chemotherapy.

In the future, advances in genetic medicine may permit pharmaceutical therapy based on an individual's unique genetic map. The evolving field of pharmacogenomics will allow physicians to select drugs that are ideally suited for individual patients based on their genetic makeup. (Weinstein 2000) Again, this approach may improve the efficiency and minimize the side effects of disease treatment. Moreover, determining the risk of developing a disease based on the genetic profile of asymptomatic patients may permit early preventive interventions that will delay or prevent the development of diseases.

The United States provides leadership in medical innovation

The United States plays a prominent role in the global development of new pharmaceuticals.

- The U.S. leads the world in spending for research and development of new drugs and biologics. (Gambardella 2001)

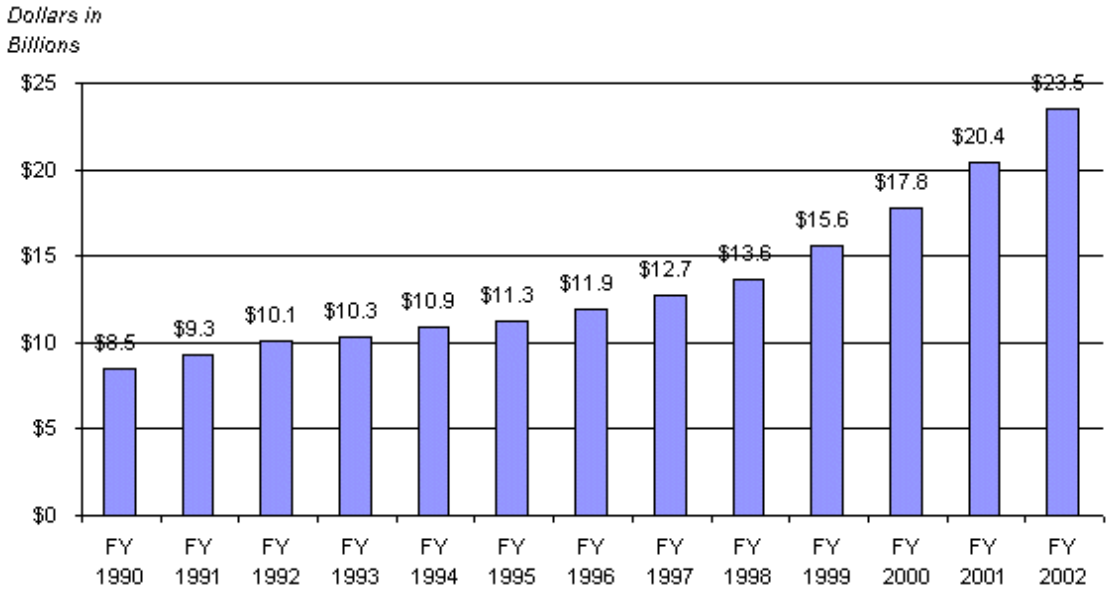
- The National Institutes of Health budget for Fiscal Year 2002 is $23.5 billion.

- Six of the world's top ten pharmaceutical companies are headquartered in the United States. (Gambardella 2001)

- The Food and Drug Administration is recognized worldwide as setting the gold-standard for quality and timely review of new drugs and biologics.

- As a result of investment in research and development, U.S. pharmaceutical companies lead the world in the introduction and sale of major innovative products.

National Institutes of Health Budget



Most of the basic research on new drugs is concentrated in a few areas of the world—namely the United States, Europe, and Japan. (United States International Trade Commission 2000) Clinical trials occur in almost every country. As reported by the United States International Trade Commission (USITC), the U.S. accounted for 45 percent of 152 globally-marketed products developed from 1975 to 1994; followed by the UK at 14 percent; Germany, 7 percent; Japan, 7 percent; and France, 3 percent. Therefore, in the past, the U.S. public and private sectors have shouldered much of the cost for research and development of new products.

Robust investment in research and development by the United States has resulted in U.S. dominance of global sales of new pharmaceuticals. In the 1990's, sales of major innovative products by U.S. multinational pharmaceutical companies increased more significantly than those of their European counterparts. (Gambardella 2001) Specifically, the U.S. share of sales of new chemical entities (drugs whose active ingredients have not been previously approved for therapeutic use) launched during the 1990's approached 70 percent. (Gambardella 2001)

Moreover, in 1999, more than 80% of total sales of the world's top 15 drugs were produced by U.S. companies. (Gambardella 2001)

Future innovations will continue to improve the health and lives of older Americans and revolutionize the treatment of chronic disease. However, since the development of new technologies may take years, continued investment in research and development is critical to ensure that new treatments are available to enrich the lives of tomorrow's seniors. Both public and private sector efforts are required to maintain a full 'pipeline' of medical innovations.

FACTORS INFLUENCING MEDICAL INNOVATION

Multiple factors influence whether new and better treatments for chronic diseases will be available for current and future generations.

- Investment in biomedical research, an efficient regulatory process to assure drug safety and efficacy, patent protection of intellectual property, and fair pricing of new drugs and biologics are important elements to ensure continued medical innovation.

- Government controls may impede medical innovation and new product development and introduction.

Developers must balance the potential value of a new drug versus the cost of bringing it to the marketplace in a certain country.

The Market for Medical Innovation

The U.S. and most other industrialized nations try to create environments that will encourage innovation and research for cures of dreaded diseases. One of the most important ways nations do that is through a system of patents and other intellectual property rights that provide incentives for individuals to perform such research. Patents grant exclusive property rights to the innovator for a limited number of years. Thus, the patent system encourages creativity and investment in innovations. [World Intellectual Property Organization (WIPO) 2002] The period of market exclusivity allows pharmaceutical companies to recapture some of their investment costs. After a patent expires, less expensive generic products can be produced and sold in the marketplace, effectively competing with brand name drugs. Since patents are granted on a territorial basis, inventors (pharmaceutical companies) must apply for a patent in each country or state separately. As a result, not all innovations are patented in every country. Moreover, some countries deem certain products, including drugs, exempt entirely from patent protection. (WIPO 2002)

Patent policy inevitably affects how much money investors will gamble on research and development of new pharmaceuticals. Moreover, patent policy potentially influences the categories or types of diseases for which pharmacological treatments are sought. Pharmaceutical companies will be more apt to develop treatments for diseases that have a relatively high prevalence in the population. (WIPO 2002)

The tenure of a patent will affect the ability of a pharmaceutical company to recoup its investment and finance development of new products. In the United States the term of patent protection is 20 years. However, the effective patent term—the time remaining after a product has gained market approval—for a specific product may be less, depending on the time it takes to bring that product to the market. Other countries may have different patent terms, which may further limit the period of effective market exclusivity. (USITC 2000) Over the last two decades, the duration of patent exclusivity among different countries has been converging, although some differences remain. Patent restoration laws have restored some of the erosion in the period of exclusivity.

At the same time, for diseases with relatively low prevalence in the population, other governmental policies can provide the necessary incentives for drug research and development where the market may not. The U.S. Orphan Drug Act of 1983, for example, has been successful at stimulating research and development on rare diseases by awarding market exclusivity to the developer of the first drug for a condition unless subsequent drugs are clinically superior. (Kremer 2000)

Access to Medical Innovation

Before a new drug can be marketed, it must pass rigorous regulatory scrutiny. The purpose of the regulatory process is, correctly, to ensure that marketed drugs are safe and efficacious for patients. Most countries have a governmental body that is charged with approving and regulating new drugs. Regulators in different countries have an impact on the development and testing of drugs, advertising, and, in some cases, the pricing and delivery of products (see below). (USITC 2000) Regulatory requirements can expedite and facilitate or, conversely, prevent or delay a drug's introduction into the marketplace. Delays in marketing will deprive individuals from receiving new drugs, which may impact both longevity and quality of life. Moreover, if a nation's regulatory process is too restrictive, a pharmaceutical company may decide to forgo seeking approval for its drug in that country completely.

Efforts to expedite the drug review process have allowed patients more timely access to new pharmaceuticals. For example, dramatic improvements in efficiency of FDA pre-market review, following the 1992 enactment and reauthorization of the Prescription Drug User Fee Act (PDUFA), have cut review time in half. With a "priority" review process, thousands of cancer patients in the U.S. have had earlier access to new cancer treatments. This in turn has extended many cancer patients' lives, or improved their quality of life. For example, a new biologic for the treatment of breast cancer (Herceptin®/trastuzumab) was approved by the FDA in less than five months. This drug took 18 months to be approved in Europe. An estimated additional 10,000 American women with advanced breast cancer received this new treatment as a result of the timely review process. This added an estimated 2,300 years of life to the population who had access to this new treatment following its market approval in May 1998.

With other new treatments, an expedited review process has helped thousands of patients to avoid significant sickness and hospitalization. For example, a six-month review and approval of a new treatment for osteoporosis (Fosamax®/alendronate sodium) is estimated to have allowed

thousands of women earlier access to this treatment, preventing as many as 3,000 hip and wrist fractures. The accompanying shift in worldwide drug research and development investments toward the U.S. has prompted the European authority to consider emulating the FDA's process, including a "priority" review for important new drugs.

Recently, the European Commission (EC) recognized the deleterious effects of delays brought on by bureaucratic drug restrictions. An EC advisory panel noted that "[t]he [pharmaceutical] price negotiating systems and reimbursement structures in a number of Member States can lead to significant delays. This is not only a problem within those Member States, but it can also result in citizens of one Member State having access to medicines months, or even years, in advance of those in other Member States." (European Commission, 2002) One study of the European drug market found that for 22 breakthrough drugs (new molecular entities, or NMEs), it could take up to four years between the time the drug was first available anywhere in Europe and the time it was available in all the countries studied. The average delay was over two years. (Europe Economics 2000)

Cost containment efforts may reduce or delay access to specific drugs. In contrast to the U.S., where individuals generally may obtain any approved product on the market, in other countries, governmental policy may limit the use of a drug to specified categories of patients or restrict its use entirely. Even when a drug is widely available, government cost-containment programs may result in an increased likelihood that older, lower-cost products will be prescribed rather than newer, more innovative products. (USITC 2000) Although generic alternatives may work just as well and may be cost saving, health care providers rather than government officials should retain the decision-making authority regarding the best treatment option for individual patients.

Many countries attempt to control public expenditures for drugs by allowing the government to influence drug pricing and coverage decisions directly. In fact, the U.S. is the only major industrialized country that does not impose some general form of government controls on insurance coverage of prescription drugs. (Calfee 2000) Approaches used by various countries include direct and indirect price controls, profit controls, reference pricing, physician budget constraints, and copayment programs. (USITC 2000) The governments enforce these controls through their ability to influence which drugs are covered for all or most of their citizens—an authority that the U.S. government has never generally had. Thus, foreign governments have the authority to restrict coverage of certain drugs to limit pharmaceutical expenditures, even when drugs prove cost-effective over other treatment options. (USITC 2000; Lichtenberg 2001; Neumann 2000; Cutler 2001)

The desire of countries to control health spending is certainly understandable. Moreover, levels of U.S. prescription drug spending have unambiguously increased in recent years due to increases in both the number of prescriptions and prices. For most of the U.S. prescription drug market, rising costs have driven employers and insurers to adopt various market-based techniques of cost containment, largely free of government intervention. Techniques such as tiered formularies, step therapy, coinsurance rather than fixed copayments, and generic substitution—with appropriate regulatory mechanisms to ensure patient safety—have kept prescription drug coverage within the reach of most Americans. Most Americans with private insurance, or the employers and others purchasing insurance on their behalf, also have choices

about coverage that are not available in the government-controlled health financing plans of other countries—so that if an insurance plan does not provide appropriate coverage for valuable treatments, individuals in the U.S. can go elsewhere for coverage. Drugs that the FDA has approved as safe and efficacious are widely available for sale when needed. At the same time, changes in U.S. drug purchasing and distribution have stimulated competition and, indirectly, encouraged innovation. (Gambardella 2001) Only 13 percent of the U.S. market is covered by Medicaid or other public programs that use direct government controls to limit costs. (USITC 2000)

Cost-containment approaches implemented by individual countries may have a significant impact on prescription drug innovation, especially in regard to essential research and development expenditures. (USITC 2000) Government controls on drug access and pricing may result in decreased revenues, which reduce monies available for research and development. (USITC 2000). As a result of reduced investment in research and development, innovation may be slowed, delaying the development and introduction of new drugs into the marketplace. Partially as a result of various administered pricing schemes, Europe seriously lags behind the U.S. in drug research, and the gap is widening. In 1990, major European research-based pharmaceutical companies spent 73 percent of their R&D budget in Europe. By 1999, they spent only 59 percent in Europe, moving most of it to the U.S. (Gambardella 2001) One recent report prepared for the European Commission found that:

> "the decline of European competitiveness in pharmaceuticals is linked to the persistence of a fragmented market and, at the same time, to major 'non-market' and bureaucratic failures in public intervention and price regulation... [Governments should] converge on a higher reliance on innovative management methods and on competitive mechanisms, moving away from schemes excessively based on administrative decisions and bureaucratic structures/rules in the regulation of the market." (Gambardella 2001)

Government controls on pharmaceuticals also inhibit research on new uses for current drugs. Fixed prices based on a government-calculated "efficacy" of an existing drug would necessarily fail to capture newly-identified benefits. Such drugs as statins for treating high cholesterol and tissue plasminogen activator for treating stroke found some of their most valuable uses through major clinical trials after the drugs had already been approved for other purposes. (Calfee 2000)

Finally, countries that have relied on centralized approaches to controlling drug costs have generally not adopted U.S.-led innovations in "disease management" and "case management" approaches to reduce drug costs. These programs provide assistance to the many physicians who may be involved in the care of a patient with chronic illnesses or multiple illnesses, to ensure that the patient is receiving the most effective treatments for their conditions. For example, the Evercare program is a specialized health plan for frail elderly patients and others with multiple disabilities. These patients generally reside in nursing homes, or have substantial functional impairments that necessitate nursing home levels of care. Because they usually have multiple chronic illnesses, managing their prescription drug needs effectively can be complex. Often, individual physicians do not even have a complete understanding of all the medications that have been prescribed for their patients by various specialists. The Evercare program has specialized

nurse practitioners who help the many medical professionals involved in the care of a frail elderly patient coordinate that care effectively, and who help the patient and their family gain better control of the patient's health needs. As a result, most patients in the Evercare program take up to eight prescriptions, whereas a typical nursing home resident takes 15 medications. Moreover, the program maintains a 95 percent satisfaction rate with families. Similar disease management programs that have been implemented by private insurance plans in Medicare help patients with diabetes, high blood pressure, heart failure, and other chronic illnesses reduce their medication needs and their medical complications.

EXAMPLES OF MEDICAL INNOVATIONS THAT HAVE IMPROVED THE QUALITY OF LIFE FOR AMERICAN SENIORS

Many seniors suffer from chronic diseases that have the potential to significantly interfere with their independence and well-being. In the past, as a result of these chronic conditions, many seniors became disabled and were forced to limit their activities. Advances in medical science and new pharmaceutical products have significantly improved the quality of life for seniors in this country, enabling many to live longer, more active, and independent lives. Medical conditions in which recent advances in pharmacotherapeutics have had a dramatic impact on the course of disease and, hence, quality of individuals' lives include cancer, osteoporosis, asthma, arthritis, high cholesterol, heart attacks, strokes, depression, Alzheimer's disease, type 2 diabetes, and migraine headaches.

However, due to government controls on access to drugs in other countries, patients who need new therapies often have to wait longer for them or may never have access to them at all. For example, in Western Europe, it took an average of 643 days for the initial approval and subsequent recognition of a drug by all European Commission countries, whereas in the U.S. it took an average of 335 days. (Davidson 2001) In Canada, approval of Rituxan®, a new treatment for non-Hodgkins lymphoma, took two more years after the drug was approved in the U.S. in 1998. (Evenson 2000) Moreover, in Canada, where patients often experience delays in treatment under the government health system, researchers attempting to quantify the cost of this waiting time for cardiac patients have estimated it to amount to $1,100 to $5,600 annually per patient. (Walker and Wilson 2001)

This section highlights recent pharmaceutical breakthroughs in the treatment of chronic diseases that are improving the life and longevity of American seniors, as well as exciting new drugs that are in the research pipeline. In addition, specific examples of reduced access to new drugs in countries with some form of government controls are discussed.

