Pharmacology: Policy Implications Of New Psychiatric Drugs
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Four background issues are important in understanding the policy debate surrounding new drugs for psychiatric care. These are the impact of scientific progress, society’s nonrational attitudes toward drugs and toward health and disease, and the “stigma” of psychiatric treatment. After touching on these issues, we then assess pharmacological treatment advances and their consequences for future policy considerations.

Background Issues

The pace of progress. We are far beyond the era when “schools” or an “expert’s” preference sufficed as the basis for rational therapeutics and when scientifically ascertainable fact was rarely deemed relevant in the treatment of psychiatric disorder. Today clinical judgments and policy can be informed by large, methodologically sophisticated, systematic studies, such as those produced for psychiatric epidemiology.

The key starting point for all physician/patient encounters is diagnosis. Explicit, precise classification systems to aid diagnosis exist, so that comparisons, improvements, and revisions can be prospectively implemented or retrospectively applied. The natural history, course, and outcomes of psychiatric disorders and the relative roles of genetic, developmental, and psychosocial predisposing and precipitating factors are under systematic study. Advanced methodologies in clinical trials for efficacy and safety in mental health treatment are in hand. Psychotherapy research now uses manuals specifying particular steps in treatment. Molecular and cellular biology and refined definitions of brain neurocircuitry are providing new territories for therapeutic and etiologic research.

In brief, precision in diagnosis, in assessing disease vulnerability and risk factors, in monitoring treatments and outcomes, and in understanding the basic mode of drug actions in psychiatric treatment is fully comparable to that for many medical disorders. As in all of medicine, there are unsolved puzzles, and disease research parameters should continue to be improved. But for policy purposes it is clear that progress is moving swiftly. The best-designed studies, when published, all too soon represent the state of yesterday’s art.

Problems that result from the pace of progress emerge in clinical decision making and in the mutual assessment by patient and physician of preferred therapeutic options. At the system level, there are problems of personnel needs, resource allocation, and the education of generalists and specialists. Political decisionmakers, policy analysts, and research policy personnel in government, the philanthropies, and industry face the challenge of incorporating the consequences of scientific advances in psychiatry (as well as appreciating the intrinsic limitations of all truly scientific methodologies).

The relative shift from ignorance to sound data is especially striking for psychiatric disorders (in which the boundary between special knowledge and “common sense” has always been particularly blurred). Psychiatric specialists trained in each decade over the past forty years discernibly differ in the readiness with which they can grasp and use modern advances. Thus, non-specialists and policymakers should be alert to the fact that “pop psychology” books and even commonly available texts most probably do not contain the most up-to-date information; such works are inadequate to convey the key variables important for contemporary mental health policy.

Attitudes toward drugs. A variety of social, cultural, and scientific factors have shaped our attitudes toward drugs and technology. From infancy forward, we are tu-
tored about the values and risks of substances that we incorporate into our bodies. Thus we inherit a basically ambivalent attitude toward incorporated substances; substances produce effects, but we cannot directly visualize how this occurs, nor can we command or calibrate the effects desired. Rational operational activity and conceptual grasp thus yield to nonrational attitudes about what "works" with medicines. In our concerns about mortality and morbidity, we seek absolute results with medicines—not the detailed explanations.

Pharmacology—the study of how medicines are developed and investigated, how they work or are tested and worried about, and how the risks are managed in practice—is not a part of the health and science curriculum of the educated laity. It is not even a sufficiently clear-cut part of the medical school curriculum, a fact that deserves future policy attention. As a result, physician/patient transactions regarding medication are generally far from ideal; policy rarely addresses this problem candidly. Further, the prevalence of self-referral to superspecialists in "body parts" reflects notions of illness as a nuisance to be eliminated by efficient technologies. "Miracle drugs" lend themselves to this wish and heighten the search for a quick fix. Superspecialists have lost the art of "physicianship" in providing comprehensive care and have forgotten the function of the physician as "advocate" for guiding the patient through the health care system. Yet special skills are increasingly required for appropriate prescribing.

