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## 1.22 Bioethical Issues in Medicinal Chemistry and Drug Treatment

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## 1.22.1 Introduction

### 1.22.1.1 Bioethics

The discipline known as bioethics is the modern manifestation of the venerable field of medical ethics. Bioethics includes the categories traditionally known as medical ethics – the proper way to treat patients, ethical principles around death and dying, abortion, euthanasia, confidentiality, and so on. One characteristic that distinguishes bioethics from its forbearers, however, is the attention it pays to biotechnological solutions for health problems. From genetic medicine, stem cells, and biologics to brain imaging, artificial hearts, and other biomechanical treatments, bioethics grapples with the impact of our extraordinary technological virtuosity on the human body.

The field of bioethics is intrinsically interdisciplinary. Philosophers, social scientists, theologians, historians, and other disciplinary academics interact with lawyers, physicians, biologists, chemists, and other clinicians and scientists to try to understand the implications of biotechnological advances and to establish ethical guidelines that will inform treatment. Given the diversity of values in our pluralistic society, the ethical complexity of the issues, and the very different religious approaches to medicine and the body that are represented in Western Society, it is not surprising that there are many bioethical challenges where there is sharp disagreement over the proper ethical course.

The degree of disagreement should not be overestimated, however. Despite media and professional attention to the disputes – that is where the action is, after all – there is overall consensus on a surprisingly large number of ethical principles. The right of individuals to have autonomy over their bodies except under specific circumstances, such as incompetence or gross self-mutilation, the importance of informed consent, the fiduciary responsibility of clinicians to their patients, the corrupting effects of monetary inducements on clinicians to promote particular treatments, the nature of individual and institutional conflicts of interest, pursuit of equity and justice in access to treatment, and many other principles have been agreed upon, and their specifics have generally been worked out, even if they are not always actualized in practice.

Of course, the use of drugs in treating illness has long been an activity with ethical implications. Even the earliest medical codes of ethics discussed the dispensing drugs as a primary topic for ethical guidance: in the Hippocratic Oath, for example, the clinician vows never to give a person a deadly drug, even if requested, and not to give a woman an abortive remedy. On the other hand, the way drugs were tested and administered before the twentieth century seems almost casual to our eyes today. Prior to the Pure Food and Drug Act of 1906, for example, there were no consumer regulations about drug development, few research subject protections, and no review bodies such as the Food and Drug Administration (FDA) or institutional review boards. The latter half of the twentieth century, in contrast, has been a time of rapid development of regulations and regulatory bodies to ensure that both clinical research and clinical care conform to ethical and safety standards. Some aspects of that development are surprisingly late: for example, the Common Rule, the set of regulations that covers ethical standards for using human beings as research subjects in all federally funded research, was not finally codified until 1991.

In this chapter, we will look at some of the important ethical implications of drug development and treatment.

### 1.22.1.2 The Ethics of Drug Treatment

Attempts to prevent illness, treat illness, or otherwise modify the functioning or malfunctioning of the human body through ingestion are as old as humanity. In fact, it is almost certainly older than humanity; animals regularly use targeted medicinal ingestion to treat or prevent symptoms.<sup>1</sup> Some scientists have even postulated a continuity between animal and human medicine.<sup>2</sup> Traditional human societies have sometimes astonishing sophistication in their knowledge of local plants, and have in many cases worked out multistep processing to prepare plants and herbs for ingestion to treat illnesses.<sup>3</sup> Medicinal preparation and ingestion is an ancient and integral part of human existence.

The fundamental ethical acceptability of treating human conditions with drugs has itself rarely been questioned. Insofar as opponents object to the use of drugs to treat disease it is usually from within a broader religious belief in the exclusive province of Divine healing (e.g., Christian Science) or it is targeted at a certain type or class of drugs (e.g., psychotropics). Some also question the increasing emphasis on drug use, especially in Western societies, over less costly, more benign, or more socially acceptable techniques or technologies for treatment. However, the prudent use of ingestible, bioactive substances is itself almost universally accepted as an ethical means to alleviate human disease and suffering.

While the use of drugs to treat the human condition is itself ethically acceptable, a variety of ethical challenges arise as we try to treat real people with our imperfect remedies. Drugs are powerful substances with a great capacity to cause harm if misused or overused. Even when used correctly, pharmaceuticals can elicit disputes about their relative harms and benefits in specific situations. The establishment of modern intermediaries – physicians or pharmacists – in the

allocation of the most powerful drugs increases the potential for conflict between those who control the resource and those who desire access to it. The size and influence of the pharmaceutical–industrial complex places disproportionate power in those whose interests lie in promoting and expanding pharmaceutical use in society. The expense of certain drugs complicates equitable allocation, and the concentration of pharmaceutical power in Western industrialized countries promotes research and drug discovery disproportionately for diseases that are prevalent in the wealthier nations. The increasing sophistication of drug action challenges the traditional model of using drugs as a means to treat pathological conditions and processes, and raises the specter of life style and enhancement uses of pharmaceuticals. New means of drug discovery, such as the use of stem cells, have elicited debate about the relative values placed on the status of the embryo and the potential treatments for intractable conditions that could result from stem cell research. Finally, the overall emphasis on drugs as the first line defense against what ails us has provoked some societal soul-searching: What messages do we want to send to ourselves and our children about how to solve problems and face difficulties in our lives?

Despite these concerns over drug use, Western industrialized nations are consuming pharmaceuticals at an unprecedented rate. The National Health and Nutrition Examination Survey found a 13% increase between 1988–1994 and 1999–2000 in the proportion of Americans taking at least one drug, and a 40% jump in the proportion taking three or more medicines. Forty-four percent reported taking at least one drug in the past month and 17% were taking three or more in the 2000 survey.<sup>4</sup> So, therein lies the paradox about ethical reflection on drug use: modern societies are taking more and more drugs even as they agonize over drug proliferation.

In this chapter we will explore a number of the more important ethical questions related to drug discovery, production, and distribution. Many of these topics are the subject of heated debate and disagreement. Thus, the goal is not so much to solve the ethical dilemmas they represent, or to provide a handbook of correct ethical action, but rather to clarify and illuminate the nature of these ethical concerns so that the reader can better reflect on his or her own values and judgments.

### 1.22.2 Safety

Drugs work by altering bodily function, which can lead to undesired results if they are taken inappropriately. A large number of drugs are toxic in nature, requiring careful dosing and monitoring when used therapeutically. Others have undesired effects if taken in the absence of a particular pathology or antigen. Safety issues include not only the side effects and toxicity of drugs, but adverse drug interactions, contraindications, off-label use, and black market trade in pharmaceuticals. It is also important to remember that in virtually every medical encounter, a value judgment is made about whether the side effects or toxicity of the treatment is outweighed by its positive therapeutic effects. Often, clinicians and patients differ about that value equation.

It is an ethical mandate that drugs be safe within the medical meaning of that term (i.e., if taken appropriately and with knowledge of possible side effects and toxicities). However, the standards for drug safety, the evaluation of drug safety, and the regulation of safe pharmaceutical development do not inherently raise ethical questions unless they violate some reasonable standard of ethical competence. A clear ethical issue does arise, however, in the attempt to avoid or minimize safety standards, especially in the pursuit of profits or market share. In a broader sense, there is also an ethical discussion to be had about taking the risk of ingesting drugs for life style or enhancement purposes, or under duress. Is it ethical to prescribe psychopharmaceuticals for people without diagnosed mental illness simply because they seek to alter their personality or sense of self?<sup>5</sup> Is it acceptable to make psychopharmaceutical treatment a condition of employment or release from jail? Is it ethical, for that matter, to mandate treatment for those facing trial or on death row in order to try them or to execute them?<sup>6</sup> Balancing the risk of life style pharmaceuticals with a growing consumer demand is one of the biggest ethical challenges of drug development in the coming decades (see Section 1.22.6.1).

Determining drug safety is complicated by the widespread off-label use of pharmaceuticals. Drugs developed and approved for a primary purpose are commonly used to treat other, sometimes unrelated, conditions.<sup>7</sup> For example, the American Pain Society, in their 1994 letter to the FDA, cited a number of drugs used for pain management in clinical practice that were not originally approved for that purpose such as antidepressants, anticonvulsants, corticosteroids, beta blockers, and amphetamines. While the FDA acknowledges the prevalence of such practices, their approach is generally to encourage the pharmaceutical industry to go through the proper channels of drug approval for new uses of drugs already approved for another purpose. It rarely happens that way, however, given the fact that these secondary applications of previously approved agents rarely have the ‘critical mass’ of potential patient volume to justify the time and expense for an additional FDA approval process.<sup>8</sup>

Recently, a number of high-profile cases have resulted in the removal of drugs from the market. Four examples are offered below, illustrating four different avenues whereby unsafe drugs come to be widely prescribed, but other

examples could be offered. In these four cases, safety became an ethical issue when: (1) marketing or hype overrode safety concerns, (2) studies that should have been conducted were resisted or deemed proprietary and, therefore, concealed from scrutiny, (3) drug combinations were used without proper precautions, and (4) faddish treatments were prescribed without proper empirical support. A fifth case is then offered, that of the use of antidepressant selective serotonin reuptake inhibitors (SSRIs) in adolescents, to illustrate the difficulties of determining when the safety concerns of a drug outweigh its benefits. The purpose of discussing these cases is not to condemn the pharmaceutical companies involved or to impugn their motives, but rather to illustrate that the significant investment put into producing and marketing a drug, the complex nature of verifying its safety, and the vagaries of prescribing drugs in a large medical system can lead to undesirable outcomes if the highest standards of safety are not upheld. Error should always be on the side of public safety.

### 1.22.2.1 Cyclooxygenase-2 (COX-2) Inhibitors and Drug Safety Regulation

For nearly 40 years, chronic pain was treated with nonsteroidal anti-inflammatory drugs (NSAIDs). However, this class of drugs caused gastrointestinal side effects. In 1987, the idea emerged that selective inhibitors of COX-2 could relieve inflammatory pain without gastrointestinal side effects. Two large studies of the concept were published in 2000, the Celecoxib Long-Term Arthritis Safety Study (CLASS) and the Vioxx Gastrointestinal Outcomes Research (VIGOR) study. CLASS did not show COX-2 inhibitors to have a gastrointestinal protective effect and researchers believed this was due to the continued use of low-dose aspirin in tested patients. VIGOR prohibited the use of low-dose aspirin, which did indeed reduce the incidence of gastrointestinal lesions, but a serious problem emerged. There was a fivefold higher incidence of myocardial infarction in the rofecoxib (Vioxx, Merck) group than in the group treated with naproxen,<sup>9</sup> an NSAID.

Researchers did not test a placebo group, so it was unclear to them whether this adverse cardiovascular side effect was due to an actual increase in cardiovascular risk associated with rofecoxib or a protective effect of naproxen. While scientists were not completely sure, evidence suggested early on that COX-2 inhibitors could induce adverse cardiovascular events by disrupting the balance between two fatty acids, prostacyclin and thromboxane, that work together to control blood clotting. Despite these early warning signs, no randomized, controlled trials were implemented to follow-up on the proposed question of cardiovascular toxicity.<sup>9</sup>

Concerns about Vioxx's cardiovascular effects were serious enough for the FDA to warrant labeling changes in 2002. Merck voluntarily withdrew Vioxx from the market in September 2004 after their adenomatous polyp prevention on VIOXX (APPROVe) trial revealed that groups assigned to 25 mg of Vioxx daily for more than 18 months had a fourfold greater incidence of serious cardiovascular events than the placebo group.<sup>10</sup> In September 2004, Merck sponsored a trial examining whether the pill could prevent precancerous colon tumors and instead found that Vioxx doubled the risk of heart attacks and stroke in patients using it for more than 18 months.<sup>11</sup>

Similarly, the National Cancer Institute halted a trial of celecoxib (Celebrex, Pfizer) when an independent panel of cardiovascular experts reviewed the data and found a greater risk of cardiovascular events in treated patients. In 2005, Pfizer published a study of cardiac surgery patients stating that participants taking valdecoxib (Bextra) reported nearly three times the rate of cardiovascular events compared with those on placebo.<sup>12</sup> Parecoxib also showed an increased incidence of cardiovascular events after 30 days among patients who had received a total of only 10 days of COX-2 inhibition.<sup>9</sup> Ultimately, the increased cardiovascular risk appeared to be a class effect. The concerns raised by these trials echoed the problems that arose over 5 years earlier.

An epidemiologist in the FDA's Office of Drug Safety, David Graham, was the first in the agency to indicate the possible cardiovascular risk of Vioxx. He conducted a study using the database of Kaiser Permanente and warned his bosses that high doses of Vioxx significantly increased the risk of heart attack and sudden death. In November 2004, Graham testified before a US Senate hearing that Vioxx had caused between 88 000 and 140 000 excess cases of serious coronary heart disease and at least 26 000 deaths from heart attacks in the US alone in the 5 years before Merck withdrew it from the market. By the time Vioxx was withdrawn, though, an estimated 80 million people had taken the drug worldwide.<sup>10</sup>

The problems associated with COX-2 inhibitors emphasized the difficulty in associating a drug directly with the increased risk of common health disorders. While it is much easier to track rare adverse drug reactions after a new drug is introduced into the market, identifying an increased incidence of common events such as heart attack and stroke proves to be more problematic, especially when an adverse event could stem from an underlying disease. Epidemiologic studies of cardiovascular events are often not clear, making it difficult to determine the true risk associated with a particular treatment.<sup>9</sup> In the end, it seems that harms are extremely difficult to anticipate or measure in extent until many patients have been exposed. The FDA relies largely on a reactive reporting system, where doctors report possible

cases of side effects that they believe to be associated with a drug. Thus, it is extremely difficult to detect dangerous side effects that already commonly occur in a population such as the heart attacks and strokes caused by COX-2 inhibitors.<sup>11</sup>

Monitoring the side effects of many types of drugs relies largely on pharmaco-epidemiological research like that performed by David Graham at the FDA. Some believe that there is a need to develop clinical databases that pharmaco-epidemiologists can use to investigate the possibility of adverse drug events. The UK General Practice Research Database is the largest database that incorporates full records of patient medical history. With over 2.5 million patient records, it proved successful in determining the risk of suicidal behavior in patients on antidepressants. The hope is that these types of studies could be extended to the US, where drugs are approved earlier and taken by larger numbers of people.<sup>13</sup> The FDA's Office of Drug Safety is responsible for monitoring and assessing the safety of existing drugs, but it has very limited funding for its own epidemiological studies. George W. Bush's proposed 2006 budget designates only 6% of the FDA's Center for Drug Evaluation and Research's (CDER's) budget for postmarket surveillance while new-drug review takes up about 80%.<sup>11</sup>

Many have criticized the FDA, saying the agency should have identified the problem and pulled COX-2 inhibitors from the market. Graham testified that the FDA's organizational structure and corporate culture were biased toward the approval of new drugs and that safety monitoring of drugs on the market was only a second priority. He further noted that reviewers at the Office of New Drugs who approve therapeutics have a vested interest in the drugs' success, often ignoring or overruling post-market safety concerns raised by those in the Office of Drug Safety. However, Janet Woodcock, former director of CDER, argues "risk and benefit are inextricably linked for any drug." She points out that drugs with risky side effects should not necessarily be denied approval, but rather their risks and benefits must be weighed up by the regulatory authorities who approve them and by the physicians and patients who use them.<sup>11</sup>

Many have argued that the FDA lacks the legal influence necessary for proper regulation of therapeutic drugs. After the FDA approves a medication, the agency cannot require a company to pay for and conduct postmarket safety studies. Nor can it limit the use of a drug to certain medical subspecialties as with medical devices. It does not have the explicit authority to change warnings on drug labels. Rather, it can negotiate label changes with manufacturers. Ultimately, the FDA does not aim to systematically monitor dangerous side effects.