Cancer

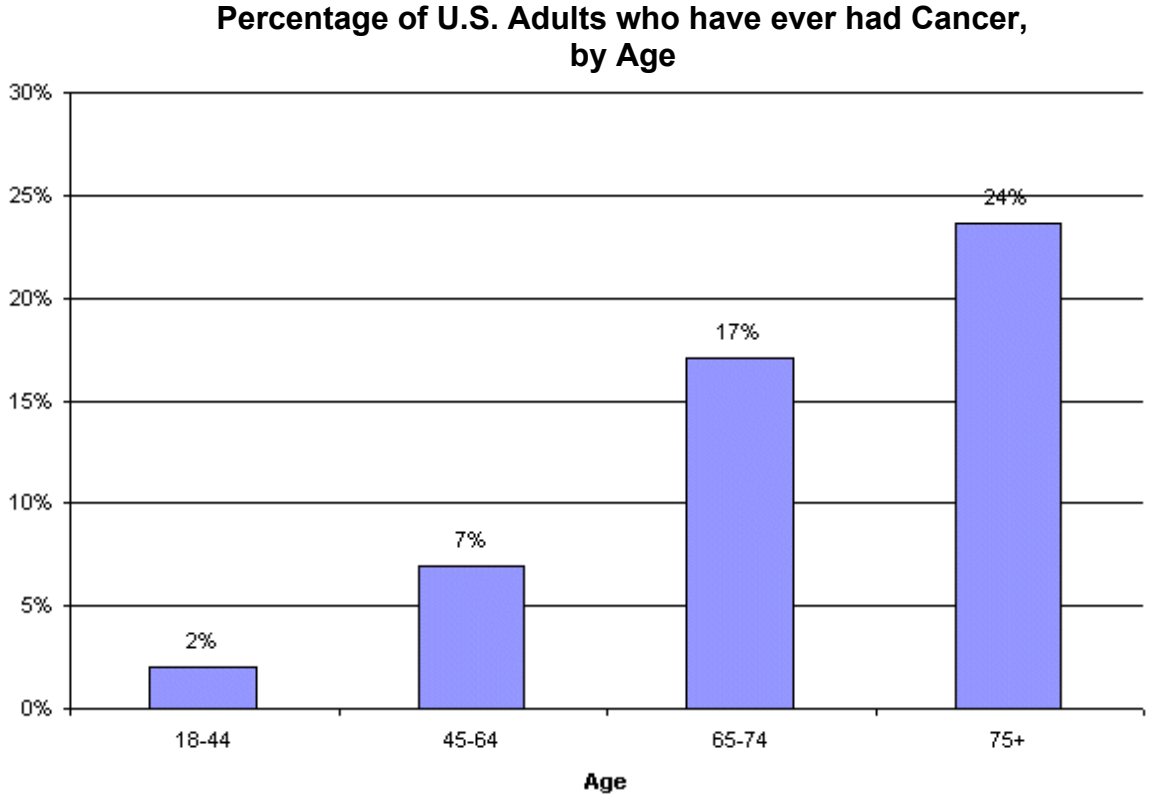
- More than 550,000 Americans will die from cancer this year. (American Cancer Society 2002)

- The National Cancer Institute estimates that approximately 8.9 million Americans alive today have a history of cancer.

- If the current incidence pattern continues, cancer diagnoses will double from 1.3 million people in 2000 to 2.6 million people in 2050. Moreover, during this period, the number of cancer patients aged 85 and older is expected to increase four-fold.

- Cancer is one of the most expensive diseases to treat. In 2001, total costs for cancer were reported to be in excess of $156 billion, with medical expenditures accounting for approximately $56 billion. (American Cancer Society 2002)

- Recent advances in biotechnology have yielded some promising new approaches to cancer treatment.



Source: National Health Interview Survey, 2000

Cancer is the second most common cause of death in the United States. Lung, colorectal, prostate, and breast cancer are the most common types of cancer. Although there has been an overall decline in U.S. cancer death rates, the cancer burden is expected to rise as the population ages. (NIH, National Cancer Institute 2002)

Lifetime Probability of Breast Cancer in Women in the United States

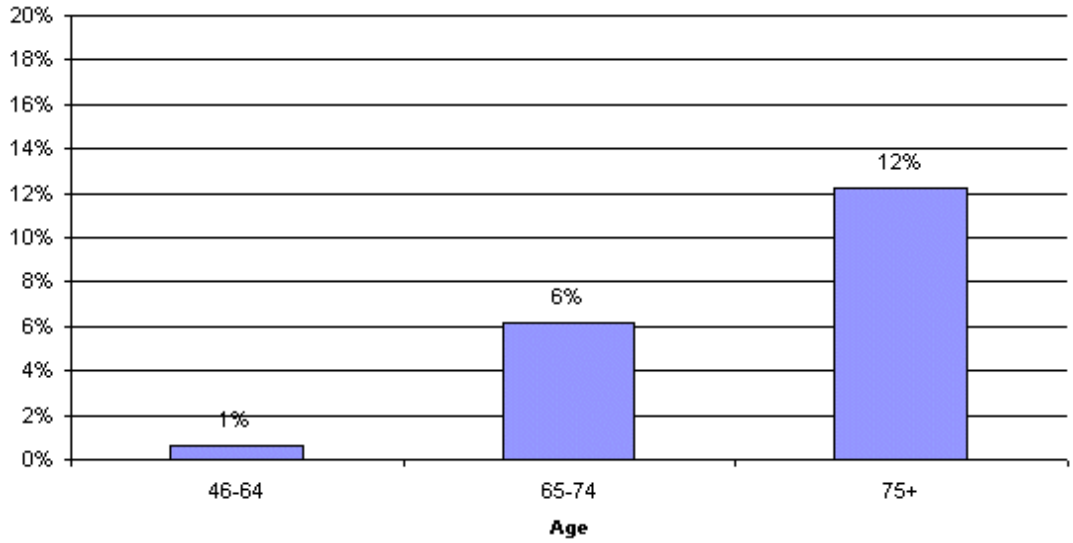
From age 30 to age 40.....1 out of 257
From age 40 to age 50.....1 out of 67
From age 50 to age 60.....1 out of 36
From age 60 to age 70.....1 out of 28
From age 70 to age 80.....1 out of 24
Ever.....1 out of 8

Source: National Cancer Institute Surveillance, Epidemiology, and End Results Program, 1995-1997

Treatment of Cancer

Treatment for cancer depends on the type of cancer; the size, location, and stage of disease; and the person's general health. Drugs and biologics play an important role in the treatment of cancer. Attempts to decipher the human genome have launched an exciting new era in biomedical research with tremendous potential for cancer treatment. New drugs are now being designed to target specific molecular features characteristic of cancer cells, including genetic mutations, epigenetic factors causing changes in gene expression, structural changes in the proteins that are products of mutated genes, and derangements in signal transduction pathways. In essence, any specific difference in the molecular composition of tumor cells can become the basis for "targeted" therapy. In the future, the treatment for each patient's cancer will be individualized based on the unique repertoire of molecular targets expressed by their particular tumor.

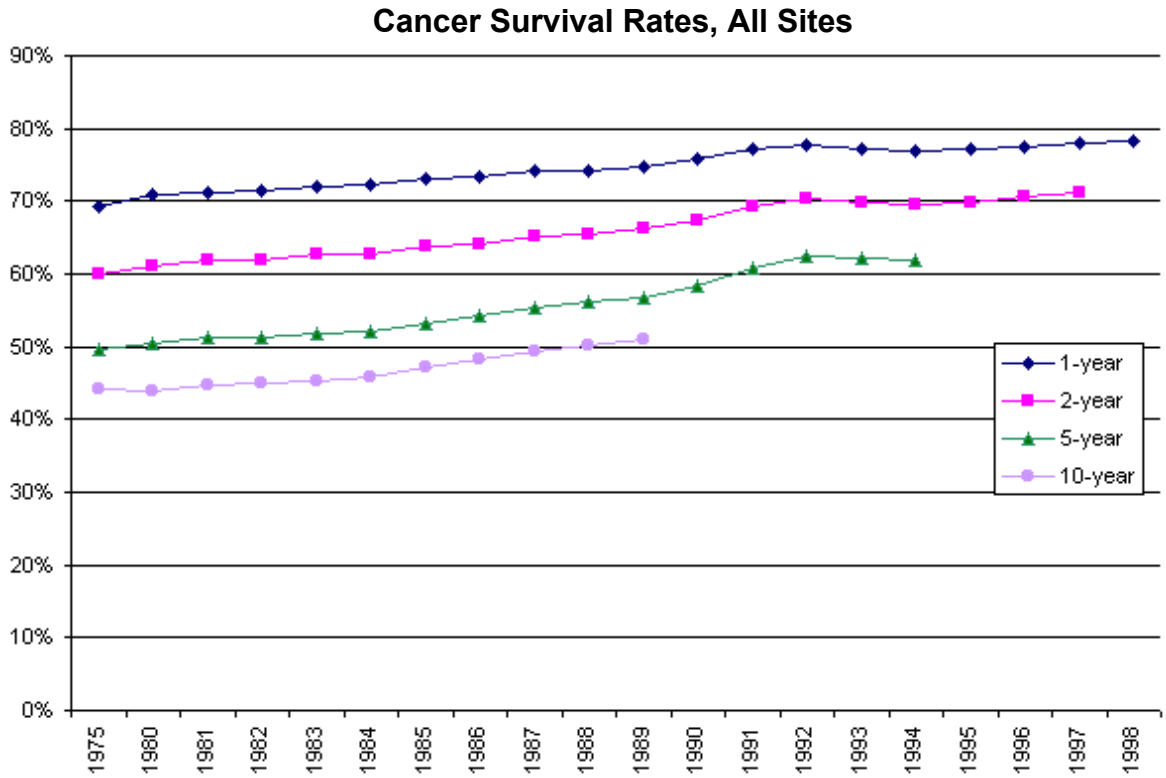
Percentage of U.S. Males who have Ever had Prostate Cancer, by Age



Source: National Health Interview Survey, 2000

Conventional anticancer drugs have tended to be non-selective, attacking both cancerous and healthy cells. Consequently, cancer chemotherapy is often accompanied by a variety of devastating short- or long-term side effects. Moreover, individual patient responses to conventional agents are highly variable, even in cases where specific cancers appear to be

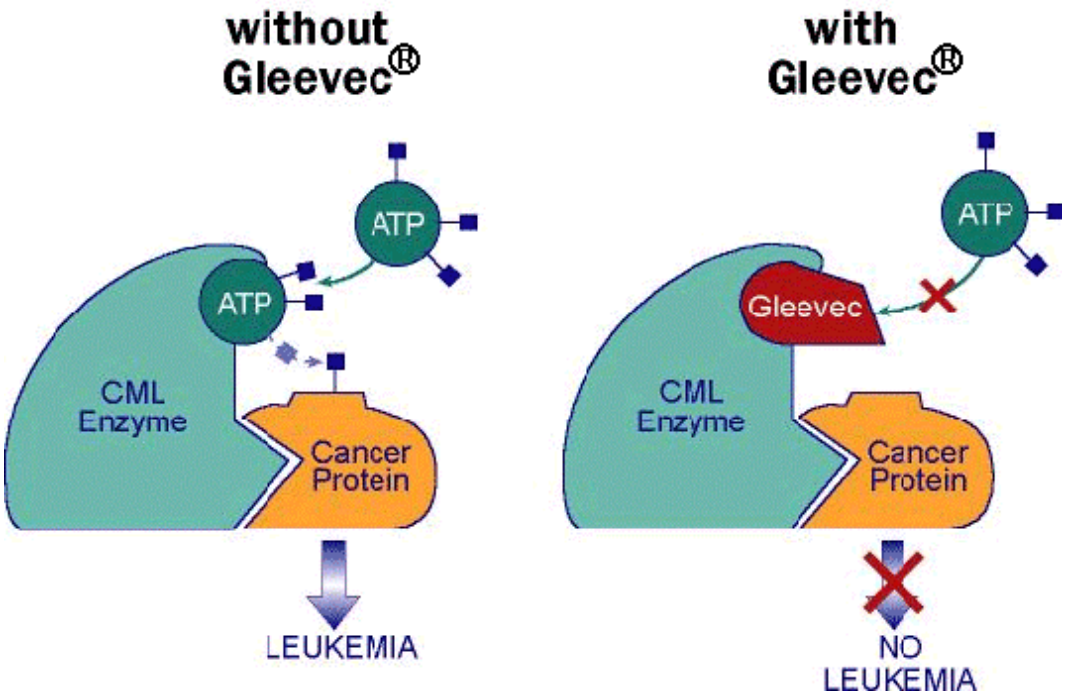
histologically identical. Molecularly targeted therapies based on recent progress in genomics and proteomics, however, hold out the promise of being far more selective, thereby drastically reducing the incidence of side effects in patients undergoing cancer treatment. (Livingston 2001)



Note: The year is the year of diagnosis or death.
Source: Surveillance, Epidemiology, and End Results Cancer Statistics Review 1973-1999; National Cancer Institute, 2002.

For example, the recently FDA-approved drug, Gleevec, which is used to treat chronic myeloid leukemia (CML), is one of the first agents using this new approach that targets abnormal proteins fundamental to the cancer. (Wall Street Journal May 16, 2002) Unlike most current cancer therapies that kill both normal and cancer cells leading to unwanted side-effects, Gleevec and other drugs in this class are designed to zero in on specific cancer-causing molecules, eliminating cancer cells while avoiding serious damage to other, non-cancerous cells. Early studies of this drug have shown that in patients with chronic myelocytic leukemia, white blood-cell counts are restored to normal levels.

Although GleevecÒ is available in the U.S., other countries have restricted its use. For example, the preliminary review of Gleevec in the UK by officials at the government-sponsored National Institute for Clinical Excellence recommended that the drug only be used in patients who had already gone into the "accelerated phase" of their disease. (Hawkes 2002) In the U.S., Gleevec is indicated for treatment of patients with CML in blast crisis, the accelerated phase or in chronic phase after failure of interferon-alpha therapy.



Drugs in the pipeline for cancer

- Drugs and biologics that target specific molecules or proteins on cancer cells are being developed. (NIH 2002, Livingston 2001)

- Vaccines against certain types of cancer are also being investigated. (NIH 2002, Livingston 2001)

- Drugs that prevent blood vessel growth in tumors are also being tested. (NIH 2002, Margolin 2001)

At present, many new compounds, some of which have novel mechanisms of action, are in development. In 2002, 402 drugs or biologics are in clinical trials for treatment of various forms of cancer. (PhRMA 2002)

Several new approaches to treat cancer are being investigated. Much research is underway to develop drugs and biologics that attack certain molecular targets on cancer cells, causing selective cell death. (NIH 2002, Livingston 2001) By specifically targeting cancer cells, damage to normal cells will be minimized, thus reducing the morbidity of chemotherapy.

Scientists are also studying different compounds that work with the body's immune system to kill cancer cells. One clinical trial is evaluating the ability of an antibody to kill lymphoma cells. In other trials, agents that manipulate different parts of the immune response to kill tumor cells are under investigation. (NIH 2002)

Tumor growth is dependent on the generation of new blood vessels to maintain blood supply to cancer cells. This new blood vessel formation is called angiogenesis. Anti-angiogenic drugs that block a tumor's ability to grow new blood vessels are in clinical trials. (NIH 2002, Margolin 2001) Finally, there is interest in developing vaccines for different types of tumors, such as colon cancer and melanoma. (NIH 2002, Livingston 2001, American Cancer Society 2002)

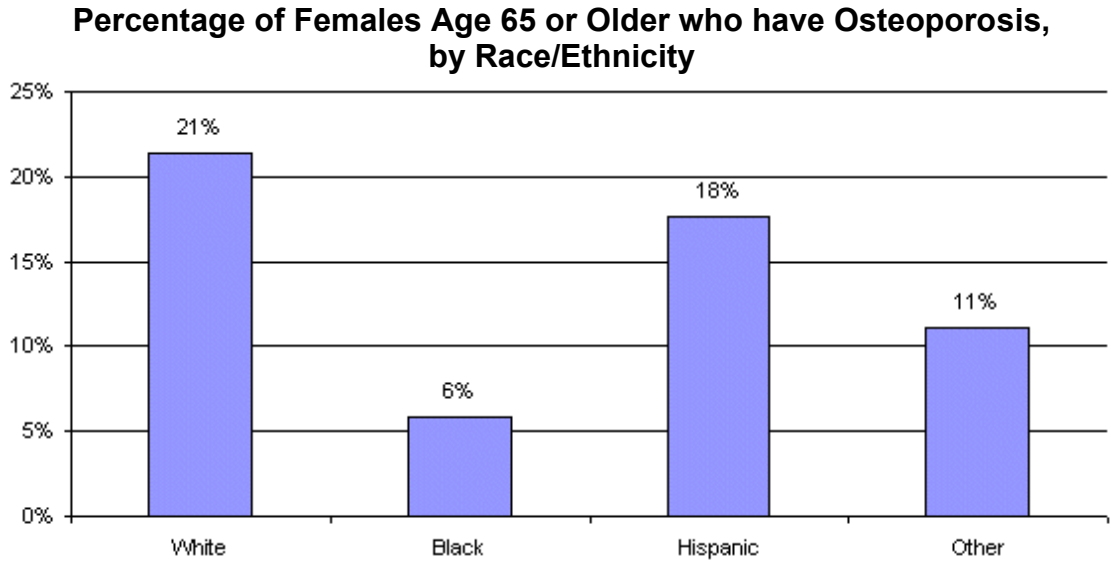
Osteoporosis

- In the U.S. today, 10 million individuals already have osteoporosis and 18 million more have low bone mass, placing them at increased risk for the disease.