Attitudes toward health and disease. Wishes for simplified, cost-contained management of dysfunction dominate our thinking about health. The federal Agency for Health Care Policy and Research, with its Forum for Quality Effectiveness in Health Care, is but the most recent device to establish practice guidelines. The recurring push is implicitly for a handy set of rules whereby neither doctor nor patient needs to observe, judge, and weigh consequences. These trends defy the "law of DNA and biology," which finds variations in disease processes and drug response that require the specialized judgment of individual practitioners treating particular patients. While clarity and summary advice are inarguably useful in communicating science findings to physicians and laity, the wish to simplify has its dangers.

The more we formulate succinct "rules," the more we tempt the physician to collect simple slogans about a drug. Robot-like "drug dispensing" can be mindlessly substituted for the act of drug giving in a collaborative doctor/patient transaction, where curiosity, monitoring, and reflection on the patient's needs and responses ought to prevail.

Risk reduction for all medicines is, we submit, best vouchsafed by a deliberative, collaborative, and informed medical practice. Policy should invite both patient and physician to assess the science base and to observe, communicate, and evaluate the individual instance. These problems must be engaged by a society that wishes to deal rationally with science and technology.

Cost containment haunts health policy and has pushed medical practice toward restricted drug formularies and standardized treatments. Such policy attitudes are often inexplicit about the value of innovations needed to cope with the inescapable variabilities in drug response. In fact, large subsets of patients require treatments beyond the guidelines.

Exaggerated hopes for efficient disease care paradoxically reinforce a focus not on disease but on its prevention. In psychiatry, early intervention and secondary prevention of relapse and complications—once disease supervenes—are possible. Crises or dysfunctional interpersonal practices of patients can be variously managed. But even though vulnerability and risk factors are now clearer, we cannot predict in advance of disease onset who will become ill, nor should we pretend to make such predictions as we once did in the psychiatric community. Undesirable behavior—such as interpersonal violence or neglect and the abuse of drugs—while a complicating factor, does not cause primary psychiatric disorders. Nevertheless, such behavior has stressful consequences that require treatment. Yet societal emphases on health and wellness
can lead to avoidance of disease care.

We need to know how better to use what disease treatments we already have in hand. The mandate to use less-expensive versions of available treatments cannot be ignored, but the key judgments may be whether or not innovations and deviations from guidelines will add authentic value rather than shortsighted cost savings or slick new for-profit schemes. “One drug for each disease” is neither a scientifically nor clinically defensible policy. The need for salient innovations—in spite of progress—is undeniable.

**Stigma.** For almost two centuries psychiatric treatments at their best have used psychosocially supportive approaches (as in the “moral” treatments of the nineteenth century) combined with whatever somatic treatments might conceivably offer promise. This is still the case, but the interventions now have proven promise. Historically, the underlying notion rationalizing crude therapeutics in psychiatry was that the biology of the mental patient was somehow inefficient. Thus, mental disorders could be seen less as a failure of will than as a lack of energy or intrinsic ability to deploy attention selectively at will and to stay responsive to the environment (whether this was due to brain “degeneration,” “tainted heredity,” or other unproven causes).

Much of the intrinsic stigma and resistance to providing or seeking psychiatric treatments still rests upon society’s wish for the power of pure will to overcome any barriers to efficient mental functioning. In scientific fact, there is a constantly shifting continuum along which one can exercise degrees of autonomy. Today the striking difference that drug therapies can produce in the ability to accomplish once formidable quotidian tasks and to pursue personal and social aims testifies to such a continuum.

Mental illness imposes real barriers to efficient social and personal operations and should not be trivialized in policy formulation. The tasks of daily life are truly different for those with mental illnesses and for those without (and our powerful medicines do relieve the ill but are upsetting to “normals”). Quality-of-life (or “coping-with-life”) measures in clinical drug trials could document such significant facts.

Public policy emphases, intentionally or not, often divert attention from the difficult to the trivial. One example of this is benzodiazepines, which are sedative, antianxiety medications. Few, if any, medicines have been more extensively and systematically investigated for their molecular mode of action, safety, correct dosage, contraindications (such as alcohol dependency), and efficacy (in certain psychiatric and neurologic disorders and phases of medical/surgical care) or for their misuse liability, toxicity, or diversion to illicit use (all, in hard fact, minimal). Yet patients for whom benzodiazepines are appropriate (and well managed) are stigmatized with sensationalized crusades by antimedical cults or full-time policy ideologues (pleasing themselves and personal injury lawyers), by members of Congress seeking purportedly “significant” Medicaid cost savings (without measures of scope and consequence), or by frustrated bureaucrats touting yet one more “final solution” to rampant drug abuse.