The hype surrounding COX-2 inhibitors emphasized its advantage over NSAIDs. However, clinical trials have shown NSAIDs, aspirin, and acetaminophen to be just as effective in relieving pain as the COX-2 inhibitors. The moderate improvements on gastrototoxicity hardly seem worth the now proven increased risk of cardiovascular events.

### 1.22.2.2 Propulsid

The popular medicine Propulsid (cisapride) for the treatment of nighttime heartburn has experienced trouble ever since it hit the market in 1993. More than 100 patients taking Propulsid had already suffered serious heart problems by March 1998. The FDA ordered strengthened warnings for the drug in June 1998 after numerous reports of heart rhythm abnormalities and nearly 38 deaths. While the FDA could not prove the drug caused any death, it noted that Propulsid was already known to cause irregular heartbeat rhythm, or arrhythmias, when taken in conjunction with particular medicines. Warnings about the drug said that Propulsid should not be used in patients taking certain antibiotics, antidepressants, antifungals, protease inhibitors, or various other drugs. The drug was also contraindicated for patients with certain disorders such as congestive heart failure, multiple organ failure, kidney failure, and chronic obstructive pulmonary disease, which causes serious respiratory problems, and advanced cancer.<sup>14</sup>

Propulsid quickly became a popular drug for the treatment of acid reflux in infants, even though they are particularly at risk for adverse side effects and the drug was not systematically tested for infants. In 1995, Johnson & Johnson failed to receive approval for pediatric sales for Propulsid and the label did not recommend it for use in children. Doctors are free to prescribe medicines beyond the confines of labels and they insisted on having access to the drug, despite the side effects, because the label was confusing. By 1996, FDA officials warned the company that reports suggested pediatric patients were at greater risk for cardiac problems. Despite this, the company continued to finance programs that encouraged the drug's pediatric use. When federal officials warned Johnson & Johnson that the drug may have to be banned for children or withdrawn, the government and the company simply negotiated new warnings for the drug's label. Following this label change, Johnson & Johnson continued to promote Propulsid's use in children, resulting in 20% of babies in neonatal intensive care units being given the drug in that year.<sup>15</sup>

By 2000, Johnson & Johnson was forced to pull Propulsid off the market when it was linked to nearly 80 deaths and hundreds of heart attacks and the government threatened to publicize the drug's history of trouble. Janssen Pharmaceutical (a unit of Johnson & Johnson) agreed to pay up to \$90 million to settle lawsuits involving claims that 300 people died and nearly 16 000 were injured as a result of taking their drug.<sup>15</sup>

Documents show that Johnson & Johnson failed to conduct safety studies urged by federal regulators and that company consultants could have easily revealed the dangers associated with the drug early on. However, the FDA also failed to disclose company research that placed serious doubt on Propulsid's effectiveness against digestive disorder, arguing that the studies were trade secrets. While Johnson & Johnson could not directly promote Propulsid for children without approval for pediatric use, FDA rules allowed the company to support educational efforts among doctors, and those programs tacitly endorsed pediatric usage. Physicians were ultimately never made fully aware of the FDA's concerns with Propulsid. In the end, the opinion of the FDA was that Propulsid was only minimally efficacious and therefore no safety risk was acceptable.<sup>15</sup>

### 1.22.2.3 Fen-Phen

In 1992, several published articles suggested that the combined use of phentermine and fenfluramine could result in significant weight loss when used over an extended period of time.<sup>16</sup> While fenfluramine and phentermine were individually approved by the FDA as appetite suppressants for the treatment of obesity, the FDA had not approved the use of the combination. Nevertheless, physicians began prescribing this drug combination, named fen-phen, for use in weight loss programs, and fen-phen became popular at commercial diet clinics. By 1996, the total number of prescriptions for fenfluramine and phentermine in the US exceeded 18 million.<sup>17</sup>

Following a study conducted at the Mayo Clinic reporting cases of cardiac valvulopathy in persons taking fenfluramine or dexfenfluramine, the FDA issued a public health advisory on 8 July 1997. The *New England Journal of Medicine* also reported that the two drugs increase the risk of pulmonary hypertension, particularly when patients receive high doses for more than 3 months. Valvular disease had been reported after exposure to serotonin-like drugs.<sup>17</sup>

This led to the voluntary withdrawal of the two drugs from the US markets on 15 September 1997. Several months later, the US Department of Health and Human Services recommended that all users of these pills undergo a medical history and cardiovascular examination. Practitioners were also encouraged to obtain an echocardiogram for all patients who had used these drugs before undergoing any invasive procedure for antimicrobial prophylaxis where endocarditis is indicated. This applied to most users because such prophylaxis is recommended even for common dental and oral procedures like teeth cleaning and fillings.<sup>16</sup> In 1999, American Home Products Corporation, makers of the fen-phen combination, agreed to pay \$3.75 billion in compensation to thousands who used the drug before it was taken off the market.

### 1.22.2.4 Hormone Replacement Therapy in Menopausal and Postmenopausal Women

By the 1980s, the US population of postmenopausal women began to increase dramatically. With this increase also came a higher incidence of cardiovascular, neoplastic, and neurologic diseases among older persons. Estrogen replacement was seen as a panacea for postmenopausal women, thought to prevent coronary artery disease and delay the onset of Alzheimer's disease.<sup>18</sup> However, later studies began to severely question these claims.

Not a single controlled trial had ever shown that hormone replacement therapy prevented cardiovascular disease, stroke, Alzheimer's disease, or wrinkles, or that it was an effective treatment for depression or incontinence. The Heart and Estrogen/Progestin Replacement Study (HERS) failed to show a benefit of hormone replacement therapy (HRT) to women with heart disease. Despite this, pharmaceutical companies persuaded physicians that HERS actually showed a benefit. They argued that women with cardiovascular disease had dysfunctional cardiovascular systems that were unable to respond to hormonal assistance, but healthy women could still benefit.<sup>19</sup>

A study by the National Cancer Institute found that women who used estrogen only replacement therapy, particularly for 10 or more years, were at significantly increased risk of ovarian cancer.<sup>20</sup> Nonetheless, the risk of HRT is being minimized by rhetoric, with the hormone promoters trivializing HRT-caused breast cancers as 'better behaved' breast cancers. Furthermore, a trial conducted by the Women's Health Initiative (WHI) found that the risk of pulmonary embolism began to rise shortly after the trial began. Stroke risk increased after the first year, and invasive breast cancer rates rose after the fourth year. In fact, the WHI was stopped early due to treated women experiencing higher rates of breast cancer, cardiovascular disease, and overall harm.<sup>21</sup> One randomized controlled trial found that HRT significantly increased daily depression compared with pretreatment levels.<sup>19</sup>

The Estrogen Replacement and Atherosclerosis Study showed no benefit of either HRT or estrogen alone in preventing progression of atherosclerosis. While many clinicians are still convinced that HRT prevents Alzheimer's disease and improves mood, incontinence, and general well-being, randomized controlled trials have proved each of these claims to be false.<sup>19</sup>

### 1.22.2.5 Antidepressants and Suicidal Behavior in Youth

Antidepressants have been criticized for a lack of efficacy and poor side-effect profiles. The advent of SSRIs changed depression treatment strategy and they have emerged as the dominant pharmacological therapy for depression, in large part because they have been marketed as safe and effective.<sup>22</sup>

However, concern has been raised about whether SSRIs increases suicidality, especially early in treatment. Even small incremental risks can have serious implications for countries like the US, where there were 24.5 million patient visits for depression in 2001, a 70% increase over 15 years. Sixty-nine percent of patient visits for depression result in prescriptions for SSRIs.<sup>23</sup> Studies evaluating the existence of increased risk of suicide attempts often contradict one another.<sup>24</sup> More recently, however, the controversy has heated up over the use of SSRIs and the increased risk of suicidality in adolescents.

According to reports by the American College of Neuropsychopharmacology (ACNP), suicide is the third leading cause of death among 15- to 24-year-olds in the US. Depression and other psychiatric disorders are the major causes behind these suicide cases. Depression occurs in 10% of youth, with a majority of these cases going untreated and undiagnosed. Controversy over the use of SSRIs in youth arose when case reports began to arise in the 1990s indicating a chance of increased suicidal tendencies in patients (mostly adults) undergoing SSRI treatment. In 2003, regulatory agencies in both the US and the UK expressed concern over the treatment of depression in children and adolescents through the use of SSRI treatment and its possible link to increased risk of suicidal thinking or behavior for depressed youth under the age of 18.<sup>22</sup> The concerns culminated in a 2004 FDA Public Health Advisory warning of the possibility of increased suicidal ideation and behavior in children and adolescents being treated with antidepressant medications. The FDA directed manufacturers of all antidepressant drugs to revise the labeling for their products to include a boxed warning and expanded warning statement.<sup>25</sup>

Regulatory agencies in both the US and UK found data on the safety and efficacy of SSRIs in children problematic. Following analysis of 24 trials involving over 4400 patients, they found that greater risk of suicidality exists during the first few months of treatment. The average risk of these events on the drug was 4%, twice the placebo risk of 2%.<sup>25</sup> The UK Committee on Safety of Medicines (CSM) also found that the risk of suicidal thoughts and behavior was between 1.5 and 3.2 times more likely in young patients taking paroxetine (Paxil) compared to placebo.<sup>26</sup> Further studies on Paxil not only found increased rates of suicidal ideation and suicide attempts, but an expert working group also concluded that Paxil did not demonstrate efficacy in depressive illness in patients under 18.<sup>27</sup>

Findings that suggest serious risks associated with SSRI treatment in youth are largely based on unpublished studies, raising questions over the appropriate level of information a drug manufacturer should be required to disclose before an antidepressant is widely available on the market. A study conducted by researchers at the Center for Outcomes Research and Effectiveness at the University College London, the Royal College of Psychiatrists' Research Unit, and other organizations reevaluated the risk–benefit profile of five SSRIs used in the treatment of depression in youth. The study was based on both published and unpublished trial data on antidepressants including Prozac, Zoloft, and Paxil and revealed that increased risk of serious adverse effects and suicide-related events greatly outweighed the benefits of treatment for all the SSRIs except Prozac. The results of this study and several others flew in the face of studies of efficacy and safety based solely on published data, which indicate favorable risk–benefit profiles. In many instances, negative trials were simply never reported.<sup>28</sup>

However, it becomes difficult to determine if attempts at suicide are a manifestation of depression or a side effect of the drug. As Christopher Varley writes in *JAMA*, “Suicide attempts may occur as depression is lifting and an individual is energized enough to act on thoughts of self-harm. Since suicide is rare in children and adolescents, ascertaining whether there is a meaningful increased risk of suicidal ideation, suicide attempts, or suicide completion associated with any medication used to treat depression will require review of large numbers of patients.”<sup>27</sup> The ACNP Task Force on SSRIs and Suicidal Behavior in Youth is quick to point out that suicidal behavior captured in adverse events reports did not include trials that set out specifically to determine whether medications led to suicidal behavior. Similarly, recent studies reported in *JAMA* note that the epidemiology of suicidal behavior in persons taking antidepressant drugs is not well documented by formal observational studies.<sup>29</sup>

The question remains whether the efficacy of newer antidepressants in childhood depression have exaggerated their benefits, while the adverse effects have been downplayed. Some researchers believe that the fact that serious adverse effects with newer antidepressants are common enough to be detected in randomized controlled trials already raises serious concerns about their potential for harm. As Jon N. Jureidini and others write in the *British Medical Journal*, “The magnitude of benefit is unlikely to be sufficient to justify risking those harms, so confidently recommending these drugs as a treatment option, let alone as a first line of treatment, would be inappropriate.”<sup>30</sup>



### 1.22.2.6 Conclusion

Determining safety in drugs that have rare side effects is difficult, and it cannot always be done before a drug is brought to market. For that reason, reports of ‘phase IV’ adverse events – that is, adverse events reported postmarketing – must be followed-up vigorously. The exact moment that a rare adverse event becomes compelling enough to require withdrawal of a drug from the market is a judgment call, and well-intentioned actors can differ on when that moment has come. In many of the cases above, however, extenuating circumstances delayed a reasonable response. It is when self-interest obscures or trumps safety that an ethical breach has occurred.

### 1.22.3 Economics

The ethics of drug use in the modern world cannot be considered in isolation from its means of production. The modern drug culture is enormously expensive. The US pharmaceutical industry hit the quarter trillion mark in annual sales for the first time in 2004,<sup>31</sup> a figure that is growing at about 12% a year (down from a high of 18% in 1999). The economic impact of pharmaceuticals on healthcare policy such as Medicare and Medicaid, employee health benefits, and corporate profitability are profound. In addition, individual decisions about such things as marriage, employment, elder care, child bearing and rearing, retirement, and so on can be influenced by the need to access pharmaceuticals.

The cost of drugs, the institutional bodies created to manufacture them, and the strategies used to distribute them have both implicit and explicit ethical repercussions. In this section, we will look at drug profitability, diseases of affluence, and equitable drug distribution.

#### 1.22.3.1 Pharmaceutical Profitability and Drug Discovery

Drug costs are the fastest growing part of the USA health-care bill, a fact that has brought much hand-wringing by those attacking and those defending the pharmaceutical industry. The elderly are particularly hard-hit; in 2002, the average price of the 50 drugs most commonly used by the elderly in the US was \$1500 for a year’s supply.<sup>32</sup> As health costs become a larger part of corporate and governmental expenditure, the pressure on big Pharma is increasing. Pharmaceutical companies are constantly faced with the conflicting pressures of research and drug discovery, public expectation, marketing and sales, and shareholder demand. For over two decades, as medicine expanded its scope, the drug industry has been the most profitable industry in the US, losing that status only in the last few years.<sup>32</sup> The recognition that brand-name drugs are more expensive in the US than in other markets has increased public resentment of pharmaceutical profits and power.

The pharmaceutical industry relies on a variety of strategies to maintain targeted levels of profitability. Industry consolidation coupled with increased shareholder demand for financial performance has created a competitive marketplace that takes full advantage of the industry’s capabilities and resources. The industry has come to rely increasingly on blockbuster drugs, but the development of such drugs can be elusive. The industry has traditionally kept its profits robust by continually pursuing new molecules and searching for new indications and formulations for existing drugs. The process of discovering, testing, and releasing new therapeutic compounds is referred to as the pipeline. In general, the pipeline for new drug introduction is drying up; according to trade publication news, for example, 56 new drugs were introduced in 1996 compared with just 21 new drugs in 2003. In addition, many blockbusters of the past are about to go off patent, further draining the industry’s potential for profit-making.<sup>33</sup>

In the US, drug prioritization falls to market forces, and the major pharmaceutical companies, as is the case for most industries, try to find the highest profit margins as an obligation to their shareholders. The pharmaceutical industry’s concern over declines in profit is complicated by nonpharma competition looming on the horizon. The growth in fields like biotechnology, genomics, and even nanotechnology threatens to surpass the pharmaceutical industry in uncovering new approaches to therapy or disease management.<sup>34</sup> In response to these kinds of pressures, the pharmaceutical industry has changed its tactics. For example, there has been a significant decline in the development of fully innovative agents in the pharmaceutical industry. In its place, the industry has increasingly relied on stopgap drugs that offer only limited therapeutic advantage but do so for a large market niche, such as, minor improvements for Alzheimer patients, life-enhancement drugs, such as medicinal remedies to relieve dry mouth in patients with Sjogren’s syndrome, life style drugs for relatively healthy people looking to enhance normal functioning (*see* Section 1.22.6.1), and me-too drugs, which closely mimic existing successful products.<sup>35</sup>

#### 1.22.3.2 Me-Too Drugs

FDA approvals for uniquely new drugs, or new molecular entities (NMEs), which provide unequivocal advances in disease treatment compared to existing pharmaceutical remedies, have been declining. As mentioned above, the NME

approvals numbered only 21 in 2003 – a startling contrast to the 35 NMEs receiving FDA approval in 1999.<sup>36</sup> The FDA classified three-quarters of the drugs it approved in 2004 as me-too drugs.<sup>37</sup> Me-too drugs can be highly profitable: Nexium, a me-too drug for stomach acid, has earned 4 billion dollars for AstraZeneca.