- Osteoporosis is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures, and approximately 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 fractures at other sites.

- It is estimated that approximately one out of two women and one out of eight men over 50 will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes.

- Effective treatments are available to prevent osteoporosis and reduce the risk of debilitating fractures.



Source: 1998 Medicare Current Beneficiary Survey

Osteoporosis is a major public health threat for 28 million Americans, 80 percent of whom are women. (NIH 2002) Osteoporosis is characterized by low bone mass that leads to an increased

risk of fracture, most frequently of the spine, hip, or wrist. Osteoporosis occurs in both men and women but is most common in post-menopausal women. Osteoporotic hip fractures, in particular, are associated with substantial morbidity, disability, and mortality. Moreover, only one-third of hip fracture patients will return to pre-fracture independence. (U. of Washington 2002) Estimated national direct expenditures (hospitals and nursing homes) for osteoporosis and related fractures are about $14 billion a year.

Treatment of osteoporosis

Osteoporosis is largely a preventable and treatable disease. Comprehensive treatment programs that focus on proper nutrition, exercise, medication, and prevention of falls, can slow or stop bone loss, increase bone density, and reduce fracture risk. (NIH 2002) First introduced in the mid-1990s, bisphosphonates, which inhibit bone reabsorption, represent one recent category of pharmaceuticals that effectively treat osteoporosis. (National Osteoporosis Foundation 2002) Alendronate and risedronate are in this category of drugs. In one study, risedronate significantly reduced the risk of hip fractures in elderly women with a confirmed diagnosis of osteoporosis. (McClung 2001)

Although treatment with these agents significantly reduces the risk of developing osteoporosis and subsequent fractures, some countries restrict reimbursement for these drugs to relatively narrow categories of patients. For example, in New Zealand, only specialists can initiate therapy with FosamaxÒ, a bisphosphonate, and then only after the patient has already suffered one previous, significant osteoporotic fracture (radiologically demonstrated) and has a substantially low bone mass density. (Merck & Co. 2002) Australia, Italy, Belgium, and France have similar restrictions on reimbursement for FosamaxÒ. In Ontario, Canada, FosamaxÒ is only reimbursed for treatment of osteoporosis in post-menopausal women who have failed to respond to etidronate (which is not even a mainstream treatment in the U.S. for osteoporosis), as evidenced by continued loss of bone mineral density after two years of treatment, a new fracture after one year of etidronate therapy, or intractable side effects or allergic reaction from etidronate. (Merck & Co. 2002)

Drugs in the pipeline for osteoporosis

- Selective Estrogen Receptor Modulators (SERMS) mimic the effects of estrogen and prevent bone loss. (Ettinger 1999)

- Novel approaches for new drugs to treat osteoporosis target different elements in bone reabsorption and formation. (NIH 2002)

- Phytoestrogens are in clinical trials. (NIH 2002)

A number of potentially very exciting agents are being developed for the treatment of osteoporosis. Some of these may have fewer side effects and, therefore, may be better tolerated by patients. Fifteen drugs were in clinical trials for osteoporosis in 2002. (PhRMA 2002)

These agents can be divided into two categories: those that prevent bone reabsorption and those that promote new bone formation. Different elements involved in maintaining healthy bone are targeted by these new compounds, including factors involved in bone cell function and regulation, cell membrane receptors and attachment proteins, and cellular enzymes and nuclear transcription factors. (Tobias 2002; Boskey 2001)

For example, a new class of drugs called Selective Estrogen Receptor Modulators (SERMS) prevents bone loss and reduces the risk of fractures, by mimicking the effects of estrogen in some parts of the body. (National Osteoporosis Foundation 2002) Raloxifene is one of the first SERMS available.

Both Ontario and Quebec, Canada, limit coverage for raloxifene. Ontario's formulary approves raloxifene treatment only for postmenopausal women who have failed to respond to etidronate (as evidenced by continued loss of bone mineral density after two years of therapy), have experienced a new osteoporosis related fracture after one year of etidronate treatment, or have experienced intractable side effects or allergy with etidronate which precludes continuation of therapy. (Ontario Ministry of Health and Long Term Care 2002) In Quebec, raloxifene treatment is not listed as an approved therapy on Quebec's formulary. (Quebec Prescription Drug Insurance Plan 2002)

In the near future, other agents may be available to treat osteoporosis. Phytoestrogens, substances derived from soy, are being tested to determine if they can reduce bone loss in older women. Many women are electing to try "natural" estrogens because these products are readily available and seem to work as selective estrogen receptor modulators. That is, they stimulate estrogen receptors on bone and slow bone breakdown, but have tissue selectivity that maximizes benefits and depresses harmful side effects. (NIH 2002)

Nitroglycerine is a drug used to treat angina pectoris (a recurring pain or discomfort in the chest that happens when some part of the heart does not receive enough blood) that has been shown in pilot studies to reduce bone loss in women who have had their ovaries removed. (NIH 2002) Nitroglycerin releases a substance (nitric oxide) that is a powerful mediator of hormone action. It is being tested in postmenopausal women, but if found to be effective could work equally well in men.

Asthma

- In 1999, 26.7 million people in the U.S. reported that they had been diagnosed with asthma sometime in their lives, and 10.5 million had experienced an asthma attack or episode in the previous 12 months. (CDC 2002)

- 7.6 percent of seniors report having asthma. (CDC 2002)

- In 1999, there were 11 million visits for asthma to private physician offices and outpatient departments, 2 million visits to the emergency department, and about one-half million hospitalizations. (CDC 2002)

- In 1999, 4,657 people died from asthma, at a rate of 1.7 per 100,000 population. (CDC 2002)

Asthma is a chronic respiratory disease involving episodes or attacks of small airway narrowing from inflammation and hyper-responsiveness to asthma "triggers." Triggers may include allergens, infections, exercise, abrupt changes in the weather, and exposure to environmental irritants such as cigarette smoke. Asthma attacks can vary from mild to life threatening, and involve shortness of breath, coughing, wheezing, chest pain or tightness, or a combination of these symptoms. Asthma has become more common over the past two decades, and it remains a key public health problem in the United States. (MMWR 2002)

Treatment of asthma

In addition to avoiding triggers, treatment of asthma usually consists of some combination of bronchodilators and anti-inflammatory agents. Bronchodilators work to relax the muscles in airway walls, opening breathing passages. Anti-inflammatory drugs work to reduce swelling, inflammation, and mucous in airways thereby relieving some of the obstruction to airflow. Corticosteroids are one common class of anti-inflammatory drugs used in treating asthma. Although effective, long-term treatment with corticosteroids, particularly when taken by pill, may have significant side effects, such as bone mineral loss, weight gain, and stomach irritation. A few nonsteroidal pharmaceuticals to reduce airway inflammation are currently available. These agents do not have the side effects that corticosteroids may produce. (Gawchik 2000)

Recently introduced leukotriene antagonists represent the first truly new approach in treating asthma in the past 30 years. Montelukast, a leukotriene receptor antagonist, is the first in this class that targets a specific receptor for a substance that is involved in the inflammatory response in the airways. Since this drug inhibits the inflammatory response, it is indicated for prophylaxis to reduce asthma attacks. Use of montelukast may eliminate or decrease the need for chronic use of inhaled corticosteroids, which can have significant side effects and which are difficult for some patients to use effectively. (Lipworth 1999)

Montelukast (SingulairÒ) is approved in the U.S. for the prophylaxis and chronic treatment of asthma. New Zealand, Australia, Belgium and Finland do not currently provide coverage for this medication. In addition, many provinces in Canada restrict coverage of montelukast only to patients who are not able to control their asthma symptoms with inhaled corticosteroids. (Quebec Prescription Drug Insurance Plan)

Drugs in the pipeline for asthma

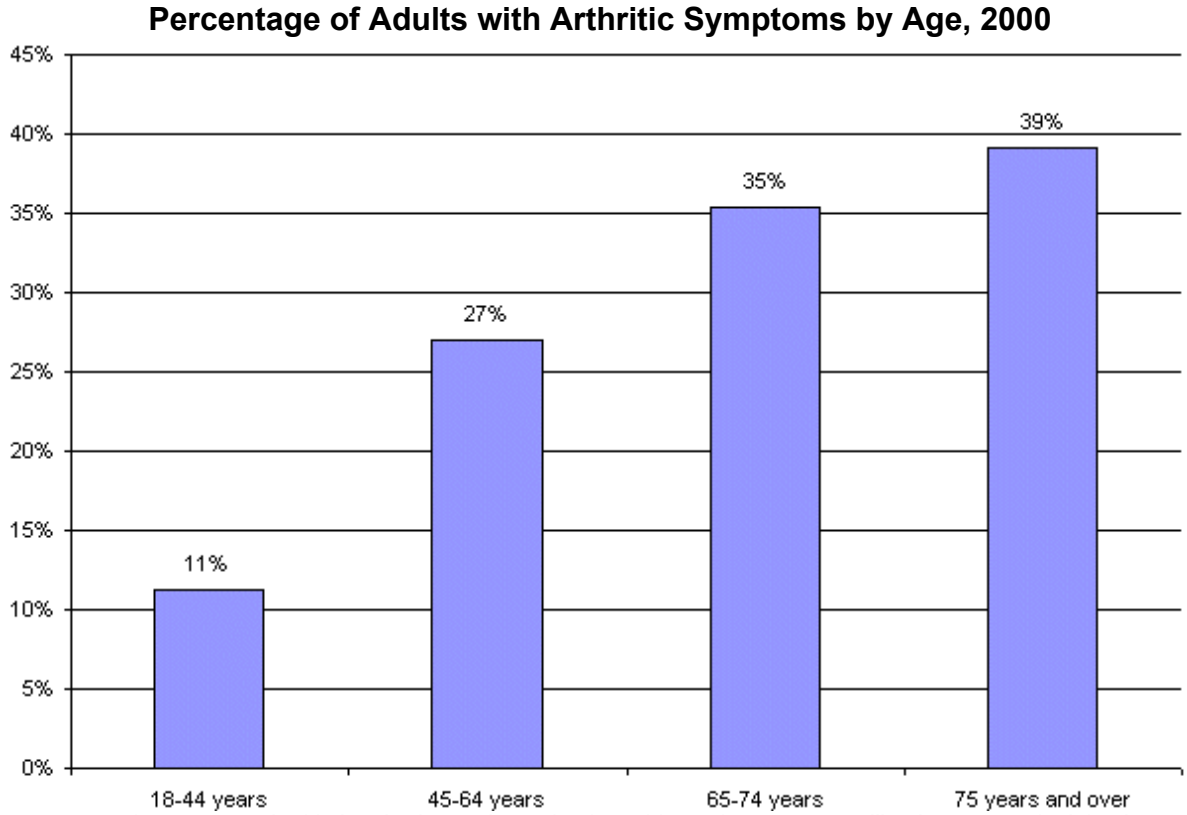
- Novel agents for the treatment of asthma that target different parts of the inflammatory cascade are in clinical development. These include compounds that target cells, antibodies, cell receptors, mediators, and cell signaling substances. (Hansel 2001)

- Preliminary studies of selective enzyme inhibitors have shown promise. (Szelenyi 2002)

- New glucocorticoids with less severe side effects are being developed. (Szelenyi 2002)

Numerous agents that attack different parts of the inflammatory response seen in asthma are in clinical development. (Crystal 2001, PhRMA 2002) By disrupting the inflammatory cascade and reducing airway inflammation, asthma may be better controlled and acute attacks prevented. These compounds target specific cells, antibodies, inflammatory mediators, cell surface proteins, and cell signaling substances that are involved in producing an acute asthma attack. (Hansel 2001) In addition, there are efforts to produce new corticosteroids that have significantly fewer side effects. (Szelenyi 2002) PhRMA reports that twenty-seven medications are currently in clinical trials for the treatment of asthma. (PhRMA 2002)

Arthritis



Note: Respondents were asked if they had experienced pain, aching, stiffness, or swelling in or around a joint that was present most days for at least one month.
Source: National Health Interview Survey, 2000

- Arthritis is the leading cause of disability in the United States.
- In this country, about one of every six people (43 million) has arthritis, and the disease limits the daily activities of seven million people.
- Approximately 21 million Americans suffer from osteoarthritis; 75% of them are women. By 2020, if current rates continue, 60 million people will have the disease, and 11 million will have activity limitations.

- Forty percent of people with arthritis are age 65 or older.

- Pharmaceutical agents are available to control the disabling symptoms, especially pain, of arthritis.

Arthritis is not a single disease but rather it is an umbrella term for a group of more than 100 conditions that involve the joints and surrounding tissues, including osteoarthritis, rheumatoid arthritis, gout, and bursitis. (CDC 1999) All of these conditions can decrease quality of life, causing pain and limiting people's ability to engage in the activities of daily living. Besides the physical toll, arthritis costs the U.S. nearly $65 billion annually. (CDC 2002) Although cost-effective interventions are available to reduce the burden of arthritis, they are currently underutilized.

New treatments for arthritis

COX-2 inhibitors represent a newer class of medications used to treat arthritis. COX-2 inhibitors interfere with an enzyme that causes pain and swelling. Moreover, these drugs do not inhibit the COX-1 enzyme, which may help maintain the normal stomach lining. Thus, COX-2 inhibitors are reported to have less gastrointestinal side effects than older drugs, such as aspirin or other nonsteroidal anti-inflammatory agents. (Silverstein 2000; Bombardier 2000) Included in the COX-2 class are rofecoxib and celecoxib.

Despite the wide availability and use of COX-2 inhibitors in the U.S., some countries restrict coverage of these agents or provide no coverage at all. New Zealand has not approved reimbursement for CelebrexÒ or VioxxÒ, both COX-2 inhibitors. (PHARMAC 2002) In Ontario, Canada, reimbursement for VioxxÒ is limited to patients with osteoarthritis who have failed prior treatment with acetaminophen, and who have a history of documented, clinically significant ulcer or gastrointestinal bleeding, or failure or intolerance to at least three other non-steroidal anti-inflammatory agents. (Ontario Ministry of Health and Long Term Care 2002) In addition, reimbursement for this drug is limited to a maximum daily dose of 25 mg, which is not always sufficient to provide effective control of symptoms.

Recent advances in biotechnology have produced novel approaches to treat arthritis. Biologic response modifiers are genetically engineered substances used to reduce the signs and symptoms of rheumatoid arthritis. (Paget 2002) Drugs in this class include etanercept, anakinra, and infliximab. Etanercept, the first in this new class of drugs, acts by inhibiting tumor necrosis factor (TNF), one of the proteins that plays an important role in the cascade of reactions that causes the inflammatory process of rheumatoid arthritis, resulting in significant reduction in inflammatory activity. Infliximab, a monoclonal antibody, also inhibits TNF. Anakinra is a recombinant IL-1 receptor antagonist that also modifies the inflammatory response.

Both etanercept and infliximab are approved by the FDA, but have limited availablity in other countries. These drugs are not covered in New Zealand, or Ontario, Canada and their use in the UK is restricted to patients who have failed arthritis treatments with other medications. (National Institute for Clinical Excellence 2002; PHARMAC 2002; Ontario Ministry of Health and Long Term Care 2001)

Drugs in the pipeline for arthritis

- Additional inflammatory response modulators to reduce the inflammation of arthritis are being studied. (Koopman 2001)

- A vaccine for rheumatoid arthritis which would prevent the autoimmune response is in development. (PhRMA 2002)

Pharmaceutical approaches that modify the inflammatory or immune response are likely candidates for new drugs to treat arthritis. (Koopman 2001) In 2002, eight new drugs for osteoarthritis were undergoing clinical trials. (PhRMA 2002) In addition, clinical trials for 22 new medications for rheumatoid arthritis, including a vaccine to prevent the autoimmune process that causes the disease, were in progress in 2002. (PhRMA 2002)

High Cholesterol

- Approximately 25 percent of the adult population in the U.S. has elevated blood cholesterol levels. (NIH 2002)

- A high blood cholesterol level is a major risk factor for heart disease and stroke.

