Aims of the Presentation
1. To appreciate the evolution of modern clinical psychopharmacology over the past half-century.
2. To be able to define forces underlying development of both modern psychopharmaceuticals and a pharmacocentric biomedical theoretical basis of modern psychiatry.
3. To consider a balanced perspective of both the major benefits and possible shortcomings of modern clinical psychopharmacology.

Disclosures: Dr. Baldessarini has been a consultant to, or collaborated in research with: Alkermes, AstraZeneca, Auritec, Biotrofix, IFI, Janssen, JDS-Noven, Leupold, Lilly, Merck, NeuroHealing, Novartis, Pfizer & Solvay Corporations, and holds several unlicensed patents for novel treatments of medical illnesses, but has no speakers’ panel or equity relationships with industrial organizations.

Summary
Clinical and theoretical psychopharmacology has evolved strikingly since the 1950s to become a leading factor in the practice and theory of modern psychiatry. This presentation traces its evolution, while evaluating the considerable benefits as well as possibly negative aspects of this movement over the past half-century. Major psychiatric illnesses are among leading causes for disability, and carry risks of excess mortality from suicide as well as co-morbid medical disorders of later life. The most commonly identified mental-health disorders in the US rank: substance abuse ≥ anxiety disorders > depressive disorders > personality disorders > bipolar disorders > schizophrenia; at least 27% of cases involve more than one DSM-IV disorder, but only about 40% of cases are professionally diagnosed and appropriately treated. From a cost-to-society perspective, major mental illnesses plus dementias cost tens-of-billions of dollars/year and are, by far, the most costly class of disorders, exceeding costs for all cardiovascular disorders, cancer, and HIV-AIDS; much of the cost-estimates are based on indirect costs of disability and long-term care, premature death, and lost income.

Psychotropic drugs are now major contributors to the global annual pharmaceutical market of nearly $725B, at over 8% (for antidepressants, antipsychotics, and anticonvulsants alone), exceeding sales of cancer drugs, cholesterol-lowering agents, diabetes agents, proton-pump inhibitors, antihypertensives, or analgesics. As such, psychotropics have come to represent very attractive drugs for discovery, development, and marketing activities that are increasingly dominated by the pharmaceutical industry and start-up biotechnology companies. Psychotropic agents that are FDA-approved and used clinically in the US currently include some 18 modern and older antidepressants, 16 first- and second-generation antipsychotics, and 5 anticonvulsants with mood-altering or mood-stabilizing properties, plus many agents used for anxiety or substance-abuse disorders. Most antidepressants have less-expensive generic competitors, and others will lose patent-protection soon. Use of modern antipsychotic agents has been rising, more by extension of FDA-approved indications than by innovation with novel or superior new drugs.

Initial discovery and development of most classes of psychotropic agents arose by purifying and synthesizing natural products, some arising from folk-medicine (such as risperidone as an early antipsychotic from Indian Vedic medicine; amphetamines through its active chemical ephedrine, and others, from traditional Chinese medicine). However, many more initial discoveries arose from unanticipated clinical observations (serendipity). Examples include discovery of: lithium carbonate (first mood-stabilizer) expected to be a treatment for gout; chlorpromazine (first phenothizine) developed as a preoperative sedative for general surgery; iproniazid (first MAO-inhibitor antidepressant) as a supposed anti-tuberculosis analogue of isoniazid; imipramine (first tricyclic
antidepressant) as a supposed structural analogue of phenothiazines and expected to be an antipsychotic; haloperidol (first non-tricyclic antipsychotic) as a non-analgesic derivative of meperidine; clozapine (first atypical antipsychotic) as a supposed structural analogue of imipramine and potential antidepressant; valproic acid (antimanic agent) as an organic solvent-component for testing anticonvulsants; and buspirone (anxiolytic, expected to be an early atypical antipsychotic).