The increased emphasis on me-too drugs has ethical implications. Critics contend that the focus on me-too drugs detracts from drug discovery, privileges profits over therapeutic need, and duplicates effort rather than pursuing new cures or less well-served diseases. Pharmaceutical firms, on the other hand, justify the development of such drugs by arguing that me-too drugs improve on existing drugs by lowering side effect profiles or targeting drug-resistant patients, can increase compliance, and are usually cheaper than the prototype.<sup>38,39</sup> While new drugs that offer improved side-effect profiles and lower prices are clearly beneficial, the pursuit of me-too drugs has clearly contributed to the diminished number of NMEs. If me-too drugs are being pursued to increase industry profits at the expense of new drug development it clearly poses an ethical problem, particularly as pharmaceutical companies use the development of new drugs as a justification for high drug prices.

### 1.22.3.3 Antibiotics: An Example

There is a major global need for new antimicrobial agents, or new antibiotics. Development of new antibiotics has lagged, and there are few new antibiotics in the pipeline. In fact, of the 89 new drugs approved by the FDA in 2002, none were new antibiotics.<sup>40</sup>

New antibiotics are needed to address the increasing incidence of antibiotic resistance, especially in relation to the prevalence of infectious disease in developing countries.<sup>41</sup> Antibiotic needs can be classified according to the three groups of infectious diseases they target. The first tier of infectious diseases accounts for nearly 4 out of every 10 deaths from communicable infection, which include diseases such as tuberculosis, AIDS, and malaria. The second-level category represents neglected diseases (e.g., schistosomiasis, onchocerciasis, and leprosy), which leave their victims with lifetime burdens of illness such as blindness, mental retardation, and extreme physical deformities. Finally, the third group of infectious diseases seems to appear without warning, often in epidemic fashion, similar to the recent outbreak of severe acute respiratory syndrome (SARS).

The pharmaceutical industry has had enormous success in tackling many of these diseases in the past. More recently, big pharmaceutical companies have dedicated relatively few dollars to developing new antibiotics despite the growing need. Malaria, for example, has become a reemergent threat in Africa, Latin America, Southeast Asia, and parts of Eastern Europe as the result of gradual resistance to antimicrobial agents, which had been adequate for decades. In the case of tuberculosis, the industry has not developed any new compounds in more than three decades. This lack of on-going responsiveness has resulted in a failure to address the needs of new subgroups disease. It has exposed the failure to address populations that require shorter or fewer supervised doses for compliance conformity, that have built resistance to existing protocols, or that harbor latent strains of the infection that could initiate a new round of the epidemic.<sup>42</sup> The reemergence of tuberculosis in inner city populations in the US has emphasized the potential for crisis when immunity to older drugs develops in the absence of newly developed agents to take their place.<sup>43</sup>

There are a number of reasons for industry neglect of antibiotic development. Certainly, the industry's search for blockbuster drugs is one key reason for the decline in new antibiotic research and development. In addition, the antibiotics that have been developed are broad-spectrum drugs rather than targeted antibiotics, designed for the widest application and thus the largest potential market. However, by avoiding the additional cost and development time necessary to create bacteria- or condition-specific antibiotics, the industry has promoted drug resistance by encouraging the overuse of a small number of generalized agents.

Congress has made little effort to correct the situation, despite a long-standing history of targeted legislative rulings mandated to specifically encourage or discourage various pharmaceutical industry trends and behavior.<sup>44</sup> Innovative incentives will be needed to encourage the pharmaceutical industry to target communicable diseases, thereby supporting a more ethical balance in public health around the world. As the development of new antimicrobial agents has been waning, so has the intellectual pool of potential scientists interested in and trained with the necessary professional and technical expertise needed in this field of study.

### 1.22.3.4 Drug Pricing

The US stands alone among developed nations in its absence of a national policy to control escalating drug prices. The cost of drugs in this country can be twice that in Europe, and three times the cost of equivalent drugs in Japan.<sup>45</sup>

The pharmaceutical industry asserts that their research and development costs account for their need to recoup expenses through pricing margins. It is true that the costs of new drug development are substantial. However, drug

companies are often not the ones incurring these R&D costs. The majority of new drug development is based on bench research funded by the federal government through grants to university research centers that the industry can then negotiate with over intellectual property rights.<sup>43</sup> Federal legislation, in fact, serves to underwrite significant dollars for pharmaceutical drug development and market distribution through tax subsidies and partial industry exemptions for patents, licenses, and intellectual property rights. The higher costs to wealthier nations are a de facto subsidy to poorer nations. While wealthier nations should burden more of the costs than poor nations, the present system accomplishes this without transparency and through arbitrary pricing determined by each nation's healthcare policy. It would be far better to set pricing policy in a rational, coordinated manner.

While economics can keep even lower price pharmaceutical agents from being utilized in developing countries, often the reverse is true of wealthier nations. When prescription medication expenses are covered by health plans, the true cost of drugs becomes less transparent to the consumer, giving way to the potential for overutilization.<sup>45</sup> The result is overutilization by wealthier countries who buy the drugs at the highest prices, and underutilization by poor countries who have subsidized prices. The pharmaceutical companies have addressed these issues through a variety of programs in specific countries and specific disease areas, and deserve credit for those programs. But there is still an enormous amount of randomness and profiteering in the system.

### 1.22.3.5 Regulation and Recommendations

The FDA is the oversight body responsible in the US for "advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health."<sup>46</sup> Over the last decade, however, questions have been raised about the FDA's impartiality. The FDA has been accused of ignoring scientists' concerns about the dangers of some approved products on the market (e.g., Vioxx) and avoiding internal debates about drug safety factors. Critical discussions have been discouraged under the combined pressures of recent approval process acceleration mandates funded by the very (pharmaceutical) corporations whose efforts the agency is judging (i.e., the 1992 Prescription Drug User Fee Act).<sup>47</sup> Similarly, the UK's National Health Service has recently been accused of lapses in their drug approval and monitoring role, and in allowing the pharmaceutical industry's influence to sway providers' and consumers' increased reliance on medication.<sup>48</sup>

The example regarding the lack of new antibiotic development efforts is indicative of a broader issue of ethical concern underlying the motives and rationale often driving the direction of pharmaceutical R&D. In the case of antibiotics, the Infectious Diseases Society of America (IDSA), a professional organization dedicated to policy, advocacy, education, and practice guidelines addressing the health impact of infectious diseases, has put forth a number of recommendations that could be applied to R&D for any number of otherwise narrowly focused agendas. Other leaders in this field have suggested measures such as better business models as well as different regulatory approaches. The recommendations include, but are not limited to<sup>40,41</sup>:

1. congressional re-casting of industry-based statutory incentives and/or disincentives for drug development prioritization, such as R&D tax credits, patent extensions, antitrust exemptions, and liability protections;
2. Congressional and National Institutes of Health (NIH) accommodations for targeted intellectual property rights;
3. expanding the NIH's role in sponsoring research to generate otherwise neglected agent needs;
4. expanding the NIH's role in encouraging the translation of bench-to-marketplace research;
5. creating an empowered independent national commission charged with setting drug discovery priorities;
6. creating a not-for-profit drug company that could work in tandem with the pharmaceutical industry and provide a noncompetitive setting for industry scientists on sabbatical to work on needed global projects. The home pharmaceutical company would receive tax incentives for their temporary leave;
7. FDA's acceleration of published guidelines for less market-popular clinical trials and drug review status;
8. restructuring the FDA review process and decision-making efforts to ensure greater public transparency;
9. requiring FDA approval of combinations of drugs (i.e., combination therapy) that target a smaller patient population, rather than approval of singular broad-spectrum agents for combating infectious diseases. Institute approval of individual pathogen-specific antibiotics, in an effort to delay the emergence of antibiotic resistance;
10. re-organizing the antibiotic approval process to evaluate applicants not only for drug safety and efficacy in relation to existing drugs on the market, but for resistance to immunity – a more difficult and costly process, but one with better long-term outcomes;
11. increasing funding and grant support directed at less profitable drug discovery;
12. supporting joint public-private ventures aimed at more widely focused needs;

13. banning new antibiotics from widespread use in healthy animals; and
14. encouraging multinational drug firms to contract their manufacturing to lower- and middle-income countries that could then benefit from both the medical and economic advances available on their own soil.

## 1.22.4 Allocation

### 1.22.4.1 Equitable Distribution of Drug Resources

At the start of the twenty-first century, one-third of the international community lacked access to critical pharmaceutical drugs. Within the world community, particularly in the impoverished regions of Africa and Southeast Asia, populations are without life-saving pharmaceuticals that are readily available to wealthier neighbors.<sup>49</sup> Communicable diseases continue to devastate Third World countries, further widening the health gap and increasing the tremendous inequities for poor people in developing nations. About 14 million children under the age of 5 in these regions die each year. Ninety-five percent of childhood deaths occur in developing countries. Seventy percent of those fatalities are caused by infectious diseases for which vaccines are elsewhere available.<sup>50</sup> Unfortunately, the pharmaceutical agents needed to treat these diseases are either unaffordable or unavailable to the populations in developed countries.<sup>51</sup>

The global expenditure on drugs in 2004 was \$550 billion. Yet 88% of that half-trillion dollars was spent by North America (248 billion), Europe (144 billion), and Japan (58 billion).<sup>52</sup> The burden of disease coupled with disparities in access to pharmaceuticals makes for a stark picture:

- In 1998, 6.1 million people in tropical Third World nations died of malaria, tuberculosis, or acute lower respiratory tract infections. That figure does not include the additionally high number of AIDS deaths in those regions for lack of access to and/or funding for AIDS drugs, which could run upwards of \$15 000 or more per AIDS victim per year.<sup>43</sup>
- By 2004, that annual number grew to more than 10 million infectious disease-related deaths estimated to have occurred in developing countries for lack of safe, inexpensive essential drugs.<sup>53</sup>
- Acute lower respiratory tract infections alone claim over 3.5 million people a year, representing the third highest cause of death in underdeveloped countries. The youngest citizens of these nations, i.e., the children, are most vulnerable.<sup>43</sup>
- From 1975 to 1997, only 1% (13 of 1223) of new drugs developed by multinational pharmaceutical corporations were targeted to treat communicable diseases that devastate tropical regions. The balance of new pharmaceuticals primarily targeted 'diseases of affluence' or conditions resulting from overconsumption.<sup>43</sup>
- 50–90% of drugs in developing and transitional economies are paid for out-of-pocket.<sup>53</sup>
- Less than one in three developing countries has fully functioning drug-regulatory authorities.<sup>53</sup>
- Antimicrobial resistance is increasing for many major infectious diseases including, but not limited to, bacterial diarrhea, gonorrhea, malaria, pneumonia, and tuberculosis.<sup>53</sup>
- \$1 billion is the World Health Organization's estimate of the cost to reduce by half the 1.1 million annual deaths caused by malaria. That amount is also estimated as Pfizer's 1999 revenue from sales of Viagra.<sup>54</sup>

### 1.22.4.2 Diseases of Affluence

The term 'diseases of affluence' has been defined as "diseases which are thought to be the result of increasing wealth in a society."<sup>55</sup> It refers to the association of a malady with a particular level of social class. Examples of such conditions include obesity, heart disease, type 2 diabetes, some cancers, high blood pressure, allergies, autoimmune diseases, asthma, alcoholism, depression, and other psychiatric disorders. These illnesses stand in sharp contrast to the infectious communicable diseases more common to Third World countries.<sup>55</sup> Different disease patterns require alternative forms of treatment, which results in different patterns of drug consumption in various regions of the world.

The relation of disease trends to class is not a new concept. During the early years of the twentieth century, health professionals were faced with the growing epidemic of poliomyelitis, and found that it did not follow the traditional path where infectious diseases were most prevalent in unsanitary environments. In fact, children living in unclean, poverty-ravaged slums at that time had a better chance of developing a certain protective level of immunity to polio, which struck at least as heavily in middle-class neighborhoods where cleanliness was the norm.<sup>56</sup> Today, chronic conditions tend to be more common in developed, industrialized nations that have a surplus of assets and resources, which encourage high-fat diets of processed foods, discourage adequate levels of health-benefiting physical activity, and

accommodate for significant rates of tobacco, alcohol, and substance abuse. The dietary trends of developed nations also contribute to diseases of affluence in their use of refined foods that lack the necessary nutritional content needed to maximize overall population health.<sup>57</sup>

The pharmaceutical industry has focused its research and development overwhelmingly on diseases of affluence, such as chronic conditions and life style enhancements.<sup>40,58</sup> Worldwide, money invested in health-care research has grown dramatically over the past two decades. In 1986, the Commission on Health Research for Development estimated an annual global health research expenditure of approximately \$30 billion per year. Ten years later, the WHO's Ad Hoc Committee on Health Research Relating to Future Intervention Options put that figure at \$55 billion for 1992. The most recent estimates, from the Global Forum for Health Research for the year 2001, suggest a global health research amount of nearly \$106 billion.<sup>59,60</sup>

Though significant in dollar values, the distribution is highly skewed. Over the past 20 years, one concept has remained fairly stable – that of the 10/90 gap. The 10/90 gap describes the imbalance between research expenditures and disease prevalence, with less than 10% of the world's health research dollars applied to diseases that represent more than 90% of the world's health challenges – most of which are concentrated in developing nations.<sup>59</sup> Evidence of the imbalance has been recently documented in an evaluation of published research in the professional literature. The analysis of eight selected disease categories, prevalent in either industrialized or developing regions, indicates an enormous range of variation in research investment. At the top of the range, an estimated \$9.4 billion is spent per year on cardiovascular research, yet only \$0.3 billion annually on research for malaria. This divergence demonstrates the emphasis currently placed on diseases of affluence to the detriment of research for communicable diseases.<sup>61</sup>

#### 1.22.4.3 Global Burden of Disease

A Global Burden of Disease Study, conducted in the early 1990s, arrived at three broad categories of cause-of-death diseases<sup>62</sup>:

- Category 1: communicable/perinatal/maternal/nutritional,
- Category 2: noncommunicable diseases (NCDs), and
- Category 3: injuries.

In developing nations, mortality rates for Category 1 diseases outweighed that of the developed nations by almost 17-fold. The study found, however, that poorer countries were catching up with wealthier nations that in 1990 with NCD rates rising to just under half that of developed countries. Thus, along with economic development comes a shift in disease emphasis.