Our point is that extensive knowledge bases in psychiatric pharmacology can no longer be dismissed in formulating public policy, if rational decision making is a goal. Nor can reimbursement policies rationally segregate mental illness treatments from general medical treatments. Similarly, the tendency to translate the specifics of mental illness into the framework of everyday life of the “worried well” should be checked. Depressive disorder and its attendant impairments are not equivalent to being “down in the dumps” during a bad week. In brief, wherever one turns—whether to lingering questions of the 1960s (the civil right to be crazy versus the sheer inability not to be) or to the sensitively publicized but rare and manageable side effects of benzodiazepines and a number of different useful psychiatric medicines—there are formidable bodies of validated clinical science knowledge that are deftly avoided in favor of popular agendas. Even the prestige press (“tabloids in gray flannels”) adds heat rather than light in
educating the public about the rational basis for the use of psychiatric medicines. In a society that values quantitative measures, sound data must be a respected part of the process of public policy formulation for mental health care.

**Therapeutic Advances**

Some specific advances. The current psychiatric drugs derive from chemical entities introduced from the post–World War II period through the 1960s. Thus, it is not precise to speak of new drugs; rather, one should speak of newly available medicines or of new uses for long–available ones. For instance, lithium to treat bipolar manic–depressive disorder works for only 60 or 70 percent of patients. However, many can now be treated by drugs long ago introduced as anticonvulsants (carbamazepine and recently valproic acid). For this and for all drug-responsive psychiatric disorders, we have (and need) a range of treatment options. Thus, in certain phases or types of bipolar illness, the addition of antipsychotic drugs used in schizophrenia, the thyroid hormone, or one of the benzodiazepines is warranted. For the major depressive disorders, there are several drug types—for example, the tricyclic antidepressants and the monoamine oxidase inhibitors. But some of these are also valuable in certain anxiety disorders and in panic disorders, for which antidepressants or benzodiazepines (or both together) along with specific behavior therapies are effective.

The most surprising development has been with obsessive-compulsive disorder, where patients are burdened by intrusive thoughts and tension-reducing rituals. A new class of agents—serotonin selective reuptake inhibitors (SSRIs), many of which are antidepressants—are specifically effective (even for compulsive, damaging feather picking in birds or paw licking in dogs). The other antidepressants used for depression and panic disorder but with no “tilt” toward brain serotonin mechanisms do not help obsessive-compulsive disorders.

Needed innovations. While we have drugs that differentially affect disorders, the drugs are not solely disorder specific. There are, for example, antipsychotic drugs (neuroleptics) but not solely “antischizophrenic” ones, and some “antidepressants” are equally effective against panic disorder. These drugs relieve specific symptoms, and tests of brain physiology show disorder differences. However, the underlying causes are not yet known. Today’s drugs thus compensate for or stabilize brain chemical imbalances but cannot yet target the initial triggers and cellular dysregulations of brain neurocircuitry that cause disease.

Better drugs (and specific psychotherapies) for all disorders and for the subset of disorders that resist treatment are urgently needed. For the future, we need research that will help to match the individual patient to the best available objective tests that will predict drug response. For depressive illnesses, drugs that take effect rapidly, rather than the current two- to six-week lag, are urgently sought. For all of medicine, it has as yet been too complicated and expensive to mount “relative efficacy” clinical trials comparing treatments; hence, “guidelines” for the choice of treatment options must rest uneasily on expert consensus.

Preventing relapse in anxiety and depressive disorders and determining the proper durations of treatments are now critical needs. Startling recent information on unipolar depressive disorder reverses revered maxims ("the lowest possible dose for the least possible period of time") with strong evidence that the high doses of the acute treatment phase must be maintained and can prevent relapse for as long as five years. For schizophrenia, as for all drug-treatable disorders, we seek compounds with fewer side effects and need drugs to manage the “negative symptoms” of apathy and withdrawal that accompany the disorder. Personality disorders currently elude effective medical interventions. Similar symptoms or temperamental traits occur across diagnoses; for instance, poor impulse control, violence, and suicide occur in depression, schizophrenia, anxiety disorders, dementias, retardation, and more. For neither Alzheimer’s disease nor drug and alcohol abuse do we have
potent remedies. Nor do prevailing rules and fear of litigation enable us to study drugs in women of child-bearing age before studies with males show efficacy. We also need more targeted drug treatment studies in children and the elderly—all of which can be done with rule changes and incentives.