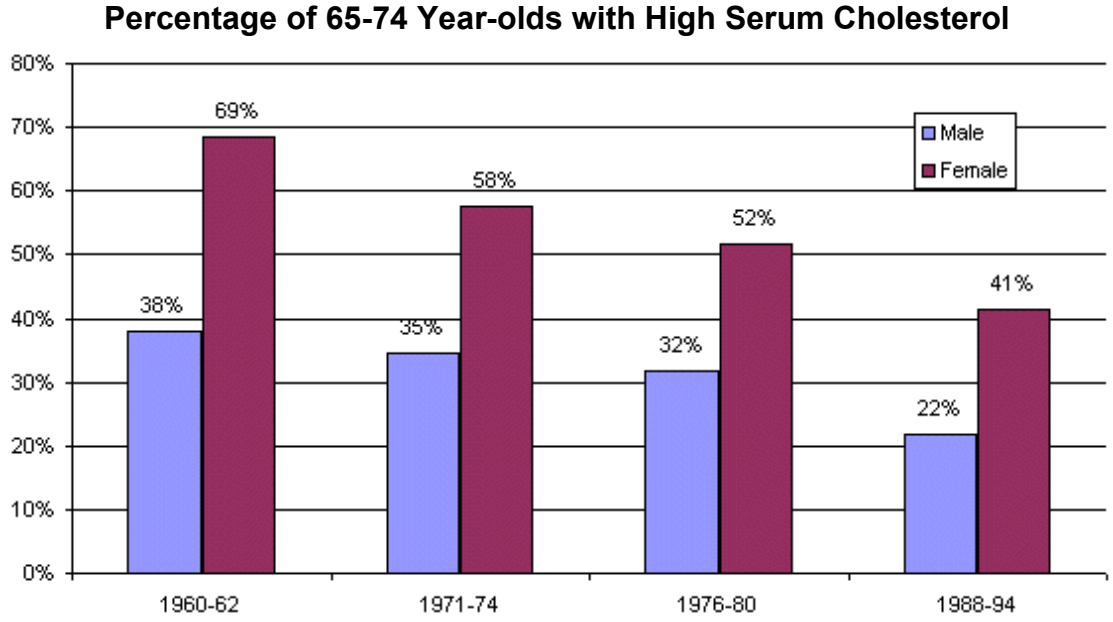
- Drug therapy can effectively lower blood cholesterol.

Cholesterol is a soft, waxy substance produced by the body and found in foods of animal origin. It is present in the blood stream and all body cells. Since cholesterol cannot dissolve in the blood, it is transported to and from the cells by two main lipoprotein carriers: LDL (low-density lipoprotein) and HDL (high-density lipoprotein). A high blood LDL-cholesterol is one of the major risk factors for coronary artery disease, which leads to heart attacks. In contrast, a high level of HDL-cholesterol tends to protect against heart disease. The higher one's blood LDL-cholesterol level, the greater the risk for developing heart disease or having a heart attack.

Treatment of high cholesterol

Since an elevated LDL-cholesterol significantly increases the risk of heart disease, treatment is directed at lowering blood levels. Statins represent a new category of LDL-cholesterol lowering drugs. There are currently five statin drugs on the market: lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin. Research has demonstrated that the use of statins results in large reductions of total and LDL-cholesterol, which decreases heart attacks and heart disease deaths. (NIH 2002) Studies using statins have reported 20 to 60 percent lower LDL-cholesterol levels in patients taking these drugs. (American Heart Association 2002) Current research findings are

pointing to other possible benefits of statins, indicating that they may be helpful in preventing and treating a variety of conditions, including cancer, strokes, Alzheimer's, adult-onset diabetes, deep vein thrombosis, and organ rejection in transplantation. (Bellosta 2000)



Source: National Health and Nutrition Examination Survey

Despite the wide use of statins to lower blood cholesterol in the United States, some countries limit access to this class of drugs. For example, Simvastatin (ZocorÒ) is a statin that is used to lower blood cholesterol. In Australia, reimbursement for ZocorÒ is restricted to patients who fail six weeks of dietary therapy. In New Zealand, only three of the five FDA-approved statins are covered by the government's health plan. (PHARMAC 2002)

<u>Drugs in the pipeline for high cholesterol</u>

- Drugs designed to interfere with intestinal reabsorption of cholesterol are being investigated. (NIH 2002, Leitersdorf 2002)

- Drugs that inhibit the cholesteryl ester transfer protein (CETP inhibitors) are in development. These drugs would work synergistically with statins to lower blood cholesterol. (NIH 2002, de Grooth 2002)

- Vaccines that prevent the conversion of HDL to LDL cholesterol are under study. (PhRMA 2002)

New pharmaceutical approaches to elevated blood cholesterol are in development. Research is underway on an investigational drug (a cholesterol absorption inhibitor) that may provide additional reductions in LDL cholesterol when taken along with some statins. (Leitersdorf 2002) In addition, PhRMA reports that there is an effort to develop a vaccine that will lower blood

cholesterol by preventing the conversion of HDL-cholesterol to LDL-cholesterol. (PhRMA 2002)

Cardiovascular Disease¾ Heart Disease and Stroke

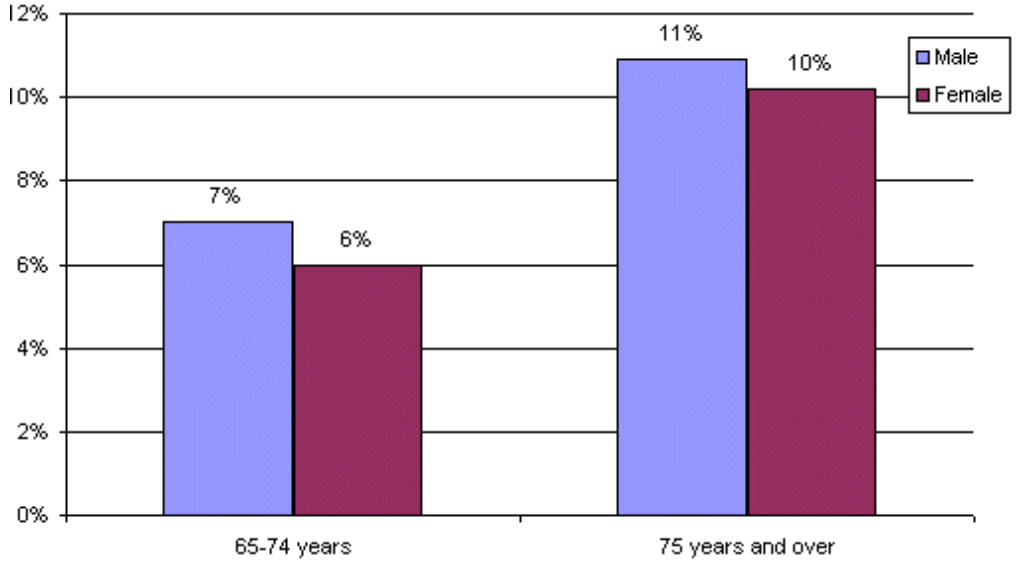
- About 950,000 Americans die of cardiovascular disease each year, which amounts to one death every 33 seconds.

- Eighty-three percent of people who die from coronary heart disease are age 65 or older. (American Heart Association 2001)

- Seventy-two percent of people who suffer a stroke in a given year are 65 or older. (American Heart Association 2001)

- New therapies for heart attacks and strokes have reduced the morbidity and improved the mortality in patients experiencing these events.

The Percentage of Persons 65 Years of Age and Over who have had a stroke

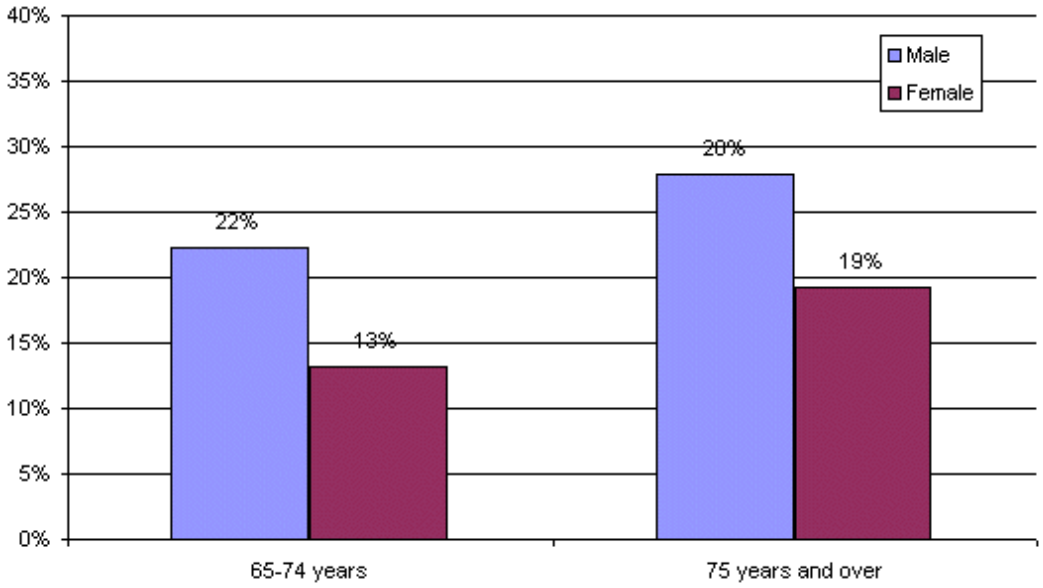


Source: National Health Interview Survey, 2000

Heart disease and stroke—the principal components of cardiovascular diseases—are the first and third leading causes of death in the United States, accounting for more than 40% of deaths. (CDC 2002) However, a consideration of deaths alone understates the burden of cardiovascular disease. About 61 million Americans (almost one fourth of the population) live with this disease. Stroke alone accounts for disability among more than 4 million Americans. Almost 6 million hospitalizations each year are due to cardiovascular disease.

Predictably, strokes and heart attacks have a higher incidence in seniors. High blood pressure and diabetes are chronic conditions that predispose individuals to develop cardiovascular disease. Both diseases have a relatively high prevalence in seniors.

Percentage of Persons 65 Years of Age or Over with Coronary Heart Disease, 2000



Note: Coronary heart disease includes coronary heart disease, angina, and heart attack.
Source: National Health Interview Survey

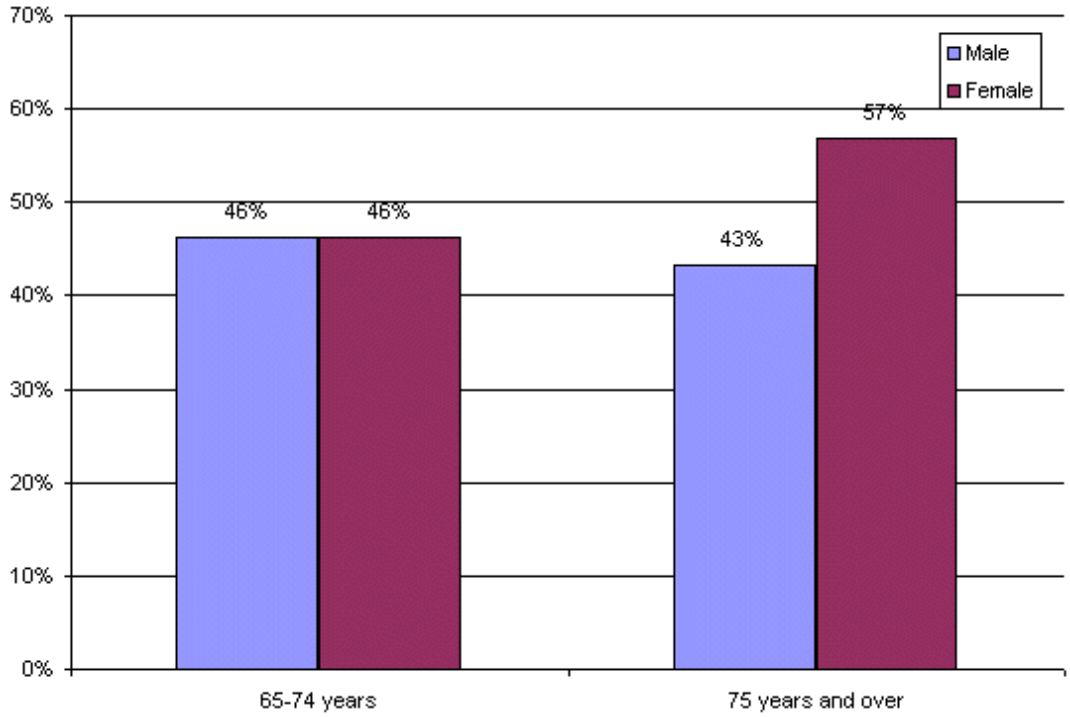
Newer treatments for cardiovascular disease

Recently developed treatment approaches for heart attacks and strokes have reduced the morbidity and improved the mortality in patients experiencing these events. For example, Tissue Plasminogen Activator (t-PA) is a thrombolytic agent, known as a "clot-busting" drug. It can dissolve blood clots, which cause most heart attacks and strokes. The FDA approved the use of t-PA for treatment of some strokes in 1996. The prompt use (within the first three hours) of t-PA following an ischemic stroke has been shown to halt damage and significantly improve recovery. In addition, prompt treatment of stroke victims with t-PA could result in substantial net cost savings to the health care system. (NIH 1995; Fagan 1998) These savings are based on the fact that t-PA-treated stroke patients, because of their decreased disability, leave the hospital sooner and require less rehabilitation and nursing after discharge than do patients who do not receive t-PA.

GP IIb/IIIa inhibitors are another example of newer pharmaceuticals that reduce the risk of atherosclerotic events (myocardial infarction and stroke) in patients with atherosclerosis documented by recent stroke, recent myocardial infarctions, or established peripheral arterial disease. (Sabatine 2000) These drugs inhibit platelet aggregation (platelet blockers), which is a factor in the initiation or evolution of acute cardiovascular or cerebrovascular events. GP IIb/IIIa inhibitors include clopidogrel, eptifibatide, and tirofiban.

In recent years, there have been significant advances in the treatment of chronic conditions, such as hypertension, that place patients at elevated risk for strokes and other cardiovascular diseases. For example, angiotensin II receptor antagonists ¾ losartan (CozaarÒ) and valsartan (DiovanÒ) ¾ represent relatively new therapies for the treatment of hypertension, a primary risk factor for heart attacks and strokes. These drugs are readily available and widely used in the U.S. to treat high blood pressure, and are preferred by many patients and doctors because of their effectiveness and the absence of side effects in many patients. However, they are often not covered in other countries. For example, as a result of formulary restrictions in Ontario and other Canadian provinces, access to these drugs is restricted to patients who have proven that they cannot tolerate other high-blood pressure medications. (Ontario Ministry of Health and Long Term Care 2001) In Australia, although CozaarÒ treatment was reimbursed approximately six years ago, the government instituted further cost controls, and as a result the drug is no longer sold in Australia. (Merck & Co. 2002) In New Zealand, only specialists (cardiologists) can initiate therapy with CozaarÒ, and then only after the patient has developed congestive heart failure and has failed treatment attempts with at least two kinds of angiotensin converting enzyme (ACE) inhibitors. DiovanÒ is not approved for coverage in New Zealand. (PHARMAC 2002)

The Percentage of Persons 65 Years of Age and Over with Hypertension, 2000



Note: This represents persons who have been told on two different visits or more that they had hypertension or high blood pressure.
Source: National Health Interview Survey, 2000

Drugs in the pipeline to treat cardiovascular disease

- Research is underway on a clot-dissolving drug made from the venom of a pit viper snake. (Sherman 2000)

- Pharmaceutical approaches to limit brain damage and to aid recovery of stroke victims represent new approaches to treatment. (NIH 2002)

- A drug that lowers the heart's need for oxygen may protect the heart muscle from damage during a heart attack. (NIH 2002, PhRMA 2002)

- Angiogenic therapies to revascularize the heart muscle are being investigated. (NIH 2002)

Advances in medical science have yielded new approaches to the treatment of cardiovascular disease. (Lefkowitz 2001) PhRMA reports that 122 new medicines are in development for cardiovascular diseases in 2002. (PhRMA 2002) Some of these new agents are directed at chronic medical conditions that are risk factors for the development of heart disease, such as high blood pressure or high cholesterol. Other compounds are new treatments for complications of heart disease including congestive heart failure and arrhythmias. For example, B-natriuretic peptide (BNP) is a small protein produced by the heart muscle that improves cardiac function. A recombinant form of BNP was recently approved by the FDA for the treatment of decompensated congestive heart failure. (NIH 2002) Other potential uses of BNP are currently being investigated.