Forty percent of the 2001 global burden of disease was represented by four communicable diseases among the top 10 leading causes of death worldwide (Table 1). Those diseases included lower respiratory tract infections, HIV/AIDS, diarrheal disease, and tuberculosis. Another 40% of the top killers were NCDs, such as ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, and pulmonary cancers. Developed countries are significantly more burdened by those conditions falling under the label of diseases of affluence. Poorer nations, while plagued by infections to a much greater degree, are also beginning to experience the burden of western life style illnesses.<sup>62–64</sup> It is now becoming apparent that what had once been considered diseases of affluence, concentrated in industrialized nations, are now impacting the morbidity and mortality rates in developing countries, in addition to the hardships of infectious communicable diseases.<sup>65</sup> Contrary to public opinion, NCDs are now responsible for more global deaths annually than the so-called infectious diseases of Third World nations.<sup>62</sup>

#### 1.22.4.4 Epidemiological Transition

The term epidemiological transition, which reflects the parallels between evolving economies and disease patterns, now suggests that chronic diseases, specifically cardiovascular disease, represent emerging threats in the less developed regions of the world. As such conditions increase in prevalence, the corresponding workforces and economies will feel the impact. Stemming the tide of this impact requires acknowledgment of the basis for the change as well as innovative proposals to minimize its toll.<sup>66</sup>

The same may be true of mental illness. For example, depression, while not in the top 10 leading causes of death, is being diagnosed and treated at increasing rates in more developed countries, as are drug dependence, anxiety, and compulsive behaviors. As a result, antidepressants are one of the key target areas for the pharmaceutical industry's profitability.<sup>67</sup> Mental illness also represents a significant 11% of the worldwide burden of disease, and approximately

**Table 1** Top 10 leading causes of death: global, developed, and developing regions (version 2) estimates, 2000 (from Mathers, 2002; adapted from WHO sources)<sup>168</sup>

<i>Rank</i>	<i>Cause of death: global</i>	<i>% Total deaths</i>	<i>Rank</i>	<i>Cause of death: developed countries</i>	<i>% Total deaths</i>	<i>Rank</i>	<i>Cause of death: developing countries</i>	<i>% Total deaths</i>
1	Ischemic heart disease	12.6	1	Ischemic heart disease	23.3	1	Ischemic heart disease	9.2
2	Lower respiratory tract infections	11.1	2	Cerebrovascular disease	13.4	2	Cerebrovascular disease	8.4
3	Cerebrovascular disease	9.6	3	Trachea, bronchus, lung cancers	4.4	3	Lower respiratory tract infections	7.9
4	Chronic obstructive pulmonary disease (COPD)	4.7	4	Lower respiratory tract infections	3.6	4	Perinatal conditions	6.0
5	HIV/AIDS	4.6	5	COPD	3.2	5	HIV/AIDS	6.0
6	Perinatal conditions	4.5	6	Colon and rectum cancers	2.3	6	COPD	5.2
7	Diarrheal diseases	3.6	7	Self-inflicted injuries	1.8	7	Diarrheal disease	4.6
8	Tuberculosis	2.9	8	Diabetes mellitus	1.7	8	Tuberculosis	3.6
9	Road traffic accidents	2.2	9	Stomach cancer	1.7	9	Malaria	2.7
10	Trachea/bronchus/lung cancers	2.1	10	Hypertensive heart disease	1.7	10	Road traffic accidents	2.4

1% of annual deaths around the globe. Although it is generally more prevalent – or better recognized – in developed societies, it is becoming increasingly significant in developing nations as well.<sup>68</sup>

On the other hand, some conditions are still disproportionately characteristic of developed nations. Obesity has not historically been categorized as a disease; therefore, treatment options covered by health insurance plans have been limited. In 2004, the US Centers for Medicare and Medicaid Services (CMS) reversed its tradition of denying Medicare coverage for obesity-related clinical care in light of the growing epidemic of overweight seniors and the impact that it has, in turn, on further escalating the cost of chronic care. According to the National Obesity Forum in Nottingham, UK, obesity itself can be the fundamental cause of numerous other illnesses and conditions, including cardiovascular disease, hypertension, stroke, hyperlipidemia, diabetes, cancers, osteoarthritis, respiratory disorders, sleep apnea, fertility problems, Alzheimer's disease, depression, and other psychological disorders.<sup>69,70</sup>

Many risk factors that serve as precursors to chronic diseases may not differ markedly from those present in developed countries. A combination of genetics, life style behaviors, and comorbidities represent the lion's share of determinants. For the poorer nations, however, additional factors may come into play. The ability to correct life style behaviors (e.g., smoking, sedentary existence, etc.) represents a clinical challenge for the medical community. Prevention is the preferred approach through avenues such as primary carebased patient education, population-based health promotion programs to manage otherwise wrongly directed societal trends, and political and economic policies that cross over more than just health-care boundaries to underscore positive behavioral priorities for individuals, local governments, and corporations.<sup>66</sup>

The People's Republic of China provides one clear example of the epidemiological transition model. Generally classified as a developing country, infectious diseases took the lives of many Chinese citizens before reaching old age. Over the last 30 years, however, China's economic improvements and urbanization have opened the way for greater longevity and the growth of an aging population. In turn, morbidity rates now reflect the prevalence of more chronic and degenerative diseases found in Western societies, or diseases of affluence.<sup>71</sup> Currently (Category 2), NCDs account for about two-thirds of China's burden of disease.<sup>68</sup> Nevertheless, both older and new forms of infectious diseases are also beginning to plague that nation.<sup>71</sup>

Finally, evolving population pyramids reflect the changes in a developing population's longevity and fertility trends. Third World children who manage to survive their early experiences with serious infectious diseases could be at increased risk and vulnerability to NCDs in adulthood.<sup>62</sup>

#### 1.22.4.5 International Policy and Regulatory Efforts

The uneven worldwide distribution of health-care assets, resources, and critical pharmaceuticals results in poor health for large populations of certain countries and regions. This, in turn, practically assures these regions dire states of poverty. Good health, in other words, is a fundamental requirement for a society to be productive economically and otherwise. Conversely, poverty supports the exacerbation of morbidity and mortality in undeveloped countries, whereby populations can either afford medicines that may be available, or are at a loss when proper agents are nonexistent.<sup>70,72</sup> The devastating cycle of poverty and poor health feeds upon itself.

Options are available to tighten the reins of pharmaceutical pricing growth and development focus. Federal negotiations with the industry for intellectual property rights and reasonable pricing can consider the public policy advantages of quid pro quo agreements to help strengthen the drug industry's social conscience in lieu of shareholders' profits.<sup>43</sup> In addition to mandated parameters for patented drug pricing, proposals for the industry's embrace of voluntary, albeit limited, licensing flexibility to aid affordability for poor nations would demonstrate good will.<sup>73</sup>

Over the past several years, the UK has established a Commission on Intellectual Property Rights to inform the government and citizenry regarding the pharmaceutical industry's role in preserving the fundamental human right to health through socially responsible development of essential drugs as a global public good.<sup>74</sup> In fact, embracing a stronger position of corporate social responsibility may serve the pharmaceutical industry's bottom line as well. As the spotlight on the industry's behavior shines ever more brightly, benchmarks are being applied, such as applicable international codes and guidelines developed by World Health Organization (WHO) and Organization for Economic Co-operation and Development (OECD), to measure their public 'goodness.' Being shown in a poor light could be undesirably costly for industry firms and their shareholders.<sup>75</sup>

Pharmaceutical companies need to anticipate the world's shifting patterns of diseases in order to protect the public from unlikely new strains of old plagues. Concern has been expressed, for example, that remaining unmonitored samples of the poliovirus previously employed in the development of the vaccine may find their way into the mainstream population and quickly spread.<sup>75</sup> Other potential threats to global health include a pandemic reemergence of pharmaceutical-resistant tuberculosis, as well as an outbreak of yellow fever in highly urbanized areas. Cholera has become pandemic for seven different outbreaks, and meningitis has reemerged in a new strain not treatable with existing vaccines. Finally, the influenza epidemic of the 2004–05 flu season hit the US in a climate of unpreparedness that should have been predictable.<sup>76</sup>

International cooperation is needed to ensure the production, availability, and adequate distribution of essential drugs determined to be crucial to public health in a variety of international settings. The term essential drugs refers to a compendium of pharmaceutical agents first compiled by the WHO in 1977, and regularly updated thereafter, to represent the basics for optimal treatment of a variety of conditions found in a population. The WHO's 1977 list included 208 drugs believed to provide "safe, effective treatment for the majority of communicable and noncommunicable diseases."<sup>77</sup>

In 2003, the Trade Related aspects of Intellectual Property Rights (TRIPS) and Public Health Decision initiatives laid groundwork for developing nations to avail themselves of necessary essential medicines more economically. Licenses issued to regulate importing and exporting mandates will increase the supply of patented pharmaceuticals released after 2004–05 (depending on the country of origin) at reduced pricing for poor nations. Market forces will still apply in an arena of negotiated prices that would encourage pharmaceutical manufacturers to reach agreements with developing countries at more economically feasible levels for the poor.<sup>73</sup> The Hastings Center is currently conducting a 2-year (2004–06) review of the relationship between TRIPS and access to beneficial biological materials, with the goal of developing recommendations for international pharmaceutical policy.<sup>49</sup>

#### 1.22.4.6 Ethical Implications

According to a WHO Working Group on medicinal R&D priorities, adequate levels of pharmaceutical agent research are currently ongoing for communicable diseases such as HIV/AIDS and other sexually transmitted diseases. Perhaps not surprisingly, these are diseases that are prevalent in Western societies as well as in developing nations, though their toll on health and life is far greater in developing regions such as Africa. Infectious disease in general receives attention in the developed world, as there is general recognition today that modern transportation renders all infectious diseases as global threats. Still, many infectious conditions no longer generally plague industrialized nations. Diseases that are prevalent predominantly in developing countries, such as tuberculosis and malaria, tend to be neglected by the research community. In addition to these more well-known illnesses, others such as trypanosomiasis, Chagas' disease, and leishmaniasis are foreign to economically established countries and receive scant attention in pharmaceutical

R&D.<sup>78</sup> A 2004 study of the relationship between published research on randomized clinical trials (RCTs) of pharmaceutical agents and the global burden of disease found that nearly half of the top 40 leading causes of death were not among any of the published RCT research articles.<sup>79</sup>

Clearly there needs to be more attention paid to the global burden of disease. Pharmaceutical companies are, of course, only one player in a complex set of institutional and political dynamics that create barriers to solving the problems of disease in the developing world. Solutions must be pursued at local, regional, and international forums, and should include nongovernmental organizations (NGOs), international relief agencies, and charitable foundations, for example, as well as national and international political entities.

Still, the level of investment in drugs that offer marginal benefits or for which there are already existing, efficacious drugs, while millions in developing nations suffer from diseases that could benefit from those funds, is ethically unsupportable. The economic factors are vexing, but ultimately unconvincing; an effective vaccine or affordable treatment for malaria or tuberculosis would be profitable, and there are avenues to subsidize R&D into less common maladies. For example, newer approaches to funding the development of necessary drug agents have partnered private and public organizations. In one instance, the pharmaceutical giant Novartis has joined with the government of Singapore to establish the Institute of Tropical Diseases. The Institute's initial goals will entail tackling remedies for dengue fever and drug-resistant tuberculosis.<sup>80</sup> Direct donor gifts of philanthropy are also making a difference. The Bill and Melinda Gates Foundation has provided \$168 million in grant funding for treatment and research targeting malaria. Overall, the Gates Foundation has contributed over \$3 billion to global health research.<sup>81</sup>

Today's international health inequities can be minimized through the equitable development and distribution of crucial pharmaceutical research agents. The increasing influence of the global economy coupled with the growth of population migration and international travel have created a climate of multinational interdependence that is difficult to ignore.<sup>50</sup> As a consequence, the health and productivity of all communities represents the vested interest of each nation in one another. As the pharmaceutical industry has strengthened its multinational influence, its presence – or absence – is keenly felt on all continents of the world. Encouraging signs such as the partnering of pharmaceutical companies and other interested parties are the proper first steps in battling the devastating toll disease takes on the developing world.

### 1.22.5 Mental Illness

The proper role of drugs in treating mental illness has been a topic of ethical concern at least since the second half of the nineteenth century and the issue periodically captures public attention. According to some medical historians, the use and distribution of psychotropic medication can be divided into three basic periods.<sup>82</sup> The first period was marked by the introduction of morphine in the late 1800s and concluded in the synthesis of barbital in 1903. The development of barbiturates characterized the second period, which took place during the first half of the twentieth century, through the 1949 discovery of the therapeutic effect of lithium for the treatment of mania. The third period commenced with the development of the first set of modern psychotropic drugs in the 1950s.

Corresponding to the development of more powerful and specific drugs in the second half of the twentieth century was a marked decrease in the number of inpatients at mental hospitals. Deinstitutionalization resulted in an increase in outpatients whose medical management consisted primarily of medication.<sup>83</sup> As a result of deinstitutionalization, effective medication, and effective education efforts on the part of psychiatry, public fears and misunderstanding of mental illness began to dispel to some degree.<sup>84</sup> By the 1970s, as pharmacotherapy became the primary treatment modality in psychiatry, the expectations for psychotropics and neuropharmacology were quite high. The emerging field of biological psychiatry was predicted to enable psychiatrists to understand the pathophysiology of mental illness. In addition, psychopharmacology was expected to generate the feedback needed to develop more effective and selective pharmacological treatments.<sup>85</sup> In the late 1980s, fluoxetine (Prozac), an SSRI, hit the market, and within 3 years it became the most highly prescribed antidepressant in the world.

#### 1.22.5.1 Treatment

In terms of prescription practices, there are five principal symptoms for which psychoactive drugs are most commonly prescribed: inability to cope, depression, anxiety, sleeplessness, and pain.<sup>86</sup> However, these common complaints may be secondary to other problems. The point at which these symptoms become severe enough to warrant medical treatment is somewhat arbitrary and varies among patients and doctors. The rate and type of psychotropic drug usage also varies greatly across the globe. While the US and Canada are the most prominent consumers of amphetamine-type stimulants, primarily methylphenidate, amphetamine, and various anorectics, many European countries consume a notably high



amount of benzodiazepine-type hypnotics, sedatives, and anxiolytics.<sup>87</sup> The blurry line between prescription of psychotropics for diagnosed mental illness and for complaints that do not fulfill criteria for mental illness makes it difficult to separate out medical and life style usages of psychotropics from treatment for recognized mental disorders.

WHO estimates that 450 million people suffer from a form of mental or brain disorder, including alcohol and substance abuse disorders.<sup>88</sup> The proportion of those suffering from mental and brain disorders on a global level is projected to rise to 15% by 2020.<sup>89</sup> In most industrialized countries, psychopharmaceuticals are prescribed for most mental illnesses, with or without additional or ancillary therapies.

There are significant ethical concerns regarding the use of many psychotropic medications. First, mental illnesses can be chronic, requiring many years or a lifetime of treatment. Yet, the side effects of psychotropics can be quite significant over the long term. Physicians are responsible for assessing the risks of, for example, long-acting neuroleptic medications, which include recovery time from adverse effects, lag time in building therapeutic dose, psychological disturbances due to injection, increased risk of neuroleptic malignant syndrome, tardive dyskinesia, and other extrapyramidal symptoms. Clearly, the introduction of atypical antipsychotic agents such as clozapine, risperidone, and ziprasidone (among others) has produced notable improvement in the treatment of mood disorders, some behavioral disorders, and other forms of mental illness.<sup>90,91</sup> While these drugs are less likely to cause the involuntary movements that are so problematic with the older antipsychotic drugs, they still have numerous side effects, including chest pain, high blood pressure, agitation, confusion and memory loss, sleep disturbances, and others. Mental illness is debilitating and involves significant suffering, yet clinical care requires a careful consideration of the long-term consequences of psychotropic drugs.