**Future policies for drug development.** Drug development is expensive (over $200 million per drug), is time consuming (up to twelve years of research), involves thousands of patients, and is quite risky. Yet this is the business of the twelve or so major worldwide pharmaceutical companies. Many thousands of compounds are synthesized annually, thousands are safety tested in animals, and hundreds are tentatively tried in humans. But, for all medical disorders, only several dozen reach the level of Food and Drug Administration (FDA)—approved Phase III clinical trials. For psychiatric illnesses, perhaps twenty entities are currently in Phase III trials throughout the world. This is not because the therapeutic opportunities of new compounds or new leads are exhausted. Rather, current incentives overwhelmingly favor the development of the safest possible psychiatric drug for the largest possible market. Billion-dollar markets are sought to recoup the costs of drug development and its attendant high risks of failure and litigation.

Until recently, many new psychiatric drugs were available only abroad, where regulatory constraints were favorable. Now, with price fixing to contain health costs abroad, drug companies are seeking a global marketplace to cover development costs. Overall, fewer companies of larger size appear to be developing the safe—but not necessarily the most needed or most effective—drugs for large markets. Two examples show how enlightened policy has led to needed medications in the United States. In both, the safer “winner’s strategy” of the pharmaceutical industry was relaxed.

The **ciomipramine (Anafranil)** story. This antidepressant, marketed for twenty years in Canada, Mexico, and abroad (and smuggled into the United States), is an SSRI-type drug that showed enticing promise for treating obsessive-compulsive disorder. Academic investigators and patients finally encouraged pharmaceutical industry sponsorship of innovative clinical trials in the context of creative and flexible regulatory guidelines. A period of marketing exclusivity for a new indication—even though the drug patent had expired—was arranged in the United States. The industry deviated from the “safe drugs/huge markets” principle since it did not expect the new market to be large. The results of targeted clinical trials were the first “breakthrough” in the treatment of obsessive-compulsive disorder. Ironically, the disorder is now known to be widely present in the population (about one in forty adults)—more frequent than the occurrence of diabetes or asthma.

Future collaborations to facilitate innovation could produce similar success. What is needed are incentives that foster excellent hypotheses based on solid pilot data with responsive industry sponsorship and flexible regulatory oversight. Most drugs are marketed for only one indication to save costs and reduce risks of adverse side effects or expiring patents. Yet there are many new uses for old drugs that are generated and validated by innovative clinical investigations. At this time, federal funding and corporate sponsorship for this socially valuable activity fall short of their potential.

The **clozapine story.** Another innovative development is the case of clozapine, which is a newly available therapy marketed for treatment-resistant schizophrenia. Not only was this an “old” drug with an aging patent, but the decision to test it in the United States was targeted to a small market, that is, to the portion (only 10–30 percent) of the schizophrenia market that did not respond to available drugs. The severe safety risk (a 1–3 percent estimated incidence of a potentially fatal blood disorder) originally caused the corporate sponsor to avoid marketing the drug in the United States. But persistent academic lobbying helped to launch the elegantly designed and controlled clinical trials. The need for regular blood counts in a nonconforming patient population led to a solution in which the marketing company began its own mandated blood-testing and patient-monitoring
system as a condition of the filling and renewal of any prescription. The exclusion of doctor/patient discretion in selecting the blood-testing agency and the cost created controversy, and some relatively less costly (although still quite expensive) discretionary arrangements were then arranged.

The result has been a novel and incrementally improved schizophrenia treatment (with fewer side effects)—the first since such drugs were introduced in 1952. Many new chemical entities for schizophrenia are now in the pipeline. Thus the prevailing rule of “safe drugs for large markets” was broken by academic, industry, and regulatory collaboration.

Looking Ahead

Many new drugs will emerge from medicinal chemistry and from the new biotechnologies. Computer-aided drug design is so elegant that a molecular target plucked from a brain membrane and structurally characterized by molecular biologists can be selectively hit, and molecular genetic techniques can “grow” sufficient quantities of such targets for research. Since more than one gene pathway to schizophrenia or depression is highly likely, marketing of gene-derived agents in the twenty-first century may produce many small markets for multiple subsets of disorders. In the near future, because of our understanding of brain science and use of “nature’s logic” (in which we can mimic or block endogenous molecules that regulate brain neural circuits), the chance of serendipitously encountering novel, much-needed therapies is greatly increased.11

Yet existing incentives have led to the current dilemma in which public health policy requires cost containment and disease care requires innovation. To improve on the information gleaned from early clinical trials requires more research funds on the gamble of ultimate cost savings.