Two broad, complementary strategies are under development, which aim to reduce morbidity from a stroke. One is to restore blood flow to the brain as quickly as possible and another is to limit the damage incurred by a stroke. Similar to t-PA, the venom of a pit viper snake is a clot-dissolving drug. While this drug has not been approved yet, early findings suggest that it helps stroke patients regain their physical and mental abilities, with many patients experiencing full recovery. (Sherman 2000)

The NIH reports that several compounds that may limit brain damage in stroke victims are now being tested in animal models. Scientists are trying to develop "neuroprotective drugs" that prevent strokes from damaging brain cells. Efforts to develop neuroprotective drugs build on very substantial research efforts that are unraveling the complex cascade of harmful events that occur in the brain in the seconds, minutes, and hours following a stroke. Each step in the cascade presents a potential target for drug intervention. Excitotoxicity occurs from excessive release of the normal neurotransmitter glutamate, and, when challenged by stroke, brain cells produce highly reactive and potentially harmful chemicals called "free radicals." Research is developing drugs that intervene at various stages of excitotoxicity, free radical damage, and other aspects of the stroke-induced cascade of events in the brain. For example, anti-oxidants to prevent free-radical damage are being evaluated. As another example, amapakines are drugs that act by modulating a subclass of nerve cell receptors for a specific neurotransmitter. Excessive release of this neurotransmitter can cause damage in stroke victims. Testing is being conducted to determine if amapakines can prevent brain damage from stroke or help improve learning and memory following stroke. (NIH 2002)

Finally, scientists have been encouraged by recent findings that the adult human brain has a surprising capacity to adapt following disease or injury, even to the extent of making new nerve

cells. As a result, researchers are trying to develop drug interventions that enhance the brain's capacity to repair itself.

Benign Prostatic Hyperplasia (BPH)

- More than half of men in their sixties and 90 percent in their seventies have some symptoms of BPH.

- In the United States, 375,000 hospital stays each year involve a diagnosis of BPH.

As a man ages, it is common for the prostate gland to become enlarged. This condition is called benign prostatic hyperplasia (BPH). Although BPH rarely causes symptoms before the age of 40, an increasing percentage of men will become symptomatic as they get older. Symptoms of BPH stem from obstruction of the urethra and gradual loss of bladder function, which results in incomplete emptying of the bladder. Common complaints of BPH include urinary urgency and frequency, and multiple instances of nocturnal urination.

Treatment of BPH

Four drugs are approved by the FDA to treat BPH. One drug, finasteride (Proscar®), inhibits production of a hormone which is involved with prostate enlargement. *Although widely used in the United States, finasteride (ProscarÒ) is not covered in New Zealand or Ontario, Canada. (Ontario Ministry of Health and Long Term Care 2001; PHARMAC 2002)*

Three newer drugs, alpha-1 blockers (alpha-1 adrenoceptor antagonists), act to relax the smooth muscle of the prostate and bladder neck to improve urine flow and to reduce bladder outlet obstruction. Using an alpha-1 blocker along with finasteride is more effective than either drug alone to relieve the symptoms and prevent BPH progression. (NIH, NIDDK 2002) The two-drug regimen reduced the risk of BPH progression by 67 percent, compared to 39 percent for an alpha blocker alone or 34 percent for finasteride alone.

Drugs in the pipeline for BPH

- Studies to evaluate phytotherapeutic agents to treat BPH are under way. (NIH 2002, Andersson 2002) [NIDDK and the National Center for Complementary and Alternative Medicine (NCCAM) currently fund a small, single-center pilot project using saw palmetto for BPH, and plan to fund a large, multi-center clinical trial using *Serenoa repens* (saw palmetto) and *Pygeum africanum* in men with BPH, beginning on about September 30, 2002.]

- Endothelin and muscarinic receptor antagonists are being evaluated for the treatment of BPH. (Andersson 2002)

- Subtypes of alpha-1 blockers are being investigated. (Andersson 2002)

There are several drugs currently in clinical trials for treatment of BPH. (PhRMA 2002) New approaches for the treatment of BPH and resulting urinary tract symptoms are being investigated. (Andersson 2002) These new approaches target sites both within and exterior to the prostate gland. By their effect on the smooth muscle in the bladder wall, muscarinic receptor antagonists may reduce the urinary urgency and frequency associated with BPH. Endothelin receptor antagonists may prevent cell proliferation in both the prostate gland and the bladder. Moreover, these agents may also affect muscle contraction in the bladder wall, decreasing some of the symptoms of BPH. In addition, drugs directed at specific subtypes of alpha-1 adrenoceptors may prove more effective and tolerable than nonselective compounds.

Depression

- An estimated six percent of Americans ages 65 and older in a given year (approximately 2 million of the 34 million adults in this age group in 1998), have a diagnosable depressive illness (major depressive disorder, bipolar disorder, or dysthymic disorder). (Narrow 1998)

- As a result of depression, older Americans are disproportionately likely to commit suicide. Although they comprise only 13 percent of the U.S. population, individuals ages 65 and older accounted for 19 percent of all suicide deaths in 1997. (Hoyert, 1999)

- New effective treatments, with fewer undesirable side-effects, are available for depression.

Major depression is a leading cause of disability in the United States and worldwide. (Murray 1996) In contrast to the normal emotional experiences of sadness, grief, loss, or passing mood states, depressive disorders can be extreme and persistent and can significantly interfere with an individual's ability to function, robbing one of the joy of living. Depression often co-occurs with other illnesses such as cardiovascular disease, stroke, diabetes, and cancer, which have a significant incidence in seniors. (AHRQ, formerly AHCPR 1993) When depression co-occurs with medical conditions, it can interfere with the patient's ability to follow the necessary treatment regimen or to participate in a rehabilitation program. It may also increase impairment from the medical disorder and impede its improvement.

Treatment of depression

Antidepressant medications are widely used effective treatments for depression. (Mulrow 1998) Existing antidepressant drugs are known to influence the functioning of certain neurotransmitters in the brain, primarily serotonin and norepinephrine. Older medications—tricyclic antidepressants and monoamine oxidase inhibitors—affect the activity of both of these neurotransmitters simultaneously. The disadvantage of these older medications is that they can be difficult to tolerate due to side effects or dietary and/or medication restrictions. Newer medications, such as the selective serotonin reuptake inhibitors (SSRIs), have significantly fewer side effects than older drugs, making it easier for patients, including older adults, to adhere to treatment. The anti-depressant effect of SSRIs is presumed to be linked to their inhibition of

CNS neuronal uptake of serotonin. SSRIs include fluoxetine, paroxetine, citalopram, and sertraline.

Other recently introduced anti-depressants include the serotonin and noradrenaline reuptake inhibitors (SNRIs), venlafaxine and milnacipran. These drugs have a mechanism of action that is similar to the tricyclic antidepressants. Another new drug is reboxetine, a selective noradrenaline reuptake inhibitor. All these newer antidepressants may be better tolerated by patients suffering from depression.

Available in the United States since the 1980s, the first SSRI treatment was not available in Japan until 1999. Perhaps related to the relative unavailability of depression medication, Japan has the highest number of psychiatric inpatient beds in the world, in both absolute and relative terms. (Tajima 2001)

Drugs in the pipeline for depression

- Nicotinic-receptor stimulators to enhance cognitive function are being tested for the treatment of depression. (NIH 2002)

- New inhibitors of neurotransmitter uptake are being studied. (NIH 2002)

- Two compounds that act as antagonists for the glucocorticoid receptor (GR) are currently being studied in patients with severe major depression. (NIH 2002)

- Antagonists of substance P and corticotropin-releasing factor receptors are in clinical trials for the treatment of depression. (NIH 2002, Pacher 2001)

- Agonists and antagonists of different serotonin (5-HT) receptor subtypes are being investigated as potential antidepressants. (NIH 2002, Pacher 2001)

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), 26 drugs for depression were in clinical trials in 2002. As medical science progresses, more effective and better tolerated treatments for depression will become available. Two principal strategies guide medication development efforts for depression. First, there are efforts to refine and reformulate existing medications known to work on "classic" neurotransmitter systems as a means of bringing more effective treatments to an expanded and more diverse population of persons with depression. Second, researchers are attempting to develop fundamentally new compounds that target novel brain mechanisms suggested by cutting edge research on the causes of depression.

Newer approaches to pharmaceutical treatment of depression target neuropeptide receptors and intracellular messenger systems. (Pacher 2001) Medications for depression currently under development include: corticotrophin releasing factor (CRF) receptor antagonists, substance P (neurokinin) receptor antagonists, and drugs that modulate glutamatergic transmission. (NIH 2002) Patients may tolerate these agents better than current drugs and, therefore, be more compliant with treatment regimens.

Abundant evidence suggests that increased production and/or release of CRF within the central nervous system occurs in patients with post-traumatic stress disorder and major depression. Preclinical studies show that CRF antagonists have anti-anxiety and antidepressant properties. Although CRF receptor antagonists appear promising as a novel class of antidepressants and anxiolytics, further study is needed into their clinical efficacy and safety.

Based on preclinical evidence suggesting anti-anxiety properties of inhibitors of the Substance P, selective compounds have been tested and found superior to placebo and equal to other antidepressants in treating depression. More evaluation of these agents is needed.

The neurotransmitter, glutamate, has been linked to anxiety and depression. Compounds that interfere with its action in the brain are among the candidate medications under development as potential antidepressants. (NIH 2002)

In addition to the approaches discussed, that have already led to the developing and testing of new types of antidepressants, rapid advances in neuroscience suggest medication development strategies that have yet to be undertaken. These include drugs that interact with second messenger systems, response elements and transcription factors, agents that enhance neuroprotective and neurogenic factors, and compounds that manipulate cytokine receptor activity.

Alzheimer's Disease

- An estimated 4 million Americans have Alzheimer's disease, a progressive, degenerative disorder. (CDC 1999)

- Approximately 10 percent of people older than 65 years and 47 percent of those older than 85 years have the disease.

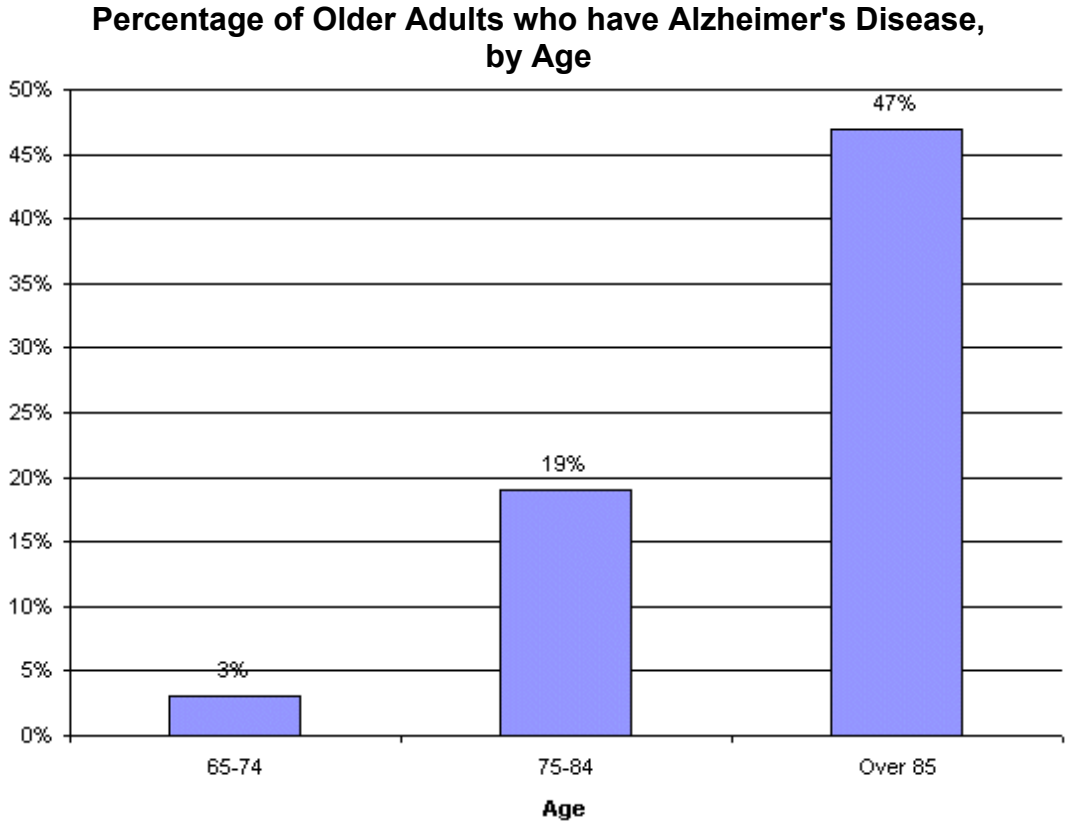
- New therapies to reduce the morbidity and mortality of Alzheimer's disease are in development.

Symptoms of Alzheimer's disease may include memory loss, cognitive deficits in language, object recognition and executive functioning, and behavioral symptoms such as psychosis, agitation, depression, and wandering. The death rate for people with Alzheimer's disease is twice as great as the rate among those of the same age without the disease. Although less than three percent of the population has Alzheimer's disease at age 65, the prevalence doubles every five years thereafter. Because the risk of Alzheimer's disease increases with age, the prevalence of the disease is anticipated to increase as the U.S. population ages. This will incur a substantial economic and social burden. The estimated annual economic toll of health care expenses due to Alzheimer's patients and caregivers in the U.S. is $80 to $100 billion. (CDC 1999) This estimate includes both direct and indirect costs for medical and long-term care, home care, and loss of productivity for caregivers. Costs are especially high among patients with behavioral symptoms, who often require earlier or more frequent institutionalization.

Pharmaceutical treatment of Alzheimer's disease

Early Alzheimer's disease is marked by a deficiency of acetylcholine in critical areas of the brain which is believed to account for some of the clinical manifestations of mild to moderate dementia. Cholinesterase inhibitors act to raise the concentration of acetylcholine in the brain by slowing the degradation of acetylcholine. Newer drugs included in this category are donepezil, tacrine, galantamine, and rivastigmine. Treating persons suffering with Alzheimer's disease with these new drugs may help to maintain function and may ease the burden on caregivers for a limited period of time.

Donepezil (AriceptÒ) is not approved for coverage in Quebec, Canada or New Zealand. (Quebec Prescription Drug Insurance Plan 2002; PHARMAC 2002) Tacrine, an acetyl cholinesterase inhibitor available in the U.S., is currently not registered for use in New Zealand. (New Zealand Guidelines Group 2002)



Source: D. Evans, et. al., JAMA, vol. 262, no. 18, 1989.

Drugs in the pipeline to treat Alzheimer's disease

Over 20 clinical trials of new drugs to treat Alzheimer's disease were underway in 2001 (PhRMA 2002) and a similar number were funded by the NIH. These include:

- A new approach under development for the treatment of Alzheimer's disease is to use drugs to limit the neurotoxicity mediated by microglia. (NIH 2002)

- Anti-oxidants and anti-inflammatory agents are being tested for effectiveness in treating Alzheimer's disease. (NIH 2002, Alzheimer's Research Forum 2002)

- A compound that activates neural growth factors in the brain is being tested. (Alzheimer's Association 2002)

- A drug that increases signaling between nerve cells is also under study. (NIH 2002, Alzheimer's Research Forum 2002)

Ideas for drugs that may be useful for the treatment and prevention of the cognitive and behavioral symptoms of Alzheimer's disease have come from a variety of sources. Clinical-pathological studies have indicated that there are a variety of brain mechanisms that may lead to or exacerbate the nerve cell dysfunction and death and loss of connections among nerve cells seen in Alzheimer's disease, including abnormal processing of proteins such as the amyloid precursor protein, beta-amyloid; oxidative damage; inflammation; and neurotrophic support of brain cells. (NIH 2002) Studies in test tubes and in animals have indicated that many of these mechanisms are potential targets for new drug discovery and development. A number of drugs targeting these mechanisms involved in Alzheimer's disease pathogenesis are currently in preclinical development or clinical testing.