In general, therapeutic decisions should be based on the clinician–patient relationship, accurate assessment and diagnosis by the clinician, and careful consideration of the various treatment options, including expected benefits and risks. Longer acting (or depot) drugs, which release slowly into the bloodstream after being injected, have recently been introduced. They can help to solve the problem of adherence to regimens in those with mental illness. According to one study, serious mental illness adherence rates are at about 50%.<sup>92</sup> The consequences of not adhering to medication include exacerbation, rehospitalization, major disruptions in relationships, loss of employment, and even loss of housing or involvement in the criminal justice system.<sup>93</sup> However, depot drugs can also complicate medical decision-making. As there is a large difference in the half-life of some depot medications compared to older medications, it takes longer to eliminate side effects. Administration of long-acting medication changes a patient's timeframe for reversing a treatment decision. Further, long-acting medication can sometimes be used to treat an individual with a mental illness against his or her will. These ethical concerns, as well as the societal value of individual choice, are responsible for the lower than expected use of long-acting antipsychotic medications in the US.<sup>94</sup> Similarly, the introduction of surgically implantable medication delivery systems can provide psychiatric patients with uninterrupted access to medication for up to 14 months. Implanted under the skin, these systems can be removed, allowing reversibility. While some patients find such technologies more desirable because they simplify drug-taking, others report feeling controlled by such technologies.<sup>95</sup>

With the increased use of psychotropics, has also come a more lax attitude toward them among the general public as well as some clinicians. Administration of psychotropic drugs has become more casual, and their distribution more common. Increased use has been criticized by some who credit it to such things as “uninformed prescribing, inconsistent or lax prescribing; willful and consistent misprescribing for misuse; self-prescribing and self-administration” caused by “inadequate training; shortage of information; lenient or lax attitudes; lack of a sense of professional responsibility; unethical behaviour; personal drug addiction; criminal behaviour or direct financial interest.”<sup>86</sup> However, the increased use of psychotropics is also part of an expansion of the definition of mental illness and the greater receptivity of both the public and practitioners for the general management of mood and cognitive states with drugs.

#### 1.22.5.2 Decision-Making, Competence, Informed Consent

Informed consent has become the legal and philosophical cornerstone of physician–patient relationships. It is a key factor for all drug treatment, though here we will discuss it in relation to mental illness. The legal basis of the doctrine of informed consent is also a philosophical one, in that persons have a right to privacy and bodily integrity, and that, generally, only the person can decide whether to be treated and in what manner. The issue of competence revolves around an assessment of whether an individual has the mental capacity to make an autonomous decision, to understand the facts, to appreciate the consequences of making a particular decision, and to be consistent in their decision-making about it. Competence, however, is a legal term, and is binary; one is either competent or incompetent. Since the ability to perform a certain action, such as making a decision about medical care, is task-specific, the notion of capacity is

preferable to the more global notion of competence. In this sense, even an individual who has been declared legally incompetent with respect to his or her financial affairs, for example, is not necessarily so incapacitated that he or she cannot make a decision about how much medication can comfortably be tolerated. Even when it has been determined that an individual is incapable of making a particular decision, protestations against continuing even indicated, standard treatment (let alone innovative or investigational therapy) should be taken seriously and weighed carefully against the expected benefits and the amount of time required to manifest them. Alternative approaches should be considered under these circumstances, considering likely benefits to the patient and the inherent cost of forced treatment to the patient's well-being. The values underlying informed consent, especially patient self-determination, have also become reference points for identifying acceptable alternatives when a patient lacks the capacity to agree to a treatment or test.

In the mental illness consumer-movement, self-determination has become the guiding principle. Practitioners should respect patient autonomy unless there is a compelling reason against doing so.<sup>96</sup> Some even argue that if the patient is capable of expressing their wishes regarding treatment, those wishes must always be respected regardless of seeming irrationality.<sup>97</sup> Mental capacity is the main issue in balancing patient autonomy and practitioner responsibility to protect the patient from harm,<sup>98</sup> but capacity remains an extremely vague and controversial standard.

Some suggestions to mitigate the capacity problem have included such things as 'Ulysses contracts' or 'psychiatric living wills.' These are documents that are written when a person with mental illness is stable or in remission, and empowers another person to act on their behalf when they become mentally incapacitated, even if they are legally incompetent. For example, a person with bipolar disorder may empower a loved one to coerce them to take drugs when they are first entering a manic phase, a point at which people are generally feeling very good and will reject the idea of taking medication. Such documents are problematic, however, if they require action while a person is still technically competent; if a person is legally competent right now and refusing treatment, by what authority does a document written before have precedence over the individual's decision now? Such a document is legally unenforceable. However, once the individual becomes impaired enough to require a surrogate decision-maker, a psychiatric living will can be a useful expression of their desires.

The Interaction Model of Client Health Behavior (IMCHB) assumes that: "(1) clients are capable of making informed, independent, and competent choices, (2) those choices are affected by client singularity and by client-provider interactions, and (3) clients should be given the maximum amount of control feasible."<sup>99</sup> There is a noted link between the medication adherence of persons with mental illness to their relationship with their provider. Including patients with mental illness in decision-making also helps in the decision-making process, increases self-perceived competencies, promotes the team-player role, teaches specific skills, empowers the client, and recognizes, addresses and even sometimes overcomes system-based barriers.<sup>100</sup> Patient involvement in health-care decision-making has led health providers to shift the focus from simply alleviating symptoms to helping patients adapt to a life with chronic mental illness. Effective health-care requires informed, active, and independent clients who participate in determining the treatment goals, monitoring symptoms, evaluating the regimen, and in revising regimens.<sup>99</sup>

### 1.22.5.3 Competence and Consent in Research

Informed consent is not only important in clinical care, but in a subject's competence to make a decision about research participation. Berg and Appelbaum<sup>101</sup> have outlined four main standards for determining decision-making competence based on a framework developed by Appelbaum and Grisso.<sup>102</sup> The first standard, most widely used by courts and legislatures, is the ability to communicate a choice. Many potential subjects fail to reach this standard because they are unable to coherently communicate, whether due to chronic schizophrenia, various levels of consciousness due to psychotic episodes, or other disorders. The ability to communicate choice does not necessarily translate into the capacity to make a choice autonomously. Comatose, mute, catatonic, or severely depressed persons, individuals with manic or catatonic excitements, and persons with severe psychotic thought disorders or severe dementia will fall under this category.

A second standard used is the ability to understand relevant information. This understanding means that the potential subjects have the ability to comprehend the concepts involved in the informed consent disclosure. Understanding itself is not enough; if a person understands the information, but is not able to retain the information long enough to make a decision, they are not competent enough to consent. Impairments of intelligence, attention, and memory can all affect this ability. A third standard is the ability to appreciate the nature of the situation and its likely consequences. The subject must be able to apply the information to his or her own situation. Denial, delusions, and psychotic levels of distortion can all impair this ability. The final standard is the ability to manipulate information rationally. It is necessary that a potential subject possess reasoning capacity and the ability to employ logic to compare the risks and benefits of the treatment options.

Recently, psychiatric research has been scrutinized out of fear that individuals with mental disorders are at a higher risk of being exploited due to the effect of mental illness on decision-making ability. Patients with schizophrenia, for example, experience delusions, apathy, lack of insight, and impaired memory and mental flexibility, which can impede informed consent to research.<sup>103</sup> Subjects with psychiatric disorders have often failed to appreciate the nature of research and its possible impact on their treatment. Two multinational studies found that a diminished ability to appreciate that one is ill is prevalent among those with schizophrenia. Patients with schizophrenia or severe depression also had an impaired ability to appreciate the potential value of treatment.<sup>101</sup> The MacArthur Treatment Competence Study<sup>104</sup> found that subjects with schizophrenia were more likely to completely deny the presence of illness than were depressed patients (35% versus 4%). Most dementia patients lack the ability to recognize that they have a memory problem. This lack of ability to recognize their mental state could indicate an impaired ability to relate the research to their own situation.

Alzheimer's disease can also affect decision-making.<sup>105</sup> While many cognitive functions account for impaired decision-making abilities in Alzheimer's disease, neuropsychological measures of executive dysfunction were the best indicators of impaired decisional ability in Alzheimer's patients.<sup>106</sup> The issue of competence in elderly patients suffering from dementia has become increasingly significant as the clinical research on Alzheimer's disease is rapidly accelerating and aiming to develop methods of early detection and prevention. Dr Scott Kim and his colleagues write in the *American Journal of Psychiatry* that more subjects with relatively mild illness will begin to be invited to participate in therapeutic and nontherapeutic Alzheimer's research. Thus, there will likely be a large range in the ability of individuals to give consent, with some "not capable even while they maintain their 'social graces' and their expressive abilities."<sup>107</sup> In assessing the competency of patients with Alzheimer's disease under various legal standards, researchers have found that even mild to moderate Alzheimer's disease has a significant impact on treatment consent capacity.<sup>108</sup> Researchers do, however, reinforce the ethical principle that diagnosis of dementia does not necessarily imply incapacity.<sup>109</sup> Therefore, distinguishing capable from incapable Alzheimer's patients remains a considerable challenge.

Unlike research involving other populations considered vulnerable, such as children, prisoners, and fetuses, no additional federal regulations specifically govern research involving potential subjects who are cognitively impaired. The recommendations of the National Commission for the Protection of Human Subjects are similar to those made with respect to children.<sup>110</sup> Many psychiatric researchers, and a number of patient advocacy groups, have argued that many patients with mental disorders still possess substantial decision-making capacity. They believe that providing additional regulations for the mentally ill is paternalistic and that it would reinforce a social stigma about the disease and further impede research.

## 1.22.6 Emerging Issues

### 1.22.6.1 Enhancement and Life Style Drugs

Human use of ingestibles to achieve mind-altering effect predates recorded history. Paleoethnobotanical evidence suggests that the Middle Paleolithic Shandinar Neanderthals may have used *ephedra altissima* to obtain amphetamine-like effects as early as 50 000 BC, in what is now modern day Iraq.<sup>111</sup> Around 3000 BC the Sumerians in the southern Mesopotamia planted poppies and extracted its juice, which they called 'lucky' or 'happy,' an indication that they utilized it for its mood-brightening properties.<sup>112</sup> The use of fermented grapes was not only an early human discovery, but its importance is written into early records of human societies and embodied in religious rituals that persist to this day. Both Western and Eastern medicines traditionally recommended eating particular foods to induce proper cognitive as well as physical health. Nineteenth century America was particularly enamored of developing nutritional philosophies of health, from the botanical medicine of Samuel Thompson to the bland diets developed by Will Kellogg (corn flakes were invented as a bland breakfast to avoid stirring up adolescent passions) or Sylvester Graham (whose now-famous cracker was designed toward the same ends as corn flakes). If the use of ingestibles to try and change the human mind is ancient, so undoubtedly is the moral debate about the degree to which the activity is acceptable.

Though the attempt to change human functioning with food and drugs is ancient, the power to do so was rather limited until recent pharmaceutical advancements brought enhancement and life style drugs to the forefront of drug development and public debate. Enhancement and life style drugs will, for our purposes, refer to pharmaceuticals that change a human function in a desirable way in the absence of pathological processes. However simple that definition seems, it is fraught with problems – problems with differentiating pathological processes from natural ones, differentiating food from drugs, and differentiating activities we tend to think of as medical from those we categorize differently.

Life style drugs have therefore been defined in a number of ways, including drugs that: (1) alleviate or enhance life style problems or conditions, regardless of the cause,<sup>113</sup> (2) address health problems for which the underlying cause is in the realm of personal responsibility,<sup>114</sup> (3) address nonhealth problems,<sup>115</sup> or (4) improve general well-being.<sup>116</sup> It is how a drug is used, rather than its medicinal chemistry, that classifies it as a life style drug.<sup>114</sup> Though the parameters of the definition may be fuzzy, the increasingly selective alteration of our cognitive and affective states through neurochemical alteration promises more frequent, and specific, use of drugs by those who desire to improve a function that is already within the normal range.

The demand for life style drugs has been fueled by advances in neuroscience and neuropharmacology. For example, better understanding of the pathophysiology of depressive disorders and the discovery of SSRIs has led to safer and more effective treatments for mood disorders. New drugs with ever more selective actions on the neurochemistry of mood, anxiety, attention, and memory are under development. New agents acting on entirely new pathways and targets are in the research pipeline and offer immense potential in the treatment of neuropsychiatric disease.<sup>115</sup>

In the wake of consumer demand, pharmaceutical companies have increasingly begun to focus on lucrative life style drugs, such as remedies for impotence (Pfizer's Viagra), baldness (Merck's Propecia), weight reduction (Abbott's Meridia), and facial wrinkles (Allergan's Botox).<sup>117</sup> The 2003 life style drug market was estimated at \$23 billion.<sup>118</sup> In 2003, the top selling drugs in the US, by therapeutic class, were cholesterol-lowering drugs, followed by drugs for treating heartburn, anemia, thyroid conditions, elevated blood pressure, and depression.<sup>36</sup> SSRI drugs are now the second largest selling class of drugs in the US, with over 146 million total dispensed prescriptions written in 2005.<sup>119</sup> The 2004 world sales for erectile dysfunction drugs rose to \$2.7 billion, with US sales for the first 11 months topping \$406 million (only \$22 million less than US sales for Coca Cola).<sup>120</sup> The increasing focus on life style drugs raises ethical questions not only about proper use of these drugs, but issues of drug company priorities and third party payer responsibilities in responding to consumer demand.

Psychological faculties such as memory, appetite, mood, libido, and sleep, and executive functions such as attention, working memory, and inhibition, represent the most attractive targets for pharmacological enhancement.<sup>121</sup> Until recently, psychotropic medications for the treatment of diseases associated with these functions carried undesired side effects and high risks that made them attractive only for the amelioration of severe mental illness. Increasing knowledge of chemical neurotransmission, however, has enabled the formulation of drugs that affect their intended targets more specifically with fewer and less severe side effects. Not only are these drugs more effective in treating diseases, but they also present unique and increased abilities to heighten normal cognition, emotional and executive functions.

#### 1.22.6.1.1 Enhancing human functions

The debate over human enhancement centers primarily on the attempt to bypass mechanisms such as learning or behavioral reinforcement and directly moderate brain electrochemistry or structure.<sup>122</sup> Drawing on the body's own resources, or manipulating the external environment to effect change, does not raise the same ethical challenges. The myriad ethical and social challenges posed by enhancement pharmaceuticals, as well as other emerging neurotechnologies, have led to the emergence of the field of neuroethics. Neuroethics is defined as the analysis of, and remedial recommendations for, ethical challenges posed by chemical, organic, and electromechanical intervention in the brain.<sup>123</sup> Rather than base itself on a specific philosophical model, neuroethics is characterized by the particular technologies it examines. These technologies include psychopharmacology as well as brain imaging, brain-computer interfaces, cell transplants, and external and internal stimulation of the brain. Neuroethical inquiry into pharmaceuticals asks under which conditions chemical intervention in mental processes is ethical. What are the implications of using a drug that is developed for the treatment of disease to alter personality or to improve normal human abilities or characteristics? What standards should exist? Will advances in psychopharmacology be used as forms of social control? Might this potentially contribute to a widening gap of social inequality? Or, at the other extreme, might it encourage conformity of personality – are those a bit more irascible going to be encouraged, or coerced, to conform to a chemically induced standard of effect?