A policy frequently considered for urgently needed drugs is to limit the marketing of incompletely studied drugs to select physicians and centers once early evidence of safety and efficacy seems promising. This strikes at the entire ethos of medical practice in which a drug once marketed is then available for any use at the discretion of any physician or, more commonly, with the support of the clinical science community. While some patients in need might benefit, whether the profession would agree to such limits or whether industry could actually lower prices is quite uncertain.

Perhaps a fantasy solution would be to imagine a world in which profits were prohibited, in which needed drugs were developed but not marketed, and in which the burden of huge product liability costs did not exist. Costs of marketing during the first three years following the launch of a product can run to tens of millions of dollars per year. If drugs were preliminarily developed by investigators in academic and government institutions (in a model similar to the National Cancer Institute’s twenty-five-year-old program for chemotherapeutic agents), promising agents could be turned over, if not to industry for full development, perhaps to a nonprofit organization or a second tier of companies dedicated to manufacturing and distribution but not encumbered by huge marketing and advertising costs. This would require major new institutional supports. For instance, the high bed costs in certain phases of drug development would need to be covered (bed costs, lamentably, are no longer covered for clinical trials by third-party reimbursement). Salaries for the requisite basic science and clinical personnel would need to be supported. And the costs of continuing medical education and the effort to educate the laity and physicians about new uses or new drugs (or even medical journal costs) would have to be underwritten by the public rather than by industry’s large marketing arm.

Government and industry collaboration is more likely than is the total abolition of the profit motive with its assumption of risks in complex drug development. Thus, for needed innovations in substance abuse, the National Institute of Drug Abuse has begun a medications development unit, and a smaller effort (the Psychotherapeutic Drug Discovery and Development Program) has begun at the National Institute of Mental
Health (NIMH).

For major psychiatric disorders, a larger effort is needed. Congress in 1956 mandated and funded a “psychopharmacology service center” that was innovative and active for well over a decade at NIMH. It helped to launch multisite clinical trials of drug efficacy and toxicity and fostered significant new science, new scientists, and drug developments. Psychiatric drugs were the tools by which the “chemical brain” was discovered. Many now believe that NIMH must not only foster its current clinical and molecular research but refocus attention on medications development. This would require new funds for bed and salary costs in academic centers and support for medicinal chemistry, molecular-receptor computer modeling, animal model development and safety testing, and tests in humans for novel effects undertaken on the National Institutes of Health (NIH) campus and outside by meritorious clinical investigators.

Conclusions

Policy on drugs; their use, costs, and development; and attendant social, technical, educational, and legal practices is a complex and broad topic. Concentrated policy expertise across the range of topics is not focused. The academic medical societies, some law specialists, or experts in small programs at universities or schools of pharmacy are involved but almost always in ad hoc drug policy review or a focus on subsets of issues (such as laws or drug abuse). On psychiatric drug policy, the American College of Neuropsychopharmacology has assembled broad expertise, usually for ad hoc review. The American Psychiatric Association monitors discriminatory reimbursement policies. The Tufts Center for the Study of Drug Development is a broadly relevant “policy assessment” resource for all medicines.

It is questionable whether the new agencies in the Department of Health and Human Services can generate and sustain the needed breadth and depth. The Institute of Medicine has no sustained support for the needed focus and breadth, and NIH is not budgeted to mount such a drug policy effort. The FDA, underfunded as it is, is the chief actor in implementing rather than studying the drug policy issues. However, among the world’s regulatory agencies, the FDA—in spite of its egregious lapses, rigidities, or improper public posturings—most discernibly has steadily valued and used the sound clinical science databases needed for rational clinical decision making. Yet without a stable assemblage of varied expertise on “drugs and society,” rationally based bodies of knowledge on medicines and health policy will be less than desirably developed. That is a future policy concern that warrants attention.

NOTES

7. Ibid.
8. Ibid.
9. Ibid.
11. Ibid.
12. Ibid.