Some of the drugs being investigated are new agents; others are compounds such as vitamins that are already on the market for other indications or uses, but may be effective against Alzheimer's disease. Epidemiological studies have suggested that some medications such as anti-inflammatory drugs, anti-oxidant vitamins, statins, and hormone replacement therapy may reduce the risk of developing Alzheimer's disease (NIH 2002)

One new approach to treating Alzheimer's disease is to disrupt the formation of plaques, the telltale sign of the disease. In the brains of Alzheimer's disease patients, certain proteins cleave the amyloid precursor protein (APP) into beta-amyloid fragments, which then aggregate into the characteristic plaques of the disease. Several drugs currently in development are targeted at the steps involved in this process. These include drugs that inhibit proteins that cleave the APP; a variety of agents that are proposed to inhibit the aggregation of beta-amyloid into plaques, including a plant extract from cat's claw; and immuno-therapeutic agents such as beta-amyloid vaccines. (NIH 2002)

A related strategy against Alzheimer's disease is the development of compounds proposed to be neurotrophic (i.e., facilitating the health of nerve cells) or neuroprotective against mechanisms that kill nerve cells. There are several of these types of agents in pre-clinical and clinical trials. (NIH 2002)

In addition, researchers are conducting clinical trials of drugs targeted at the behavioral symptom of agitation in people with Alzheimer's disease. Finally, substances that may protect against the development of Alzheimer's disease are in clinical trials. (NIH 2002)

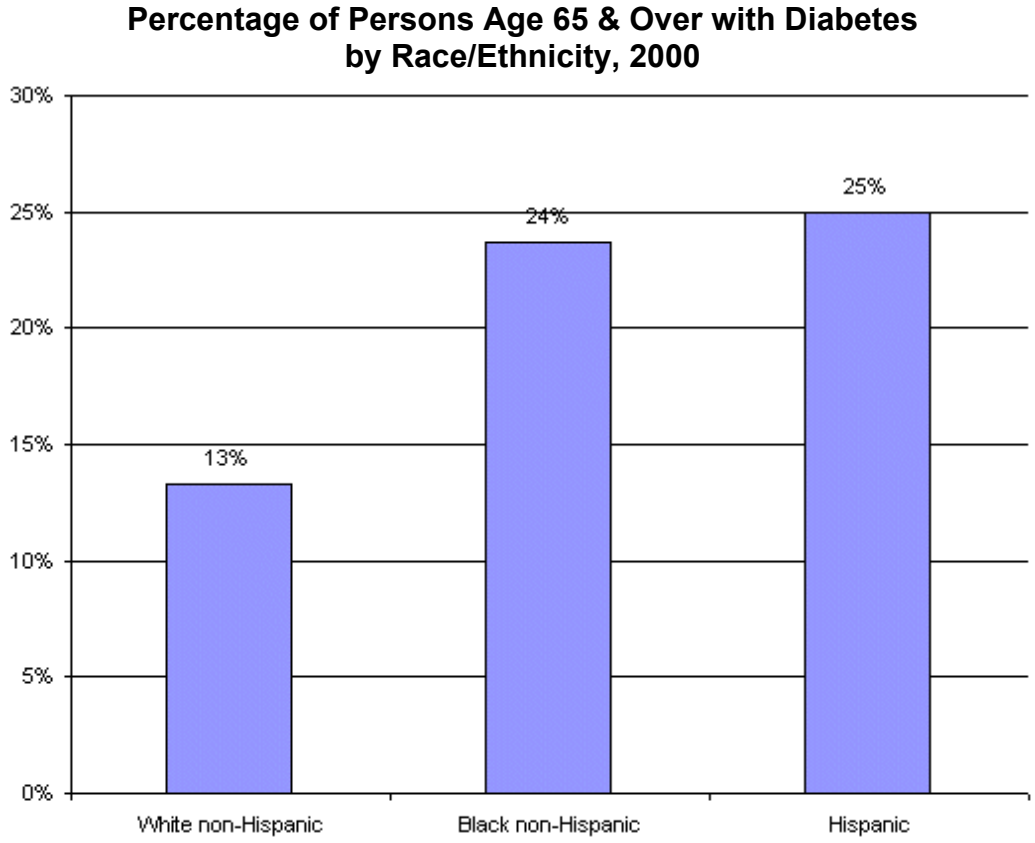
Type 2 Diabetes

- Seventeen million Americans have diabetes, and over 200,000 people die each year from related complications of their disease. (CDC 2002)

- Diabetes afflicts approximately 20 percent of all Americans age 65 and older, and about one quarter of African-Americans and Hispanics over age 65.

- Clinical trials have shown that intensive control of blood glucose, blood pressure, and lipids can dramatically reduce the risk of complications.

- New approaches to diabetes management are in development that potentially will reduce the morbidity and mortality from the disease.



Note: Respondents were asked if they had ever been told by a doctor or other health professional that they had diabetes. Persons who said they had borderline diabetes were considered "unknown."
Source: National Health Interview Survey, 2000

Diabetes is a chronic disease of high blood glucose related to the impairment of blood glucose regulation. It can result from too little of the regulatory hormone, insulin, resistance to insulin, or both. Complications include heart disease, strokes, blindness, kidney failure, and peripheral vascular and nerve disease resulting in leg and foot amputations. Among U.S. adults, diagnosed

diabetes increased 49 percent from 1990 to 2000. (CDC 2002) Diabetes disproportionately affects the elderly and certain ethnic and racial groups.

Diabetes incurs a tremendous personal, social, and financial burden. Seniors with diabetes often experience a reduced quality of life. Moreover, diabetes is an expensive disease for older Americans. In 1997, for persons aged 65 and older, total direct medical expenditures attributable to diabetes in the U.S. exceeded $32 billion. (CDC 1999) The high price of diabetes includes frequent physician and emergency room visits and admissions to hospitals and nursing homes.

Optimal treatment of diabetes can improve the quality of life and reduce health care costs. A study published in JAMA in 1998 found that treating Type 2 diabetes with a medicine to improve blood glucose (glycemic) control improved the quality of life for patients and helped keep them out of the hospital and on the job. (Testa 1998) The study also showed that patients' perceptions of their own physical and emotional health improved, while the number of bed days and hospital visits declined. Improved glycemic control can also significantly reduce the risk of developing microvascular complications (eye, kidney, and nerve disease). (CDC 2002)

Treatment and prevention for type 2 diabetes

Many patients initially control their diabetes with diet and exercise. Oral hypoglycemics are one popular form of drug treatment for type 2 diabetes. Oral hypoglycemic agents include sulfonylurea agents, metformin, and thiazolidinediones. Ultimately, most patients will require insulin. Improved formulations of insulin and methods of insulin delivery are currently in development.

Treatment with hypoglycemic agents may prevent individuals from developing diabetes. In the Diabetes Prevention Program, a clinical trial involving over 3,000 people at high risk for type 2 diabetes, diet and exercise that achieved a 5 to 7 percent weight loss reduced diabetes incidence by 58 percent in participants randomized to the study's lifestyle intervention group. (Diabetes Prevention Program Research Group 2002) Treatment with metformin reduced the risk of developing diabetes in individuals at high risk for type 2 diabetes by 31 percent over 2.8 years. (Diabetes Prevention Program Research Group 2002) Starch blockers which delay the digestion and absorption of sugars from food, were also demonstrated to cut the odds that high-risk adults would develop diabetes by 25% over three years. (Chiasson 2002)

Rosiglitazone (Avandia®) is a newer oral hypoglycemic drug approved by the FDA in 2000. This drug is not covered in Ontario, Canada or New Zealand. (Ontario Ministry of Health and Long Term Care 2001; PHARMAC 2002)

In addition to glycemic control, blood pressure control and the use of angiotensin-converting enzyme (ACE) inhibitors in people with diabetes have been demonstrated to delay the progression of kidney disease. (Golan 1999; Parving 2001; Kshirsagar 2000) Kidney failure in diabetics reduces their quality of life and often shortens their life. Treatment of diabetics with relatively inexpensive ACE inhibitors improves their quality of life and results in dramatic cost savings. (Swislocki 2001; Golan 1999)

Drugs in the pipeline for type 2 diabetes

- New drugs to target the problem of insulin resistance, which is a factor in the pathophysiology of type 2 diabetes are being investigated. (NIH, NLM 2002)

- One compound, an enzyme involved in pathways contributing to small blood vessel damage, shows promise in treating diabetic peripheral neuropathy. (United Press International 2002)

- Drugs that regulate gene expression in fat and insulin responsive tissues are also being studied. (NIH 2002)

- A compound that stimulates insulin-producing cells in the pancreas is being studied. (NIH 2002)

Type 2 diabetes generally arises from a combination of insulin resistance and inadequate production of insulin in the beta cell of the pancreas; new therapies are targeted at both of these defects. Molecular mechanisms involved in glucose toxicity underlying the development of diabetes complications have also been elucidated, yielding new targets for therapy. Moreover, scientists anticipate additional new therapeutic targets will emerge from genetic studies underway to identify genes predisposing to type 2 diabetes and to diabetes complications. (NIH 2002)

In 2002, 23 drugs were in clinical trials for the treatment and prevention of diabetes. (PhRMA 2002) Some of the agents in development are aimed at optimizing glycemic control, reducing insulin resistance, reducing obesity, and preventing the complications of diabetes. (Olefsky 2001)

Multiple pharmaceutical companies are developing new insulin sensitizing drugs for treatment or prevention of type 2 diabetes. One class of drugs acts through a nuclear receptor to regulate gene expression in fat and other insulin responsive tissues. (NIH 2002) Agents in this class have been shown to improve glucose control in type 2 diabetes, and also to delay or prevent type 2 diabetes in high-risk women with a history of gestational diabetes. Since earlier drugs in this class had significant side effects, nearly all the major pharmaceutical companies are trying to develop improved drugs that are more potent and less toxic. Several companies are investigating other mechanisms to increase insulin sensitivity (i.e. decrease insulin resistance). (NIH 2002)

Preservation or enhancement of function of the insulin producing beta cells in the pancreas is an important target for therapeutic development for diabetes. Identification of the molecular events involved in beta cell growth and development and in glucose sensing and insulin secretion by this critical cell type has important implications for therapy. (NIH 2002) Several drugs are under development based on the activity of glucagon-like peptide-1 (GLP-1) which appears to enhance growth and function of insulin producing beta cells.

Understanding of molecular mechanisms involved in glucose toxicity and development of complications of diabetes is also yielding new therapeutic strategies. For example, NIH funded

research identified a key signaling molecule involved in glucose toxicity. (NIH 2002) A phase II trial of an inhibitor of this protein for treatment of diabetic peripheral neuropathy has been recently completed. Phase III trials are planned or underway using this drug to treat neuropathy (nerve damage) and it will also be studied for retinopathy, the leading cause of blindness in American adults. (NIH 2002)

Migraines

- Migraine headaches affect 28 million Americans, 75 percent of whom are women. (NIH, NINDS 2002)

- One in four households in the United States have someone affected by migraine headaches.

- Over two million seniors have migraines or severe headaches. (CDC 2002)

The most common type of vascular headache is the migraine. The cause of migraine headaches is not precisely known. It is clear that genetic factors play a role in determining who develops migraine headaches, and abnormal genes have been identified for some forms of migraine headaches. (NIH, NINDS 2002) Migraine symptoms occur in various combinations and include pain, extreme sensitivity to light and sound, nausea, and vomiting. Some individuals can predict the onset of a migraine with telltale signs that include visual disturbances, called an aura. Triggers for migraines include: lack of food or sleep, exposure to light, anxiety, stress, and hormonal irregularities.

Treatment of migraine headaches

There are two ways to approach the treatment of migraine headaches with drugs: prevent the attacks, or relieve symptoms after the headache occurs. Several drugs for prevention and treatment of migraines have been developed in recent years, including serotonin agonists which mimic the action of this key brain chemical. (NIH, NINDS 2002) Referred to as the triptans, these agents represent an important advance in the treatment of migraine headaches. (Goadsby 2002) Triptans selectively activate the serotonin 5-HT receptor which results in three actions: constriction of cranial blood vessels, inhibition of neurotransmitter release, and reduced transmission in nerve pain pathways. In comparison to other types of drugs for migraine headaches, triptans have distinct advantages including selective pharmacology, fewer side effects, safety and efficacy, and simple consistent pharmacokinetics. (Goadsby 2002) Triptans are not recommended for use in individuals with cardiovascular disease.

Rizatriptan benzoate (Maxalt®), a triptan, is indicated for the acute treatment of migraine headaches. *Although MaxaltÒ has generally been covered in private insurance plans in the U.S. for years, it is still not covered by France's state-run health-care system. (Fuhrmans 2002) MaxaltÒ is also not covered in New Zealand, Australia and Portugal; its use is restricted in many Canadian provinces. (see appendix)*

Drugs in the pipeline for migraine headaches

- Compounds that target nerves but have no vascular side effects are being tested for the treatment of migraine headaches. (Goadsby 2002)

Many of the current treatments for migraine headaches have vascular effects that produce unwanted side effects and make them contraindicated in certain subsets of patients. Since it is believed that migraine headaches primarily result from neural events that result in dilation of blood vessels, pain and further nerve stimulation, novel approaches are currently directed at nerve activation. Several neuronally active compounds are being tested. In 2001, 10 new medicines were in development for the treatment of migraine headaches. (PhRMA 2002)

CONCLUSION

Current seniors are the beneficiaries of medical innovations which have dramatically improved their quality of life in their golden years. With the recent discoveries in medical science, future breakthroughs in treating and curing chronic diseases are probable. To ensure continued progress in the fight to treat and prevent chronic disease, society must provide a nurturing environment in which research and development can flourish. Efforts to encourage medical innovations should include investing in biomedical research, protecting intellectual property rights, providing for an efficient regulatory process, and fairly compensating industry for its products.

REFERENCES

Agency for Healthcare Research and Quality (AHRQ, formerly AHCPR). Depression Guideline Panel. *Depression in primary care: volume 1. Detection and diagnosis. Clinical practice guideline, number 5.* AHCPR Publication No. 93-0550. Rockville, MD, Agency for Health Care Policy and Research, 1993.

Alzheimer's Association. Leteprinim potassium (Neotrofin®) for treating Alzheimer's. http://www.alz.org/research/clintrials/neotrofin.htm. Accessed on June 25, 2002.

Alzheimer Research Forum. Drugs in clinical trials. www.alzforum.org Accessed on July 2, 2002.

American Cancer Society. Cancer facts & figures 2002. Atlanta, GA. American Cancer Society, 2002.

American Cancer Society. Cancer vaccines show continuing improvement. May 16, 2001. http://www.cancer.org. Accessed on June 25, 2002.

American Heart Association. 2002 heart and stroke statistical update. Dallas, TX, American Heart Association. 2001.

Andersson KE, Chapple CR, Hofner K. Future drugs for the treatment of benign prostatic hyperplasia. World Journal of Urology. 19(6), 436-442, 2002.

Bellosta S, Ferri N, Bernini F, et al. Non-lipid-related effects of statins. Annals of Medicine. 32(3), 164-76, 2000.

Birkett D, Mitchell A, and McManus P. A cost-effectiveness approach to drug subsidy and pricing in Australia. Health Affairs. 20(3), 104-114, 2001.

Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. New England Journal of Medicine. 343(21), 1520-1528, November 2000.

Boskey AL. Musculoskeletal disorders and orthopedic conditions. Journal of the American Medical Association. 285(5), 619-623, 2001.

British National Formulary (BNF). www.bnf.org. Accessed July 9, 2002.

Bumol TF, Watanabe AM. Genetic information, genomic technologies, and the future of drug discovery. Journal of the American Medical Association. 285(5), 551-555, 2001.

Burt C. National trends in the use of medications in office-based practice, 1985-1999. Health Affairs. 21(4), 206-214, July/August 2002.

Calfee, J.E. The unintended consequences of price controls. American Enterprise Institute website. www.aei.org/ra/racalfee3.htm. Accessed July 1, 2002.

Centers for Disease Control and Prevention. Healthy aging: preventing disease and improving quality of life among older Americans. www.cdc.gov/nccdphp/aag-aging.htm. Accessed on June 24, 2002.

Centers for Disease Control and Prevention. Morbidity and mortality weekly report: surveillance for asthma—United States, 1980-1999. March 29, 2002.

Centers for Disease Control and Prevention, National Center for Health Statistics. Trends in causes of death among the elderly. Aging Trends No.1. Atlanta, GA, March 2001.

Center for Disease Control and Prevention, National Center for Health Statistics. New asthma estimates: tracking prevalence, health care, and mortality. October 5, 2001. www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm. Accessed on July 1, 2002.