The use of life style or enhancement drugs poses thorny questions. The more philosophical questions are about categorization: what do terms such as average or normal functioning mean if we can improve functioning across the entire range of human capability? If Prozac can lift everyone's mood, what, then, is a normal or typical affect?<sup>5</sup> Will sadness or inner struggle be pathologized? If we can all be happy and well adjusted through Prozac, should insurance companies pay to reach that state of bliss? Should physicians be the vehicles for prescribing life style mood-altering technologies to their patients? What are the implications of using drugs or other neurotechnologies to micromanage mood, improve memory, maintain attentiveness, or improve sexuality?<sup>122</sup> Is there anything wrong with the emerging

field of 'cosmetic neurology,' i.e., using pharmaceuticals to achieve the same ends as cosmetic surgery.<sup>124</sup> The questions are both medical, in terms of the proper role of healthcare professionals, and social, in terms of whether broader society should encourage or discourage people to ingest pharmaceuticals to enhance behaviors, skills, and traits.

The specificity of modern neuropharmaceuticals raises concerns that are distinct from the generalized effects of previous life style drugs such as alcohol or nicotine. Let us take as an example the effort to develop drugs targeted at improving memory in humans.<sup>125</sup> The improvement of memory sounds attractive in the abstract, and certainly the development of drugs to boost or enhance memory function is desirable for those suffering from Alzheimer's or other conditions that affect memory. But there are many unknowns in the use of such drugs in the cognitively intact. The assumption is that memory drugs will simply increase the amount of memory we have available, leaving all other cognitive and affective processes unaffected. But in fact, memory is a selective, delicate process. There are experiences and data that the brain filters out, choosing specific kinds of data to remember, while specifically forgetting others. Who needs to remember the hour waiting in a long line at the bank, staring at the ceiling tiles, or to recall the amnesia induced directly after a personal trauma? Will memory enhancement drugs impair our selectivity process? Or might they target and enhance only certain kinds of memories, such as the traumatic or emotional memories, positive and negative, that the brain tends to retain? Might we end up awash in memories that are troubling to us, unable to forget a painful past? And how might a memory drug affect associated mental processes – such as mood (which is closely connected to memory) or attentiveness (daydreaming is often fueled by a sudden recollection)? Perhaps evolution has stabilized at a particular level of memory capacity because any additional capacity would sacrifice a certain cognitive flexibility, a plastic brain may have advantages over one crammed with memory.<sup>122</sup>

The concern is not only speculative: in 1999, scientists reported in *Nature* that they had genetically engineered mice with increased ability to perform learning tasks.<sup>126</sup> The scientists inserted a gene in mouse zygotes that increased the production of the protein subunit NR2B, part of the NMDA receptor. The mice also displayed physiological changes in the hippocampus (associated with learning) when compared to nontransgenic mice. However, subsequent research demonstrated that the mice with enhanced NR2B seemed to have a greater sensitivity to pain.<sup>127</sup> The original creators of the mice argued the mice may not feel the pain more acutely, but simply learn about pain more readily and thus seem to react more strongly. Still, it is troubling that even the most preliminary research on memory enhancement has already raised the question of whether enhancing memory might have unexpected collateral effects. Perhaps there is a link we do not understand between memory and pain, either at the structural or behavioral level. What other unexpected linkages might be discovered in attempts to change cognitive functions through induced physiological modification?

While most of the cognitive enhancement discussed in the literature focuses on memory or attentiveness, the range of cognitive abilities, of course, exceeds just these two traits. Learning, language, skilled motor behaviors, and executive functions (e.g., decision-making, goal setting, planning, and judgment) are all part of general cognition, and a drug that manages to enhance a greater range of function (especially executive function) may be more desirable than one that narrowly enhances memory alone.<sup>128</sup> But if memory drugs alone have collateral effects, how much more so might a drug that influences a greater range of cognitive functioning?

As a variety of such drugs begin appearing on the market, each individual will be challenged to explicitly consider the kind of self he or she wants to be. The debate is already engaged, with one group arguing that our astounding ability to manipulate our own biology is an integral part of who we are as human beings.<sup>129,130</sup> Opposed to them are those who believe that new technologies are an affront to our humanity, that they diminish what is essentially human nature.<sup>131,132</sup> The argument has no fundamentally right or wrong answers, emerging as it does from two philosophically different visions of human life. It will, however, have a profound impact on the reception of life style drugs in the coming decades.

An illustrative example of the use of a drug for a range of symptoms ranging from the clearly pathological through to enhancement is the debate over Ritalin and its analogs in children diagnosed (or not) with attention deficit disorder (ADD) and attention deficit/hyperactive disorder (ADHD). An examination of the case reveals a broader set of concerns about enhancement technologies.

#### 1.22.6.1.2 Ritalin in attention deficit disorder/attention deficit/hyperactive disorder

Attention deficit/hyperactivity disorder (ADHD) is a commonly diagnosed neurobehavioral disorder in children. Prevalence rates are estimated to be anywhere from 1.7% to 17.8% depending on diagnostic criteria and population studies,<sup>133</sup> though the rate is more commonly cited as being between 3% and 10%.<sup>134,135</sup> The Center for Disease Control reported that among the almost 4 million children 3–17 years old in US, about 6% of that group were diagnosed with ADHD in 2003.<sup>136</sup> Although diagnostic criteria have evolved over time, the condition remains characterized by above normal levels of impulsivity, inattention, and hyperactivity. The most obvious manifestations, as well as the most

common reason children are referred to physicians for diagnosis and treatment, are unacceptable classroom behavior and poor academic achievement. Currently, boys are more commonly diagnosed than girls, though that may be changing.<sup>137</sup>

There are no clinical tests for ADHD, so the diagnosis is subjective and situational. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), a manual published by the American Psychiatric Association that provides standardized criteria for diagnosis of psychiatric conditions, symptoms must begin before the age of 7 years and be present for at least 6 months and cause a significant impairment of function in more than one setting (e.g., social, academic, familial). However, determining the appropriateness of a preschooler's impulsivity in various settings is highly subjective. Children are prescribed stimulants in the absence of DSM criteria for ADHD, often at the behest of teachers and particularly when the children tend to demonstrate oppositional defiant disorder.<sup>138</sup> Even the youngest children are being diagnosed and treated, pharmacoepidemiological studies have documented a rise in overall psychoactive medication treatment for preschool children in the last decade, with a threefold rise in prescription rates specifically for stimulants in this age group since 1990.<sup>139</sup>

The treatment of choice for ADHD is amphetamines. Ritalin (methylphenidate) is a stimulant medication originally developed to treat ADHD, and newer stimulants have since entered the market, including Adderall, Strattera, and Concerta. Stimulants improve "disruptive behavioral inhibition, impulse control, selective attention, active working memory and executive functioning."<sup>140</sup> Significantly, Ritalin confers these benefits on normal people as well as those with ADHD.<sup>141</sup>

Controversy has surrounded the diagnosis of ADD and ADHD in children. While the use of stimulants to improve children's behavior was used as far back as the 1930s,<sup>142</sup> alarm has been raised at the rapid increase in diagnosis prescription rates. From 1990 to 1995, the annual US production of Ritalin increased fivefold, far exceeding that of any other country. By the late 1990s, the US was producing and consuming 90% of the world's Ritalin.<sup>143</sup> Concern over the use of drugs in small children led to widespread media and medical attention. A general perception arose that ADHD was overdiagnosed and stimulants overprescribed. Others have argued, in contrast, that the trends reflect better diagnosis, more effective treatment, and increased education and recognition of the syndrome.<sup>144</sup>

Part of the controversy lies in how children tend to be diagnosed. Teachers are often the first to bring up the possibility of ADHD when the child does not conform to classroom behavioral standards.<sup>145</sup> As children with ADHD are fidgety and seek out sources of stimulation, it has been suggested that the modern classroom setting, where children are required to sit still in a chair facing a teacher for long periods of time, is precisely the wrong kind of learning environment for these children.<sup>146</sup> Classrooms that permit more physical activity and interactive learning and are more developmentally appropriate are more likely to have fewer referrals for ADHD diagnosis.<sup>147</sup>

Pharmaceutical amphetamines have become an enhancement technology used by thousands of otherwise healthy people.<sup>148</sup> College students freely admit to using each others' stimulant pills as study aids, and students with prescriptions can do a brisk business in the dormitories, prescription amphetamines are among the most used and abused drugs among young people.<sup>143</sup> In younger children, it is difficult to determine the degree to which pressure from parents and teachers to put unruly children on stimulants can be untangled from more objective diagnoses. It is clear that some schools have pressured parents of difficult-to-manage children to administer Ritalin, some even by using threats of expulsion.<sup>147</sup> In wealthier school districts where competitive performance pressure is high, however, it tends to be parents who push the use of stimulants. In the absence of clear physiological pathologies or discrete functional identifiers, the constellation of traits that characterize ADHD are applicable to some degree or another in a large percentage of children.

Stimulant use for ADHD is a perfect example of how the line between medical treatment for recognized disorders and the use of drugs for enhancement is becoming blurred. There is little doubt that ADHD and ADD are seriously impeding the ability of certain children to perform well in school, get along with peers, and cooperate in family units. However, the disproportionate diagnosis of ADHD in the US suggests a strong cultural component. It has been said that American culture, with its emphasis on speed and constant sensory stimulation, is particularly ADD-ogenic.<sup>149</sup> However, the distinction may also stem from differences in cultural tolerances for specific child behaviors.<sup>150</sup>

#### 1.22.6.1.3 Conclusion: paying for life style drugs

The difference between a life style drug and a clinically therapeutic medicine can come down to the simple matter of who pays. US health plans deny coverage for pharmaceuticals not prescribed for a specific medical diagnosis. For the US federally funded Medicare program, as well as for national health plans in other developed countries such as the UK, pharmaceuticals that some could construe as primarily life style drugs are often covered by insurance. Examples include drugs for erectile dysfunction, menopausal symptoms, smoking cessation, and birth control. It is not the intention here to trivialize these conditions by giving them a life style classification, nevertheless, it can be argued that they are outside

the realm of pathology as classically defined. They do, however, bring into question the challenge of allocating scarce national (economic) healthcare resources intended for medical necessity. While rationing may not be the preferred method of allocating healthcare dollars, funds that support research, development, and distribution of pharmaceutical agents for anything less than medical need increase the challenges for government and employer-based funding.<sup>116</sup> A number of states (Washington, New Jersey, Illinois) in the US are currently considering imposing a vanity tax on cosmetic surgery and Botox injections – another indication that such pharmaceutical agents are viewed as not only elective in nature, but also unrelated to health matters requiring curative or medical care.

Clearly, we are currently witnessing only the leading edge of a wave of pharmaceuticals that will be used, and may even be intended and designed to be used, to enhance functions that would otherwise be considered in the normal range. The market will be lucrative and pharmaceutical companies may feel the pressure to dedicate more and more resources to developing markets that include large populations of nonmedical consumers. The danger is that drugs for specific pathological conditions may be neglected.

### 1.22.6.2 Pharmacogenomics/Pharmacogenetics

Pharmacogenomics and pharmacogenetics are both terms referring to the science of how genetics influences an individual's response to medication. The terms are often used interchangeably, although technically pharmacogenetics refers to the study of inherited differences in drug metabolism (pharmacokinetics) and response (i.e., receptors, pharmacodynamics), while pharmacogenomics refers to the study of the overall array of different genes that determine drug behavior. The field in general is being touted as a significant advance in improving how drugs will be developed and prescribed in the future. Despite major advances in drug therapy for many diseases, treatment remains suboptimal for a significant proportion of individuals because of unpredictable side effects or lack of response. Understanding how small differences (called single nucleotide polymorphisms (SNPs)) in genetic make-up can predict drug response may allow clinicians to tailor drug therapy to individual patients and avoid the morbidity and costs associated with adverse drug reactions or lack of effectiveness.

Right now companies are engaged in cataloging as many SNPs as possible, hoping to capitalize on their usefulness once the field matures. The development of pharmacogenomic research has opened up the potential for widespread changes in the way we approach the discovery and development of medical therapies and drugs. The ability to use genomic technology to understand how individuals with particular genotypes will respond to various drugs may allow manufacturers to streamline clinical testing and drug development. Pharmacogenetic drugs will allow targeted therapies, and may thus save money by avoiding less than optimal treatment strategies. They will improve dosing by helping predict optimal doses in a particular patient, and may decrease drug interactions. Collective pharmacogenomic statistics may aid national medication programs and formularies to choose the best overall drugs for a population. Finally, increased pharmacogenomic knowledge promises advanced screening for genetic disease, better preventive medicine, and even perhaps targeted genetic vaccines. At the same time, pharmacogenomics also holds the potential to drastically alter how we view the relationship between genes and disease, while posing ethical questions concerning the treatment of patients and data in pharmacogenomic clinical trials.

Current clinical trials aim to determine the efficacy of medical therapies and procedures through the use of pharmacogenetic profiling, attempting to correlate genotypes with disease or drug responsiveness. In order to reduce pharmacokinetic variability or the incidence of adverse events, these studies typically stratify research subjects, including or excluding subjects from the trial based on genotype.<sup>151</sup> It is precisely this type of genotypic stratification that poses several ethical as well as scientific challenges.

First, genotyping as either an inclusion or exclusion criteria could lead to a loss of benefits in research participation, unfair representation in clinical trials, or subject selection biases.<sup>151</sup> The categorization of patients into responders and nonresponders of drugs could lead to the development of new drugs licensed only for the specific genetic group of good responders.<sup>152</sup> Also, there has historically been underrepresentation of groups such as women, children, and the elderly in trials. Could the same underrepresentation occur with genetic subgroups such as race and ethnicity?<sup>153</sup> This is problematic because studies involving subject selection biases will not accurately reflect the response and adverse event profiles of the general population.

Some have argued that pharmacogenomics and the dawn of tailored medicine has the potential to create new therapeutic orphan populations. These would be genetically defined groups with limited access to new and more effective therapy, justified either by their small numbers, making drug development uneconomical, or by the nature of their genotype whereby no effective therapy can be discovered for them from existing technology.<sup>152</sup> It is precisely these genetically and socially marginalized groups that may be the ones most in need of genetically tailored treatment.

There could be several economic ramifications to the tailoring of drugs to specific subpopulations. Will the market incentive to develop drugs for particularly small groups be lessened or eliminated? Orphan populations may also be defined as too small in size to be economically advantageous; drugs for these groups would be very expensive if developed. The US Orphan Drug Law (in effect since 1983) provides financial incentives for companies to direct their efforts toward the development of pharmaceutical therapies for the 5000 or so orphan conditions.<sup>154,155</sup>

Pharmaceutical companies can also use pharmacogenomic studies largely to their advantage. Experts have suggested that pharmaceutical companies may design trials that are focused toward favoring certain drugs, using pharmacogenomic profiling to position their particular drug advantageously in the market.<sup>156</sup> Others suggest that the development of pharmacogenomics-based drugs targeted to specific subpopulations will lead to a narrowing of the markets for drugs.<sup>157</sup> Companies could create demand for drugs by offering tests to identify people who respond to that drug, while entire populations might be ignored in this market-driven style of drug development.<sup>151</sup> With this in mind, regulatory guidelines over pharmacogenomic trial design and conduct need to prevent companies from luring certain patients or avoiding particular genotypes that could adversely affect the positioning of their drug in the market.