Center for Disease Control and Prevention, National Center for Health Statistics. Summary health statistics for U.S. Adults: National Health Interview Survey, 1997. CDC, Department of Health and Human Services. May 2002.

Centers for Disease Control and Prevention. Preventing heart disease and stroke: addressing the nation's leading killers. http://www.cdc.gov/nccdphp/cvdaag.htm. Accessed on June 24, 2002.

Centers for Disease Control and Prevention. Arthritis: the nation's leading cause of disability. http://www.cdc.gov/nccdphp/arthritis. Accessed on June 24, 2002.

Centers for Disease Control and Prevention. Diabetes: disabling, deadly, and on the rise. http://www.cdc.gov/diabetes/pubs/glance.htm. Accessed on June 24, 2002.

Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Preventing the diseases of aging. Chronic Disease Notes & Reports. 12(3),1999.

Chiasson J-L, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. Lancet. 359, 2072-2077, 2002.

Crystal RG. Research opportunities and advances in lung disease. Journal of the American Medical Association. 285(5), 612-618, 2001.

Cutler DM, McClellan M. Is technological change in medicine worth it? The Value of Rx Innovation: A Primer. Health Affairs. Pages 1-19, 2001.

Davidson, S. Quicker drug approvals on the way for Europe. Nature Biotechnology. Nature Publishing Group. 10, 798-799, September 2001.

de Grooth GJ, Kuivenhoven JA, Stalenhoef AF, et al. Efficacy and safety of a novel cholesteryl ester transfer protein inhibitor, JTT-705, in humans: a randomized phase II dose-response study. Circulation. 105(18), 2159-65, 2002.

Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New England Journal of Medicine. 346(6), 393-403, 2002.

Dykes, L. Why price controls are the wrong prescription. Pacific Research Institute. June 13, 2001. www.pacificresearch.org/pub/act/2001/act_01-06-13a.html. Accessed July 1, 2002.

Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Journal of the American Medical Association. 282(22), 2124, 1999.

Europe Economics. Access to important new medicines: where and why do patients wait? Europe Economics. London, UK. 2000.

European Commission. High level group on innovation and provision of medicines: recommendations for action. European Communities. Brussels, Belgium. May 7, 2002.

Evenson B. Health Canada finally approves lymphoma drug: Rituxan an effective anti-cancer agent with few side-effects. National Post. April 5, 2000.

Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. Neurology. 50(4), 883, 1998.

Federal Interagency Forum on Aging-Related Statistics. Older Americans 2000: key indicators of well-being. Federal Interagency Forum on Aging-Related Statistics. Washington, DC, US Government Printing Office, 2000.

Freedman VA, Aykan H, Martin, LG. Another look at aggregate changes in severe cognitive impairment. Journal of Gerontology. Series B, Psychological Sciences and Social Sciences. 56(2), S100-11, 2002.

Freedman VA, Martin, LG. Contribution of chronic conditions to aggregate changes in old-age functioning. American Journal of Public Health. 90(11), 1755-60, 2000.

Freedman VA, Martin, LG. Understanding trends in functional limitations among older Americans. American Journal of Public Health. 88(10), 1457-62, 1998.

Fuhrmans V, Naik G. In Europe, drug makers fight against mandatory price cuts. The Wall Street Journal. June 7, 2002.

Gambardella A, Orsenigo L, Pammolli F. Global competativeness in pharmaceuticals, a European perspective. Report prepared for Enterprise Directorate-General of the European Commission. European Communities. 2001.

Gawchik SM, Saccar CL. Role of antileukotriene agents in asthma therapy. Journal of the American Osteopathic Association. 100(1), 32, 37-43, January 2000.

Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. New England Journal of Medicine. 346(4), 257-268, 2002.

Golan L, Birkmeyer JD, Welch HG. The cost-effectiveness of treating all patients with type 2 diabetes with Angiotensin-converting enzyme inhibitors. Annals of Internal Medicine. 131(9), 660-667, 1999.

Hansel TT, Barnes PJ. Novel drugs for treating asthma. Current Allergy and Asthma Reports. 1(2), 164-173, 2001.

Hawkes N. Patients are denied life-saving cancer drug. London Times. May 28, 2002.

Health Canada Online. Drug product database. www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/dpd.html. Accessed on July 9, 2002.

Hoyert DL, Kochanek KD, Murphy SL. Deaths: final data for 1997. National Vital Statistics Report, 47(19). DHHS Publication No. 99-1120. Hyattsville, MD: National Center for Health Statistics, 1999.

Koopman WJ. Prospects for autoimmune disease: research advances in rheumatoid arthritis. Journal of the American Medical Association . 285(5), 648-650, 2001.

Kremer, M. Creating markets for new vaccines part II: design issues. NBER working paper 7717. National Bureau of Economic Research. Cambridge, MA. May 2000.

Kshirsagar AV, Joy MS, Hogan SL, et al. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. American Journal of Kidney Disease. 35(4), 297-307, 2000.

Lawrence, F. The battle over immunization. The Guardian. London, U.K. http://www.guardian.co.uk/medicalscience/story/0,1129,541949,00.html. Accessed July 2, 2002.

Lefkowitz RJ, Willerson JT. Prospects for cardiovascular research. Journal of the American Medical Association. 285(5), 581-587, 2001.

Leitersdorf E. Selective cholesterol absorption inhibition: a novel strategy in lipid-lowering management. International Journal of Clinical Practice. 56(2), 116-119, March 2002.

Lewin Group. The impact of the Canadian system on access to new medical technology including prescription drugs. The Lewin Group. March 7, 2000.

Lichtenberg FR, Are the benefits of newer drugs worth their costs? Evidence from the 1996 MEPS. The Value of Rx Innovation: A Primer. Health Affairs, pages 21-31. 2001.

Lipworth BJ. Leukotriene-receptor antagonists. Lancet. 353(9146), 57-62, 1999.

Livingston DM, Shivdasani R. Toward mechanism-based cancer care. Journal of the American Medical Association . 285(5), 588-593, 2001.

Margolin K. Inhibition of vascular endothelial growth factor in the treatment of solid tumors. Current Oncology Reports. 4(1), 20-8, 2001.

McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. New England Journal of Medicine. 344(5), 333-340, 2001.

Merck & Co. E-mail communication to the Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services. June 28, 2002.

Mulrow CD, Williams JW Jr., Trivedi M, et al. Evidence report on treatment of depression-newer pharmacotherapies. Psychopharmacology Bulletin. 34(4), 409-795, 1998.

Murray CJL, Lopez AD, eds. Summary: the global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge, MA; published by the Harvard School of Public Health on behalf of the World Health Organization and the World Bank, Harvard University Press, 1996.

Narrow WE. One-year prevalence of depressive disorders among adults 18 and over in the U.S.: NIMH ECA prospective data. Population estimates based on U.S. Census estimated residential population age 18 and over on July 1, 1998. Unpublished. Accessed on June 24, 2002. http://www.nimh.nih.gov/pubicat/elderydepsuicide.cfm.

National Institute for Clinical Excellence. (NICE) Press releases. www.nice.org.uk. Accessed on July 9, 2002.

National Institutes of Health. Medications under development for the treatment of seniors. E-mail communication. June 27, 2002.

National Institutes of Health. New agents in development. E-mail communication. July 2, 2002.

National Institutes of Health, National Library of Medicine. Cholesterol. Medline Plus Health Information Database. www.nih.nlm/medlineplus/ Accessed on June 24, 2002.

National Institutes of Health, National Heart, Lung and Blood Institute. Cholesterol Lowering Medicines. http://rover.nhlbi.nih.gov/chd/meds.htm Accessed on June 24, 2002.

National Institutes of Health, National Cancer Institute. Annual report shows overall decline in U.S. cancer death rates; cancer burden is expected to rise with an aging population. May 14, 2002. http://newscenter.cancer.gov/pressreleases/2002reportnation.html. Accessed June 24, 2002.

National Institutes of Health, NIDDK. Prostatic enlargement: benign prostatic hyperplasia. www.niddk.nih.gov/health/urolog/pubs/prostate/index.htm. Accessed on July 1, 2002.

National Institutes of Health, National Institute of Neurological Disorders and Stroke. Headache—hope through research. www.ninds.nih.gov/health_and_medical/pubs/headache_htr.htm?format=printable. Accessed July 1, 2002.

National Institutes of Health, National Institute of Neurological Disorders and Stroke. Migraine update. www.ninds.nih.gov/health_and_medical/pubs/migraineupdate.htm?format=printable. Accessed July 1, 2002.

National Institutes of Health, National Institute of Neurological Disorders and Stroke t-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. New England Journal of Medicine. 333(24), 1581-1587, 1995.

National Institutes of Health, National Library of Medicine. Diabetes mellitus, non-insulin-dependent. http://www.clinicaltrials.gov. Accessed on June 25, 2002.

National Institutes of Health. Osteoporosis and Related Bone Diseases, National Resource Center. Osteoporosis overview. http://www.osteo.org/osteo.html. Accessed on June 24, 2002.

National Institutes of Health, National Library of Medicine, National Institute of Diabetes and Digestive and Kidney Disease. Clinical alert: diet and exercise dramatically delay type 2 diabetes; diabetes medication metformin also effective. August 8, 2001. http://www.nlm.nih.gov/databases/alerts/diabetes01.html. Accessed on June 24, 2002.

National Osteoporosis Foundation. Patient Info: medications and osteoporosis. http://www.nof.org/patientinfo/medications.htm. Accessed on June 24, 2002.

Neumann PJ, Sandberg EI, Bell CM, et al. Are pharmaceuticals cost effective? A review of the evidence. Health Affairs. 19(2),92-109, 2001.

New Zealand Guidelines Group. Guidelines for the support and management of people with dementia: cognition of enhancing drug treatments in dementia. Enigma Publishing Limited. 2002. http://www.nzgg.org.nz/library/gl_complete/dementia/treatment.cfm. Accessed July 9, 2002.

Olefsky JM. Prospects for research in diabetes mellitus. Journal of the American Medical Association. 285(5), 628-632, 2001.

Ontario Ministry of Health and Long Term Care. Ontario drug benefit formulary, number 37. March 7, 2001. www.gov.on.ca/health/english/program/drugs/obdf_mn.html. Accessed on July 9, 2002.

Pacher P, Kohogyi E, Kecskemeti V, et al. Current trends in the development of new antidepressants. Current Medicinal Chemistry. 8,89-100, 2001.

Paget SA. Efficacy of anakinra in bone: comparison to other biologics. Advances in Therapy. 19(1), 27-39, 2002.

Parving HH, Hovind P, Rossing K, et al. Evolving strategies for renoprotection: diabetic nephropathy. Current Opinion Nephrology and Hypertension. 10(4), 515-522, 2001.

Pharmaceutical Management Agency (PHARMAC). New Zealand pharmaceutical schedule. www.pharmac.govt.nz. Accessed on July 9, 2002.

Pharmaceutical Research and Manufacturers of America (PhRMA). 2002 Survey: new medicines in development for older Americans. www.phrma.org. Accessed July 9, 2002.

Pharmaceutical Research and Manufacturers of America (PhRMA). Online clinical trials database, respiratory disorders, asthma. www.phrma.org. Accessed July 2, 2002.

Pharmaceutical Research and Manufacturers of America (PhRMA). New medicines in development for neurologic disorders. www.phrma.org. Accessed July 2, 2002.

Pharmaceutical Research and Manufacturers of America (PhRMA). Selected medicines in development for heart disease and stroke. January 2002. www.phrma.org. Accessed June 24, 2002.

Pharmaceutical Research and Manufacturers of America (PhRMA). Selected drugs in development for cancer. January 2002. www.phrma.org. Accessed June 24, 2002.

Quebec Prescription Drug Insurance Plan. List of medications. www.ramq.gouv.qc.ca/crc/eng/cit/assmed/cond.shtml. Accessed on July 9, 2002.

Sabatine MS, Jang I-K. The use of glycoprotein IIb/IIIa inhibitors in patients with coronary artery disease. American Journal of Medicine. 109, 224-237, 2000.

Sherman DG, Atkinson RP, Chippendale T, et al. Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. Stroke Treatment with Ancrod Trial. Journal of the American Medical Association. 283(18), 2395-403, 2000.

Sliverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. Journal of the American Medical Association. 284(10), 1247-55, September 2000.

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. New England Journal of Medicine. 344(11), 783-792, 2001.

Swislocki AL, Siegel D. Renal effects of Angiotensin-converting enzyme inhibitors that result in cost savings and improved patient outcomes. American Journal Managed Care. 7(3), 283-295, 2001.

Szelenyi I. Asthma therapy in the new millennium. Inflammation Research. 51(6),273-282, 2002.

Tajima O. Mental health care in Japan: recognition and treatment of depression and anxiety disorders. Journal of Clinical Psychiatry. 62(suppl 13), 39-44, 2001.

Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus. Journal of the American Medical Association. 280(17), 1490-1496, 1998.

Tobias JH, Flanagan AM, Scutt AM, Novel therapeutic targets in osteoporosis. Expert Opinion on Therapeutic Targets. 6(1),41-56, 2002.

Tufts Center for the Study of Drug Development. How new drugs move through the development and approval process. 2001. http://www.csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=4. Accessed June 28, 2002.

United Nations. World population aging: 1950-2050. United Nations. New York, NY. 2002.

United Press International. 'Breakthrough' diabetes drug tested. June 18, 2002. http://www.nlm.nih.gov/medlineplus/news/fullstory_8144.html. Accessed on June 24, 2002.

United States International Trade Commission. Pricing of Prescription Drugs. United States International Trade Commission. Publication 3333. December 2000.

University of Washington School of Medicine. OsteoEd website http://osteoed.org/cases/overview.html. Accessed on June 27, 2002.

Walker, M. Wilson, G. Waiting your turn: hospital waiting lists in Canada. Fraser Institute. Eleventh edition. September 2001.

Wall Street Journal. Cancer-gene drugs flourish, yielding hope, but no quick fix. May 16, 2002.

Weinstein JN. Pharmacogenomics – teaching old drugs new tricks. New England Journal of Medicine. 343(19), 1408-1409, 2000.

World Intellectual Property Organization (WIPO). Discussion paper. Policy Advisory Task Force Meeting. Beijing, China. May 22, 2002.

Appendix
Selected FDA Approved Drugs and Biologics with Restricted Access in Other Countries

Appendix
Selected FDA Approved Drugs and Biologics with Restricted Access in Other Countries

Indication	Product	Market*	Nature of Government Plan Restriction**	Comment
Acne	Azelaic acid (Azelex)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 9/13/95)
Alzheimer's	Donepezil (Aricept)	Ontario, Canada	Restricted Coverage	Coverage is restricted to patients who have mild to moderate Alzheimer's and have demonstrated benefit after 3 months of treatment.
		Quebec, Canada	Not Covered	Not listed on Quebec's prescription drug formulary.
		New Zealand	Not Covered	Not approved for coverage by PHARMAC of New Zealand.
Allergies	Azelastine (Astelin)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 11/1/96)
	Pemirolast (Alamast)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 9/24/99)
Amyotrophic Lateral Sclerosis	Riluzole (Rilutek)	Canada	Not Covered	Riluzole has not been approved for use in Canada.[1]
Arthritis/Pain	Celecoxib (Celebrex)	Ontario, Canada	Restricted Coverage	Coverage is restricted to patients with arthritis who have failed an adequate trial of other pain medications and have a history of ulcer or gastro-intestinal bleeding.
		New Zealand	Not Covered	Not covered for use by PHARMAC of New Zealand.
	Etanercept (Enbrel)	Britain	Restricted Coverage	Britain's National Health Service (NHS) covers etanercept only as a second line therapy for children aged 4-17 with non-responsive arthritis in at least 5 joints and in adults with active rheumatoid arthritis who are nonresponsive to other medications.
		Japan	Not Approved	Not approved for use in Japan.
		Ontario, Canada	Not Covered	Not listed on Ontario's prescription drug formulary.
		New Zealand	Not Covered	Not covered for use by PHARMAC of New Zealand.
	Infliximab (Remicade)	Britain	Restricted Coverage	Britain's NHS covers infliximab only as a second line therapy in combination with methotrexate for adults with active rheumatoid arthritis who are not responsive to other medications.
		Ontario, Canada	Not Covered	Not listed on Ontario's prescription drug formulary.
		New Zealand	Not Covered	Not covered for use by PHARMAC of New Zealand.

[1] ALS Society of Canada. Drug Trials. www.als.ca/manual-whatisals-drugtrials.shtml Accessed on July 8, 2002.

* This table is not intended to be a comprehensive list of markets where access to selected medications is limited. There may be additional countries/markets that restrict access to the medications listed.

** Sources include government websites, reports in news media, communications with pharmaceutical manufacturers, peer-reviewed literature and other sources. See the final page of the appendix for a list of government websites used as source material. Not all examples have been independently verified for all countries listed.

Indication	Product	Market	Nature of Government Plan Restriction	Comment
	Rofecoxib (Vioxx)	New Zealand	Not Covered	Available since March 2000, but not approved for coverage by PHARMAC.
		Australia	Restricted Coverage	Coverage is restricted to symptomatic treatment of patients with osteoarthritis
		British Columbia, Canada	Restricted Coverage	Coverage is restricted to patients who have failed to benefit from acetaminophen and at least three other funded non-steroidal anti-inflammatory drugs (NSAIDs).
		New Brunswick and Saskatchewan, Canada	Restricted Coverage	Coverage is restricted to patients who meet one of the following criteria: age 65+, past history of ulcers, concurrent warfarin therapy, concurrent prednisone therapy, or failure or intolerance to at least two other NSAIDs.
		Ontario, Canada	Restricted Coverage	Coverage is restricted to a maximum daily dose of 25 mg for the treatment of osteoarthritis. Prior therapy with acetaminophen for several weeks must have failed, and the patient must have a history of documented clinically significant ulcer or GI bleed, or failure or intolerance to at least three NSAIDs.
	Tramadol (Ultram)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 3/3/95)
Asthma	Montelukast (Singulair)	New Zealand	Not Covered	Available since 1998, but not covered.
		Australia	Not Covered	Currently not covered, but negotiations for listing are on-going.
		Belgium	Not Covered	Available, but not covered.
		Finland	Not Covered	Pediatric strengths are available, but not covered.
		British Columbia, Canada	Not Covered	Coverage was restricted in 1999 and discontinued in 2001
		Newfoundland, Canada	Restricted Coverage	Coverage is restricted to patients uncontrolled on therapeutic doses of inhaled corticosteroids who have failed to respond to or have a contraindication to zafirlukast.
		Nova Scotia, Canada	Restricted Coverage	Coverage is restricted to 4 and 5 mg chewable format for patients younger than 12.
		Ontario and New Brunswick, Canada	Not Covered	Available, but not covered. Not listed on formulary.
		Prince Edward Island, Canada	Restricted Coverage	Coverage is restricted to patients on concurrent steroid therapy or patients not well controlled with inhaled corticosteroids.
		Saskatchewan, Canada	Restricted Coverage	Coverage is restricted to patients with Special Authorization for adjunctive treatment of asthma who are not well controlled with inhaled corticosteroids.
	Zileuton (Zyflo)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 12/9/96)

Indication	Product	Market	Nature of Government Plan Restriction	Comment
Benign Prostatic Hyperplasia	Finasteride (Proscar)	New Zealand	Not Covered	Available, but not listed on formulary. (FDA approved 3/20/98)
		Ontario, Canada	Not Covered	Not listed on Ontario's prescription drug formulary.
Cancer	Bexarotene (Targretin)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 12/29/99)
		Japan	Not Approved	Not approved for use in Japan.
		New Zealand	Not Approved	Not approved for use by Medsafe of New Zealand. (FDA approved 12/29/99)
	Imatinib (Gleevec or Glivec)	Britain	Restricted Coverage	In a preliminary assessment of imatinib prepared for Britain's National Institute for Clinical Excellence (NICE), it is recommended that imatinib only be used for treatment of accelerated phase of chronic myeloid leukemia and not for the routine treatment of the chronic or blast crisis stages. This is a preliminary recommendation that has not yet been finalized.
		New Zealand	Not Covered	Not covered for use by PHARMAC of New Zealand.
	Interlukin-2	Canada	Restricted Coverage	Interlukin-2 is generally not covered in Canada for treatment of metastatic kidney cancer.[2]
	Irinotecan (Camptosar)	Britain	Restricted Coverage	Britain's NHS restricts irinotecan coverage, either alone or in combination, as a first-line treatment for colorectal cancer. Reimbursement for this drug is permitted if other treatments fail.
		New Zealand	Not Covered	Available, but not covered.[3]
	Oxaliplatin (Eloxatin)	Britain	Restricted Coverage	Britain's NHS restricts coverage for oxaliplatin as a first-line treatment for colorectal cancer, except in patients whose cancer has spread to the liver and may become operable with treatment. Reimbursement for this drug is permitted if other treatments fail.
	Rituximab (Rituxan)	Britain	Restricted Coverage	Britain's NHS restricts coverage of rituximab to last-line treatment for stage 3 or 4 non-Hodgkin's lymphoma. Reimbursement for rituximab is permitted only after conventional chemotherapy agents have failed.
		Ontario, Canada	Not Covered	Not listed on Ontario's drug formulary.
		New Zealand	Not Covered	Not covered for use by PHARMAC of New Zealand.
	Tratuzumab (Herceptin)	Britain	Restricted Coverage	Britain's NHS restricts coverage of tratuzumab to women with advanced HER2 positive breast cancer who meet specific clinical criteria.
	Raltitrexed (Tomudex)	Britain	Not Covered	Britain's NHS restricts does not cover raltitrexed for use outside of appropriately designed clinical studies.

[2] Cancer Guide. Steve Dunn's Kidney Cancer Page. www.cancerguide.org/kidney.html Accessed on July 8, 2002.
[3] The Daily News (New Plymouth). Society outraged at cancer drug funding. May 19, 2001.

Indication	Product	Market	Nature of Government Plan Restriction	Comment
Cancer Continued...	Other new cancer drugs	Austrailia	Delays in Approval	In Austrailia, cancer treatment drugs take 3.5 times as long to approve as anti-HIV therapies. The Therapeutic Goods Administration (TGA) is markedly slower than the U.S. FDA in getting both groups of medications on the market.[4]
		New Zealand	Not Covered	In four of New Zealand's six regional cancer centers, patients have been denied access to new cancer treatments due to lack of funding in the regional health care system.[5]
Crohn's Disease	Infliximab (Remicade)	Japan	Unavailable	
Cushing's Syndrome	Corticorelin (Acthrel)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 5/23/96)
Depression	Bupropion (Wellbutrin)	Canada	Restricted Coverage	Covered as a limited use benefit only in patients who are unresponsive to other antidepressants under Health Canada's Non-Insured Health Benefits Program.
	Fluvoxamine (Luvox)	New Zealand	Not Covered	Not approved for coverage by PHARMAC of New Zealand.
	All SSRI's	Japan	Delays in Approval	The first SSRI marketed in Japan, fluvoxamine, was launched in 1999.[6] SSRI's were first approved for sale by the FDA in 1987.
Diabetes	Rosiglitazone (Avandia)	Ontario, Canada	Not Covered	Not listed on Ontario's prescription drug formulary.
		New Zealand	Not Covered	Not approved for coverage by PHARMAC of New Zealand.
End Stage Renal Disease (ESRD)	Selvamer (Renagel)	Japan	Not Approved	Not approved for use in Japan
		New Zealand	Not Approved	Not approved for use by Medsafe of New Zealand. (FDA approved 11/2/98)
Fetal Respiratory Distress	Poractant Alpha (Curosurf)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 11/18/99)
GI and Ulcer	Amlexanax (Aphthasol)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 12/17/96)
	Omeprazole (Prilosec)	Canada	Restricted Coverage	Implementation of resource based pricing caused physicians to replace omeprazole with cimetidine, which is less effective in preventing gastric bleeding

[4] The Mercury Hobart. Alarm at cancer drug lag. December 2, 2000.
[5] The Dominion (Wellington). Cancer patients miss out on new drugs. May 12, 2001.
[6] Tajima O. Mental health care in Japan: recognition and treatment of depression and anxiety disorders. Journal of Clinical Psychiatry. 62(suppl 13), 39-44, 2001.

Indication	Product	Market	Nature of Government Plan Restriction	Comment
GI and Ulcer Continued...	Rabeprazole (Aciphex)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 8/19/99)
High Cholesterol	Simvastatin (Zocor)	New Zealand	Restricted Coverage prior to Feb. 2001	Until the expiration of simvastatin's patent, coverage for simvastatin was restricted to patients with a >20%, 5-year risk of cardiovascular disease who met minimum cholesterol thresholds.
		Australia	Restricted Coverage	Coverage restrictions are complex, including the failure of 6 weeks prior dietary therapy.
	Atorvastatin (Lipitor)	New Zealand	Restricted Coverage	As of July 1, 2002, coverage of lipitor is restricted to patients who receive special authority approval from the government. Patients who have not approved special authority must switch to an alternate statin.
	Lovastatin (Mevacor)	New Zealand	Not Covered	Not covered for use by PHARMAC of New Zealand.
	Pravastatin (Pravachol)	New Zealand	Not Covered	Not covered for use by PHARMAC of New Zealand.
Hyperpara-thyroidism	Paricalcitol (Zemplar)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 4/17/98)
Hypertension	Fenoldopam (Corlopam)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 9/23/97)
	Losartan Potassium (Cozaar)	New Zealand	Restricted Coverage	Only specialists (cardiologists) can initiate therapy, and then only if the patient suffers from congestive heart failure and treatment attempts with at least two types of ACE inhibitors have not been tolerated.
		Australia	Not Covered	The product was covered approximately 6 years ago, but the government instituted a reference price/reimbursement limit that was commercially unacceptable. It is no longer offered on the market.
		Canada (British Columbia, Ontario, New Brunswick, Newfoundland)	Restricted Coverage	Generally restricted to patients who cannot tolerate ACE inhibitors.
	Losartan Potassium/ hydrochloro-thiazide (Hyzaar)	British Columbia, Canada	Restricted Coverage	Coverage is restricted to patients who have experienced a cough with ACE inhibitors and also require a diuretic.
		New Brunswick, and Newfoundland, Canada	Restricted Coverage	A "special authorization" may be considered if the doctor justifies the need. There are no published criteria.

Indication	Product	Market	Nature of Government Plan Restriction	Comment
Hypertension Continued...	Losartan Potassium/ hydrochloro-thiazide (Hyzaar) Continued...	Ontario, Canada	Restricted Coverage	Coverage is restricted to patients who cannot tolerate beta-blockers or in whom beta-blockers and diuretics alone are not effective; and who have experienced adverse effects with ACE inhibitors, and who require the addition of a diuretic to achieve adequate hypertension control.
	Moexipril (Univasc)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 4/19/95)
	Nisoldipine (Sular)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 2/2/95)
	Valsartan (Diovan)	Ontario, Canada	Restricted Coverage	Restricted to patients who cannot tolerate diuretics, beta-blockers, and ACE inhibitors.
		New Zealand	Not Covered	Not approved for coverage by PHARMAC of New Zealand.
	Enalapril mal-eate/HCTZ (Vaseretic)	British Columbia, Canada	Restricted Coverage	Coverage is listed as a “partial benefit” under Pharmacare’s Reference Drug Pricing (RDP) program.
Infectious Disease	Albendazole (Albenza)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 6/11/96)
	Ivermectin (Stromectol)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 11/22/96)
	Rifapentine (Priftin)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 6/22/98)
Insomnia	Zaleplon (Sonata)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 8/13/99)
Eye Disorders	Dorzolamide (Trusopt)	New Zealand	Restricted Coverage	Specialist required to initiate therapy, and restricted only to patients with primary open-angle glaucoma with very high intra-ocular pressure that cannot be controlled using other therapies.
	Loteprednol (Lotemax)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 3/9/98)
Migraine Headache	Rizatriptan (Maxalt)	New Zealand	Not Covered	Available since 1999, but not approved for use by PHARMAC.
		Australia	Not Covered	Not available.
		Belgium	Not Covered	Available, but not covered.
		France	Not Covered	Not available.
		Portugal	Not Covered	Available, but without reimbursement.
		Alberta, Canada	Restricted Coverage	Coverage is restricted to patients 18-24 years of age for treatment of acute migraine attacks where standard therapy has failed. Special authorization is required for treatment of acute migraine attacks in patients 65+ where standard therapy has failed and for those who were using Maxalt prior to turning 65.

Indication	Product	Market	Nature of Government Plan Restriction	Comment
Migraine Headache Continued...	Rizatriptan (Maxalt) Continued...	Nova Scotia, Canada	Restricted Coverage	Coverage is restricted to patients experiencing moderate migraines (if other therapies have not been effective) or severe migraines.
		Ontario, Canada	Not Covered	Not listed on Ontario's prescription drug formulary.
		Saskatchewan, Canada	Restricted Coverage	Coverage is restricted to patients when other standard therapies, such as analgesics and/or ergotamine, have failed. Eligibility is restricted to beneficiaries 18-65 years of age.
Multiple Sclerosis (MS)	$-Interferon (Avonex, Betaseron) Glatiramer acetate (Copaxone)	Britain	Not Covered	Britain's NHS does not cover $-Interferon and glatiramer acetate for the treatment of MS.
Osteoporosis	Alendronate (Fosamax)	New Zealand	Restricted Coverage	Only specialists can initiate this therapy, and then only if the patient has suffered one previous, significant osteoporotic vertebral or hip fracture (radiologically demonstrated).
		Australia	Restricted Coverage	Coverage is restricted to patients who have sustained a fracture due to minimal trauma and established the existence of osteoporosis.
		Belgium	Restricted Coverage	Coverage is restricted to patients with fracture or low bone density.
		France	Restricted Coverage	Coverage is restricted to patients with fracture.
		Italy	Restricted Coverage	Coverage is restricted to patients with vertebral or hip fracture.
		Alberta, Canada	Restricted Coverage	Coverage is restricted to patients with vertebral of other fractures. Special authorization is granted for 24 months.
		British Columbia, Canada	Restricted Coverage	Coverage is restricted to patients who have fractures due to osteoporosis, and an adequate trial of etidronate (at least one year) that has failed to prevent fractures.
		Newfoundland, Canada	Restricted Coverage	Coverage is restricted to patients with low bone mass or fractures, or women who have failed or are intolerant to hormone replacement therapy (HRT).
		Nova Scotia, Canada	Restricted Coverage	Coverage is restricted to patients who have a fracture, and have failed HRT. Other restrictions also apply.
		Ontario, Canada	Restricted Coverage	Coverage is restricted to postmenopausal women who have failed to respond to etidronate or experienced fracture during etidronate therapy
		Saskatchewan, Canada	Restricted Coverage	Coverage is restricted to patients who have not responded to etidtronate or didrocal and have new fractures or Paget's disease.
	Raloxifene (Evistia)	Ontario, Canada	Restricted Coverage	Coverage is restricted to patients who have failed to respond to etidronate or experienced a new fracture
		Quebec, Canada	Not Covered	Not listed on Quebec's prescription drug formulary
		New Zealand	Not Covered	Not covered for use by PHARMAC of New Zealand

Indication	Product	Market	Nature of Government Plan Restriction	Comment
Reproductive Health	Ganirelix Acetate (Antagon)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 7/29/99)
Seizures	Levetirace-tam (Keppra)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 11/30/99)
	Tiagabine (Gabitril)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 9/30/97)
Vascular Disease	Cilostazol (Pletal)	Canada	Not Approved	Not approved for use by Health Canada. (FDA approved 1/15/99)

Sources:

Canada

Health Canada. Non-insured Health Benefits Drug Benefit List. www.hc-sc.gc.ca/fnihb/nihb/index.htm Accessed on July 9, 2002.

Health Canada Online. Drug Product Database. www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/dpd.html Accessed on July 9, 2002.

Ontario Ministry of Health and Long Term Care. Ontario Drug Benefit Formulary, Number 37. March 7, 2001. www.gov.on.ca/health/english/program/drugs/odbf/odbf_mn.html Accessed on July 9, 2002.

Quebec Prescription Drug Insurance Plan. List of Medications. www.ramq.gouv.qc.ca/crc/eng/cit/assmed/cond.shtml Accessed on July 9, 2002.

Great Britain

British National Formulary (BNF). www.bnf.org Accessed on July 9, 2002.

National Institute for Clinical Excellence. Press Releases. www.nice.org.uk Accessed on July 9, 2002.

New Zealand

Medsafe. Consumer Medical Information. www.medsafe.govt.nz Accessed on July 9, 2002.

Pharmaceutical Management Agency (PHARMAC). New Zealand Pharmaceutical Schedule. www.pharmac.govt.nz Accessed on July 9, 2002.

United States

Food and Drug Administration (FDA). www.fda.gov Accessed on July 9, 2002.