Additionally, many are concerned that pharmacogenomic technology may exacerbate current global inequities in medical care. If these drugs and therapies are premium priced, will these innovations be restricted to the wealthy? What do we make of less developed countries who will have limited access to improved therapeutic treatments and expensive pharmacogenomic testing technology?<sup>152</sup>

Pharmacogenomic profiling and patient stratification could lead to the creation of new disease classifications or categories of conditions that are largely social in origin. Individuals with no serious health problems who are informed that they possess a drug-associated genetic polymorphism may now label themselves as ill. Genotyping could result in individuals being categorized as difficult to treat, less profitable to treat, or more expensive to treat.<sup>158</sup> Not only does this contribute to the social construction of disease, but introduces implications for how insurance is determined and how medical care is rationed, especially in the age of managed care. Fear of stigmatization may also affect willingness to participate in clinical trials.

How closely are differences in drug response related to genetic differences that arise from race and ethnicity? There exists an ongoing discussion over this precise question.<sup>159</sup> The recent development of ethnically targeted therapies has reopened the controversial debate over pharmacogenomics and race. BiDil, a new drug treatment for heart failure tested solely in one racial group, recently became the first drug to be approved by the FDA to treat heart failure in African-Americans only.<sup>160–162</sup> NitroMed began the African-American Heart Failure Trial (A-HeFT) in 2001, the first ever heart failure trial to be comprised solely of African-American patients. The study claimed that “observed racial disparities in mortality and therapeutic response rates in Black heart failure patients may be due in part to ethnic differences in the underlying pathophysiology of heart failure.”<sup>163,164</sup> This raises some important questions. Are there significant genetic differences between ethnic and racial groups? How good are current racial labels as indicators of genetics differences? Should these classifications even be used in this manner? It is possible that developments like these can breed discrimination and racism, reinforcing “discredited crude biological notions of race,”<sup>165</sup> with whole population groups becoming stigmatized.<sup>166</sup> Historically, clinical decisions based on ethnic or racial classification often leads to poor or ineffective care.<sup>167</sup>

## 1.22.7 Conclusion

In this chapter we have attempted to profile some of the ethical issues in drug development and delivery. The use of pharmaceuticals to cure a variety of ills is one of the great success stories of human technology, and has resulted in symptom relief and cures that were scarcely imagined by our forebears. In order to continue developing and using drugs as they increase in strength and specificity, it is important to clearly define the ethical basis of proper drug use and the pitfalls of our current means of creating and distributing them. To do so is to ensure continued development for the health and well-being of future generations.

## References

1. Engel, C. *Wild Health: How Animals Keep Themselves Well and What We Can Learn from Them*; Weidenfeld & Nicolson: London, 2002.
2. Fabrega, H., Jr. *Evolution of Sickness and Healing*; University of California Press: Berkeley, CA, 1997.
3. Martin, G. J. *Ethnobotany: A Methods Manual*; Earthscan: London, Sterling, 2004.
4. National Center for Health Statistics. *Health, United States, With Chartbook on Trends in the Health of Americans*. National Center for Health Statistics: Hyattsville, MD, 2004; p 1232.
5. Kramer, P. D. *Listening to Prozac*; Viking: New York, 1993.
6. Zonana, H. V. *J. Am. Acad. Psychiatry Law* **2003**, *31*, 372–376.



7. Conroy, S.; Choonara, I.; Impicciatore, P.; Mohn, A.; Arnell, H.; Rane, A.; Knoepfel, C.; Seyberth, H.; Pandolfini, C.; Raffaelli, M. P. et al. *Br. Med. J.* **2000**, *320*, 79–82.
8. Angarola, R. T.; Joranson, D. E. *Am. Pain Society Bull.* **1995**, *5*, 14–15.
9. Drazen, J. M. *N. Engl. J. Med.* **2005**, *352*, 1131–1132.
10. Maxwell, S. R.; Webb, D. J. *Lancet* **2005**, *365*, 449–451.
11. Wadman, M. *Nature* **2005**, *434*, 554–556.
12. Couzin, J. *Science* **2005**, *307*, 1183–1185.
13. Frantz, S. *Nature* **2005**, *434*, 557–558.
14. New Warning for Heartburn Drug Propulsid. CNN Interactive: Washington DC, June 30, 1998. <http://www.cnn.com/HEALTH/9806/30/heartburn.drug/> (accessed March 2006).
15. Harris, G.; Koli, E. Lucrative Drug, Danger Signals and the F.D.A. *New York Times*, June 10, 2005; p A1.
16. Blanck, H. M.; Khan, L. K.; Serdula, M. K. *Prev. Med.* **2004**, *39*, 1243–1248.
17. Connelly, H. M.; Cray, J. L.; McGoon, M. D.; Hensrud, D. D.; Edwards, B. S.; Edwards, W. D.; Schaff, H. V. *N. Engl. J. Med.* **1997**, *337*, 581–588.
18. Noller, K. L. *JAMA* **2002**, *288*, 368–369.
19. Fugh-Berman, A.; Pearson, C. *Pharmacotherapy* **2004**, *22*, 1205–1208.
20. Lacey, J., Jr.; Mink, P. J.; Lubin, J. H.; Sherman, M. E.; Troisi, R.; Hartge, P.; Schatzkin, A.; Schairer, C. *JAMA* **2002**, *288*, 334–341.
21. Writing Group for the Women's Health Initiative Investigators. *JAMA* **2002**, *288*, 321–333.
22. American College of Neuropsychopharmacology (ACNP). *Executive Summary: Preliminary Report of the Task Force on SSRIs and Suicidal Behavior in Youth*, Nashville, TN, Jan 21, 2004.
23. Fergusson, D.; Doucette, S.; Glass, K. C.; Shapiro, S.; Healy, D.; Hebert, P.; Hutton, B. *Br. Med. J.* **2005**, *330*, 396–403.
24. Jick, H.; Kaye, J. A.; Jick, S. S. *JAMA* **2004**, *292*, 338–343.
25. U.S. Food and Drug Administration (USFDA). *Public Health Advisory: Suicidality in Children and Adolescents Being Treated with Antidepressant Medications*, Oct 15, 2004. <http://www.fda.gov/> (accessed March 2006).
26. Meek, C. *Can. Med. Assoc. J.* **2004**, *170*, 455.
27. Varley, C. K. *JAMA* **2003**, *290*, 1091–1093.
28. Whittington, C. J.; Kendall, T.; Fonagy, P.; Cottrell, D.; Cotgrove, A.; Boddington, E. *Lancet* **2004**, *363*, 1341–1345.
29. Jick, H.; Kaye, J. A.; Jick, S. S. *JAMA* **2004**, *292*, 338–343.
30. Jureidini, J. N.; Doecke, C. J.; Mansfield, P. R.; Haby, M. M.; Menkes, D. B.; Tonkin, A. L. *Br. Med. J.* **2004**, *328*, 879–883.
31. NDC Health Corporation. NDCHealth Reviews 2004 Pharmaceutical Market Information. [http://www.pnewswire.com/cgi-bin/micro\\_stories.pl?ACCT=603950&TICK=NDC&STORY=/www/story/05-02-2005/0003537082&EDATE=May+2,+2005](http://www.pnewswire.com/cgi-bin/micro_stories.pl?ACCT=603950&TICK=NDC&STORY=/www/story/05-02-2005/0003537082&EDATE=May+2,+2005) (accessed March 2006).
32. Angell, M. The Truth About the Drug Companies. *New York Review of Books* [Online] **2004**, *51*, July 15, 2004. <http://www.nybooks.com/articles/17244> (accessed March 2006).
33. Viswanathan, S. *Pharmaceutical Formulation and Quality* [Online] **2004**, March/April. <http://www.pharmaquality.com/Cover%20Story5.htm> (accessed March 2006).
34. Burke, M. A.; de Francisco, A. *Managing Financial Flows for Health Research*; Global Forum for Health Research: Geneva, Switzerland, 2004.
35. L. Goshman, *J. Pharmacy Soc. Wisconsin* 2001, July/August.
36. Peters, C. P. *Fundamentals of the Prescription Drug Market*; National Health Policy Forum: Washington, DC, 2004.
37. Spector, R. *Stanford Med. Magazine* [Online] **2005**, *22*. <http://mednews.stanford.edu/stanmed/2005summer/drugs-metoo.html> (accessed March 2006).
38. Garattini, S. *J. Nephrol.* **1997**, *10*, 283–294.
39. Lee, T. N. *N. Engl. J. Med.* **2004**, *350*, 211–212.
40. Infectious Diseases Society of America. *Bad Bugs, No Drugs*; Alexandria, VA, 2004.
41. Nathan, C. *Nature* **2004**, *431*, 899–902.
42. Global Alliance for TB Drug Development. *The Economics of TB Drug Development*; New York, 2001.
43. Silverstein, K. Millions for Viagra, Pennies for Diseases of the Poor. *The Nation*. July 19, 1999. <http://www.thenation.com/doc.mhtml%3Fi=19990719&s=silverstein> (accessed March 2006).
44. US Food and Drug Administration. *Milestones in U.S. Food and Drug Law History*. <http://www.fda.gov/opacom/backgrounders/miles.html> (accessed March 2006).
45. Doran, E.; Robertson, J.; Henry, D. *Social Sci. Med.* **2004**, *60*, 1437–1443.
46. US Food and Drug Administration. *FDA's Mission Statement*. <http://www.fda.gov/opacom/morechoices/mission.html> (accessed March 2006).
47. Okie, S. N. *N. Engl. J. Med.* **2005**, *352*, 1063–1066.
48. Kmietowicz, Z. *Br. Med. J.* **2005**, *330*, 805.
49. Wasunna, A.; Johnston, J. *Intellectual Property Rights in Pharmaceuticals and Biological Materials: Ensuring Innovation or Barring Access?* July 2002–March 2006. <http://www.thehastingscenter.org> (accessed March 2006).
50. Obaro, S. K.; Palmer, A. *Vaccine* **2003**, *21*, 1423–1431.
51. Mayor, S. *Br. Med. J.* **2005**, *330*, 748.
52. IMS Health. *IMS Reports 2004 Global Pharmaceutical Sales Grew 7 percent to \$550 Billion*; Press Release; Fairfield, CT, March 9, 2005. [http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599\\_3665\\_71496463,00.html](http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_71496463,00.html) (accessed March 2006).
53. World Health Organization. *What are Essential Medicines? Access, Quality and Rational Use of Medicines and Essential Medicines*. <http://www.who.int/> (accessed March 2006).
54. World Watch Institute. *Viagra, Malaria, and the Future of Health Care*. *World Watch: Matters of Scale* [Online] **2000**, May/June. <http://www.worldwatch.org/pubs/mag/2000/133/mos/> (accessed March 2006).
55. Wikipedia. *Diseases of Affluence*. [http://en.wikipedia.org/wiki/Diseases\\_of\\_affluence](http://en.wikipedia.org/wiki/Diseases_of_affluence) (accessed March 2006).
56. Tomes, N. J. N. *N. Engl. J. Med.* **1993**, *328*, 670.
57. Ely, J. J. *Rev. Environ. Health* **2003**, *18*, 111–129.
58. Leeb, M. *Nature* **2004**, *431*, 892–893.
59. The Global Forum for Health Research. *The 10/90 Gap Now 2005*. <http://www.globalforumhealth.org/site/003...The%2010%2090%20gap/001...Now.php> (accessed March 2006).

60. White, C. *Br. Med. J.* **2004**, *329*, 1064–1065.
61. Lewison, G.; Rippon, L.; de Francisco, A.; Lipworth, S. *Outputs, Expenditures on Health Research in Eight Disease Areas, 1996–2001*, Global Forum for Health Research, Forum 8, Mexico City, Nov 2004.
62. Murray, C. J.; Lopez, A. D. *Lancet* **1997**, *349*, 1269–1276.
63. World Health Organization. *The World Health Report 2002: Reducing Risks, Promoting Healthy Life*, Geneva, Switzerland, 2002.
64. World Health Organization. *Epidemiology and Burden of Disease*, Geneva, Switzerland, 2003.
65. Swafford, S. *Br. Med. J.* **1997**, *314*, 1367.
66. Greenberg, H.; Raymond, S.U.; Leeder, S. R. *Health Affairs* [Online] 2005, DOI: 10.1377/hlthaff.w5.31.
67. Hamilton, C. Diseases of affluence and other paradoxes. *The Australian Financial Review*, Oct 15, 2004, p 8.
68. Medical College of Wisconsin. *Global Health in the 21st Century*. <http://www.healthlink.mcw.edu/article/977858884.html> (accessed March 2006).
69. Roche UK. *Weight Management*. <http://www.rocheuk.com/html/health/WeightManagement.asp> (accessed March 2006).
70. Hilton, I. A bitter pill for the world's poor. *The Guardian*, London, Jan 5, 2000.
71. Cook, I. G.; Dummer, A.; Trevor, J. B. *Health Policy* **2004**, *67*, 329–343.
72. Triggler, D. J. *Drug Devel. Res.* **2003**, *59*, 269–291.
73. Granville, B. The Right Response for the Pharmaceutical Industry. In *Delivering Essential Medicines: The Way Forward*; Attaran, A., Ed.; Royal Institute of International Affairs: London, 2003.
74. Foster, J. W. North-South Institute; Social Watch 2004 [cited March 5, 2005]. <http://www.socwatch.org/en/informesTematicos/81.html> (accessed March 2006).
75. Bulter, D. *Nature* **2003**, *424*, 604.
76. World Health Organization. Global Defense against the Infectious Disease Threat. In *Communicable Diseases 2002*; Kindhauser, M. K., Ed.; World Health Organization: Geneva, Switzerland, 2003, pp 56–103.
77. World Health Organization. What are Essential Medicines? Access, Quality and Rational Use of Medicines and Essential Medicines. <http://www.who.int/> (accessed March 2006).
78. World Health Organization/Industry Drug Development Working Group. Working Paper on Priority Infectious Diseases Requiring Additional R & D. WHO-IFPMA Round Table: Geneva, Switzerland, July 2001.
79. Rochon, P. A.; Mashari, A.; Cohen, A.; Misra, A.; Laxer, D.; Streiner, D. L.; Dergal, J. M.; Clark, J. P.; Gold, J.; Binns, M. A. *Can. Med. Assoc. J.* **2004**, *170*, 1673–1677.
80. Butler, D. *Nature* **2003**, *426*, 754.
81. Butler, D. *Nature* **2003**, *425*, 331.
82. Ban, T. A. *Prog. Neuro-Psychopharmacol. Biol. Psych.* **2001**, *25*, 709–727.
83. *The Triumph of Psychopharmacology and The Story of CINP*; Ban, T. A.; Healy, D.; Shorter, E., Eds.; Animula Publishing House: Budapest, 2000, pp 9–10.
84. Ghodse, H.; Khan, I. *Psychoactive Drugs: Improving Prescribing Practices*; World Health Organization: Geneva, Switzerland, 1988.
85. Ban, T. A. They Used to Call it Psychiatry. In *The Psychopharmacologists*; Healy, D., Ed.; Chapman and Hall: London, 1996, pp 587–620.
86. Ghodse, H. *Br. J. Psychiatry* **2003**, *183*, 15–21.
87. International Narcotics Control Board. *Report of the International Narcotics Control Board for 2000 (E/INCB/2000/1)*. United Nations: New York, 2001.
88. World Health Organization. *The World Health Report 2001. Mental Health: New Understanding, New Hope*; Geneva, Switzerland, 2001.
89. World Health Assembly. *Mental Health: Responding to the Call for Action*. Report by the Secretariat A55/18. World Health Organization: Geneva, Switzerland, 2002.
90. Buckley, P. F. *Biol. Psychiatry* **2001**, *50*, 912–924.
91. Dawkins, K.; Lieberman, J. A.; Lebowitz, B. D.; Hsiao, J. K. *Schizophr. Bull.* **1999**, *25*, 395–405.
92. Fenton, W. S.; Byler, C. R.; Heinssen, R. K. *Schizophr. Bull.* **1997**, *3*, 637–651.
93. Pyne, J.; Bean, D.; Sullivan, G. *J. Nervous Mental Dis.* **2001**, *89*, 146–153.
94. Roberts, L. W.; Geppert, C. M. *Compreh. Psychiatry* **2004**, *45*, 161–167.
95. Irani, F.; Dankert, M.; Brensinger, C.; Bilker, W. B.; Nair, S. R.; Kohler, C. G.; Kanes, S. J.; Turetsky, B. I.; Moberg, P. J.; Ragland, J. D.; et al. *Neuropsychopharmacology* **2004**, *29*, 960–968.
96. Rand, C. S.; Sevick, M. A. *Control. Clin. Trials* **2000**, *21*, 241S–247S.
97. Chamberlin, J. *Psychiatr. Rehab. J.* **1998**, *21*, 405–408.
98. Wong, J. G.; Clare, I. C. H.; Gnn, M. J.; Holland, A. J. *Psychol. Med.* **1999**, *29*, 437–446.
99. Mahone, I. H. *Arch. Psychiatr. Nursing* **2004**, *18*, 126–134.
100. Barrett, K. E.; Taylor, D. W.; Pullo, R. E.; Dunlap, D. A. *Psychiatr. Rehab. J.* **1999**, *21*, 241–249.
101. Berg, J. W.; Appelbaum, P. S. Subject's Capacity to Consent to Neurobiological Research. In *Ethics in Psychiatric Research*; Pincus, H. A., Lieberman, J. A., Ferris, S., Eds.; American Psychiatric Association: Washington DC, 1999, pp 81–106.
102. Appelbaum, P. S.; Grisso, T. N. *Engl. J. Med.* **1988**, *319*, 1635–1638.
103. Cohen, B. J.; McGarvey, E. L.; Pinkerton, R. C.; Kryzhanivska, L. *J. Am. Acad. Psychiatry Law* **2004**, *32*, 134–143.
104. Appelbaum, P. S.; Grisso, T. *Law Human Behav.* **1995**, *19*, 105–126.
105. National Bioethics Advisory Commission. *Research Involving Persons With Mental Disorders That May Affect Decision-making Capacity*. NBAC: Rockville, MD, 1998.
106. Marson, D. C.; Annis, S. M.; McInturff, B.; Bartolucci, A.; Harrell, L. E. *Neurology* **1999**, *53*, 1983–1992.
107. Kim, S. Y. H.; Caine, E. D.; Currier, G. W.; Leibovici, A.; Rayn, J. M. *Am. J. Psychiatry* **2001**, *158*, 712–717.
108. Marson, D. C.; Ingram, K. K.; Cody, H. A.; Harrell, L. E. *Arch. Neurol.* **1995**, *52*, 949–954.
109. Kim, S. Y. H.; Karlawish, J. H. T.; Caine, E. D. *Am. J. Geriatr. Psychiatry* **2002**, *10*, 151–165.
110. Penslar, R. L. *Institutional Review Board Guidebook. Chapter VI: Special Classes of Subjects*. [http://www.hhs.gov/ohrp/irb/irb\\_chapter6.htm#g5](http://www.hhs.gov/ohrp/irb/irb_chapter6.htm#g5) (accessed March 2006).
111. Merlin, M. D. *Econ. Bot.* **2003**, *57*, 295–323.
112. Spiegel, R. *Psychopharmacology: An Introduction*; Wiley: West Sussex, England, 2003.
113. Mitrany, D. *PharmacoEconomics* **2001**, *19*, 441–448.
114. Farah, M. J.; Wolpe, P. R. *Hastings Cent. Rep.* **2004**, *34*, 35–45.
115. Gilbert, D. *Br. Med. J.* **2000**, *321*, 1341–1344.

116. Carlsson, A. *Brain Res. Bull.* **1999**, *50*, 363.
117. *Physician's Desk Reference* (web version). Thomson Healthcare: Montvale, NJ, 2005. <http://www.pdr.net> (accessed March 2006).
118. Coe, J. *The Lifestyle Drug Outlook to 2008: Unlocking New Value in Well-Being*; Business Insights: Dallas, 2003.
119. IMS. *Leading 20 Therapeutic Classes by Total U.S. Dispensed Prescriptions, MAT (Moving Annual Total)*. [http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599\\_73914140\\_73916014,00.html](http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_73914140_73916014,00.html) (accessed March 2006).
120. Shmit, J. Impotence drugs selling slowly. *USA Today* [Online] February 2, 2005.
121. Farah, M. J.; Illes, J.; Cook-Deegan, R.; Garnder, H.; Kandel, E.; King, P.; Parens, E.; Sahakian, B.; Wolpe, P. R. *Nat. Rev. Neurosci.* **2004**, *5*, 421–425.
122. Wolpe, P. R. *Brain Cogn.* **2002**, *50*, 387–395.
123. Wolpe, P. R. Neuroethics. In *Encyclopedia of Bioethics*, 3rd ed.; Post, S. G., Ed.; Macmillan Reference: New York, 2004; Vol. 4, pp 1894–1898.
124. Chatterjee, A. *Neurology* **2004**, *63*, 874–968.
125. Furey, M. L.; Pietrini, P.; Haxby, J. V. *Science* **2000**, *290*, 2315–2319.
126. Tang, Y. P.; Shimizu, E.; Dube, G. R.; Rampon, C.; Kerchner, G. A.; Zhuo, M.; Liu, G.; Tsien, J. Z. *Nature* **1999**, *401*, 63–69.
127. Wei, F.; Wang, G. D.; Kerchner, G. A.; Kim, S. J.; Xu, H. M.; Chen, Z. F.; Zhuo, M. *Nat. Neurosci.* **2001**, *4*, 164–169.
128. Whitehouse, P. J.; Juengst, E.; Mehlman, M.; Murray, T. H. *Hastings Center Report* **1997**, *27*, 14–22.
129. Hughes, J. H. *Citizen Cyborg*; Westview Press: Boulder, CO, 2004.
130. Stock, G. *Redesigning Humans*; Houghton Mifflin: Boston, MA, 2003.
131. Fukuyama, F. *Our Posthuman Future*; Farrar, Straus and Giroux: New York, 2002.
132. McKibben, B. *Enough: Staying Human in an Engineered Age*; Times Books: New York, 2003.
133. Elia, J.; Ambrosini, P. J.; Rapport, J. L. *N. Engl. J. Med.* **1999**, *340*, 780–788.
134. Spencer, T. J.; Biederman, J.; Wilens, T. E.; Faraone, S. V. *J. Clin. Psychiatry* **2002**, *63*, 3–9.
135. Swanson, J. M.; Seargent, J. A.; Taylor, E.; Sonuga-Barke, E. J.; Jensen, P. S.; Cantwell, D. P. *Lancet* **1998**, *351*, 429–433.
136. Dey, A. N.; Bloom, B. *Vital & Health Statistics; Series 10: Data From the National Health Survey*, **2005**, *223*, 1–78.
137. Robison, L. M.; Skaer, T. L.; Sclar, D. A.; Galin, R. S. *CNS Drugs* **2002**, *16*, 129–137.
138. Angold, A.; Erkanli, A.; Egger, H. L.; Costello, E. J. *J. Am. Acad. Child Adolesc. Psychiatry* **2000**, *39*, 975–984.
139. Connor, D. F. *J. Dev. Behav. Pediatr.* **2002**, *23*, S1–S9.
140. National Health and Medical Research Council (Australia). *Attention Deficit Hyperactivity Disorder – Part II Management, Section 4.2 Stimulant Medication*, 1997. Commonwealth of Australia. <http://www.nhmrc.gov.au/publications/adhd/contents.htm> (accessed March 2006).
141. Kuhn, C.; Swartzwelder, S.; Wilson, W. *Buzzed: The Straight Facts About the Most Used and Abused Drugs from Alcohol to Ecstasy*, 2nd ed.; W.W. Norton & Company: New York, 2003.
142. Bradley, C. *Am. J. Psychiatry* **1937**, *94*, 577–588.
143. Elliott, C. *Better than Well*; Norton: New York, 2003.
144. Accardo, P.; Blondis, T. A. *J. Pediatr.* **2001**, *138*, 6–9.
145. Powers, T. Race for perfection: children's rights and enhancement drugs. *J. Law Health* **1998**, *13*, 141–169.
146. Yaroshevsky, F.; Bakiaris, V. Deficit of Attention Disorder. In *Family Therapy as an Alternative to Medication*; Prosky, P. S.; Keith, D., Eds.; Brunner-Routledge: New York, 2003.
147. Kohn, A. *What to Look for in a Classroom: and Other Essays*; Jossey-Bass: San Francisco, 1998.
148. Farah, M. *Nat. Neurosci.* **2002**, *5*, 1123–1129.
149. DeGrandpre, R. *Ritalin Nation*; W.W. Norton: New York, 1999.
150. Cohan, J. A. Psychiatric ethics and emerging issues of psychopharmacology in the treatment of Depression. *J. Contemp. Health Law Policy* **2003**, *20*, 115–172.
151. Issa, A. M. *Nat. Rev.: Drug Disc.* **2002**, *1*, 300–304.
152. Smart, A.; Martin, P.; Parker, M. *Bioethics* **2004**, *18*, 322–343.
153. Wolpe, P. R. *Pharm. Therapeut.* **2001**, 16–17.
154. National Organization for Rare Diseases (NORD). *Understanding the Orphan Drug Act*. <http://www.rarediseases.org> (accessed March 2006).
155. Food and Drug Administration. *Miscellaneous Provisions Relating to the Orphan Drug Act*. <http://www.fda.gov/> (accessed March 2006).
156. Bodenheimer, T. *N. Engl. J. Med.* **2000**, *342*, 1539–1544.
157. Regaldo, A. *Am. J. Health Sys. Pharm.* **1999**, *56*, 40–50.
158. Rothstein, M. A.; Epps, P. G. *Nat. Rev. Genet.* **2001**, *2*, 228–231.
159. Burchard, E. G. *N. Engl. J. Med.* **2003**, *384*, 1170–1175.
160. Rahemtulla, T.; Bhopal, R. *Br. Med. J.* **2005**, *330*, 1036–1037.
161. Khan, J. D. *Yale J. Health Policy Law Ethics* **2004**, *4*, 1–46.
162. Food and Drug Administration. FDA Approves BiDil Heart Failure Drug for Black Patients. *FDA News* July 23, 2005.
163. NitroMed, Inc. *NitroMed Initiates Confirmatory BiDil Trial in African American Heart Failure Patients*; Press Release March 17, 2001. <http://www.nitromed.com/press/03-17-01.html> (accessed March 2006).
164. Taylor, A. L.; Ziesche, S.; Yancy, C.; Carson, P.; D'Agostino, R.; Ferdinand, K.; Taylor, M.; Adams, K.; Sabolinski, M.; Worcel, M. et al. *N. Engl. J. Med.* **2004**, *351*, 2049–2057.
165. Witzig, R. *Ann. Intern. Med.* **1996**, *125*, 675–679.
166. Dolgin, J. L. *Studies in the History and Philosophy of Biological and Biomedical Sciences* **2001**, *32*, 705–721.
167. Bhopal, R. *Br. Med. J.* **1998**, *316*, 1239–1242.
168. Mathers, C. D.; Stein, C.; Fat, D. M.; Rao, C.; Inoue, M.; Tomijima, N.; Bernard, C.; Lopez, A.D.; Murray, C. J. L. Global Burden of Disease 2000: Version 2 Methods and Results. In *Global Programme on Evidence for Health Policy*; WHO: Geneva, Switzerland, 2002, pp 32–37.

## Biographies



**Paul Root Wolpe, PhD**, is a professor in the Department of Psychiatry at the University of Pennsylvania, where he also holds appointments in the Department of Medical Ethics and the Department of Sociology. He is a Senior Fellow of Penn's Center for Bioethics, is the Director of the Program in Psychiatry and Ethics at the School of Medicine, and is a Senior Fellow of the Leonard Davis Institute for Health Economics. Dr Wolpe serves as the first Chief of Bioethics for the National Aeronautics and Space Administration (NASA), where he is responsible for formulating policy on space ethics and safeguarding research subjects. Dr Wolpe is also the first National Bioethics Advisor to the Planned Parenthood Federation of America, advising them on the reproductive implications of emerging reproductive technologies and changing social dynamics.

Dr Wolpe is the author of numerous articles and book chapters in sociology, medicine, and bioethics, and has contributed to a variety of encyclopedias on bioethical issues. His research examines the role of ideology, religion, and culture in medical thought, especially in relation to emerging biotechnologies, including nanotechnology, reproductive and genetic technology, and neurotechnology. Dr Wolpe is a founder of the field of neuroethics, which specifically focuses on the social, legal, and ethical issues related to new brain technologies and psychopharmaceuticals, and is considered an expert on the impact of biotechnology and psychopharmaceuticals on the human body. He is the author of the textbook *Sexuality and Gender in Society* and the end-of-life guide *In the Winter of Life*, and is currently writing a book on emerging technologies.

Dr Wolpe sits on a number of national and international nonprofit organizational boards and working groups, and is a consultant to the biomedical industry. He is Associate Editor of the *American Journal of Bioethics*, and is a member of the National Board of the American Society for Bioethics and Humanities. He serves on the Ethical Advisory Board of the State of Pennsylvania, and is bioethics advisor to the Philadelphia Department of Human Services, Children and Youth Division. A dynamic speaker who has won a number of teaching and writing awards, Dr Wolpe has been chosen by The Teaching Company as a 'Superstar Teacher of America,' and two of his courses are nationally distributed on audio and videotape. Dr Wolpe is a regular columnist on biotechnology for the *Philadelphia Inquirer*, and appears frequently in the broadcast and print media.



**Michelle Sahl** is principal and owner of MJSahl Consulting, a Philadelphia healthcare management and consultancy firm specializing in strategic planning, market assessment, economic feasibility studies, and public policy analyses for

healthcare, governmental, and nonprofit organizations. For over 20 years, Ms Sahl's healthcare industry experience has ranged from mental health research and program administration in major academic medical centers, to university-level teaching engagements. Prior to establishing her own consultancy business, Ms Sahl held positions in various organizations, including New England Medical Center, Harvard University, Laventhol & Horwath, and the University of Pennsylvania Health System. Recently, Ms Sahl has focused her interests in the areas of urban health, medical ethics, and population-based healthcare analyses. She holds degrees from Northwestern University (BA), Boston University (MEd), and Northeastern University (MBA). Currently, Ms. Sahl is completing dual programs for a Master's degree in Bioethics (University of Pennsylvania) and a doctoral degree in Health Policy (The University of the Sciences in Philadelphia). More information on Ms Sahl's experience is available on her website at <http://home.earthlink.net/~healthypublicpolicy/index.html>



**James R Howard** is from Concord, New Hampshire. He received his Master of Bioethics from the University of Pennsylvania in 2005. He served as a Clinical Research Project Manager for the University of Utah Department of Neurology, and performed research on diencephalic amnesia while an undergraduate at the University of New Hampshire. He is currently the Administrator for the University of Pennsylvania Institutional Review Board #1. He has worked with the American Association for the Advancement of Science, the Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization, and DuPont/Pioneer Hi-Bred on projects related to bioethics, health policy, and regulatory affairs.