The advent of modern clinical psychopharmacology can be dated from John Cade’s initial report of the antimanic and mood-stabilizing effects of lithium carbonate in bipolar disorder patients in Australia 1949, or the introduction of reserpine and chlorpromazine into psychiatry as the first antipsychotic agents 1952. By 1960, a process of empirical developments heavily dependent on serendipity had yielded at least one agent of every major class of psychotropic agents recognized today: antimanics (lithium and chlorpromazine); antipsychotics (chlorpromazine and many structural analogues, haloperidol, and even clozapine); antidepressants (iproniazid and imipramine and growing numbers of structural and functional analogues of both); stimulants (amphetamines had been in use since the 1930s); sedative-anxiolytic-hypnotics (barbiturates since the end of the 19th century, chlordiazepoxide as the first clinically employed benzodiazepine, and a growing number of non-barbiturate sedatives that are no longer used clinically [ethchlorvynol, meprobamate, methaqualone, and others]).

The 1960s brought profound conflicts between growing interest in seemingly simple and effective drug-based treatments and longer, seemingly less efficient psychotherapies, along with major shifts in academic psychiatry toward exploring biological theories based on emerging, partial understanding of some actions of psychotropic drugs (a pharmacocentric approach to biological psychiatry), as well as gradual replacement of psychoanalysts from the leadership of American academic psychiatry with biomedical-descriptive psychiatrists who pursued a renaissance of late 19th-century, European traditions. That decade also brought a large number of chemical-structural analogues of the initially discovered agents (“me-too” products that worked and could be sold, but were not innovative in principle). There was also some interest in seeking functional analogues of known compounds identified largely through animal behavioral models, not necessarily of mental illnesses, but of the actions of known drugs (e.g., discovery of haloperidol: chemically very different from the phenothiazines, but induced bradykinesia, like older neuroleptics). That decade also brought increasing application of quantifiable but clinically questionable, standardized symptom-rating-scale based methods of clinical assessment, and the rise of the placebo-controlled, parallel-groups, randomized clinical trial (RCT), with or without an established treatment, as a standard for testing the efficacy and safety of new drugs for particular indications (yielding, at least, some “proofs of concepts”) and regulatory approval through a series of increasingly standardized steps (including Phases I, II, III, and postmarketing).

The 1970s and 1980s brought further refinements in partial understanding of the actions of most psychotropic drugs (pharmacodynamics), including increased emphasis on identification, isolation, and application of molecular target sites from brain tissue (mainly protein monoamine receptors and transporters) as a basis of identifying even more agents of types similar to those already known. Limited knowledge of drug actions led to probable over-valuation of available concepts, and a somewhat circular process of developing more agents of similar types. In addition, the over-valuation strongly encouraged fundamental confusion between drug-actions and pathophysiology of mental disorders, and to increasingly pharmacocentric theorizing (based on opposites of what the drugs were believed to do). The process also encouraged expansion of DSM and other diagnostic schemes so that, sometimes, it was unclear whether disorders begot treatments, or if new treatments encouraged recognition or marketing of new or old disorders. The >300 diagnostic categories of DSM continue to be debated as largely inadequately supported by clinical research, and include many examples of how a new treatment encouraged new or renewed emphasis on a disorder (e.g., lithium: “bipolar disorder”; antipsychotics: “schizophrenia”; imipramine & fluoxetine: “major depression”; high-potency benzodiazepines: “panic-agoraphobia”; later serotonin-reuptake inhibitors: obsessive-compulsive disorder).

The 1990s were declared the Decade of the Brain by the first President Bush, and brought great interest in the application of new brain-imaging technologies and the methods of molecular genetics to the study of the mentally ill, as each generation had done with then-fashionable technologies, dating back nearly two centuries. By the 1990s, the psychopharmaceutical industry had become a very big business, with a series of new agents that earned more than a billion dollars/year (first, fluoxetine, a presumably safe antidepressant and anxiolytic at least as
effective as imipramine-like and MAO-inhibitor agents; and later olanzapine, a presumably safe and quite
effective successor to such drugs as the potentially lethally toxic clozapine, and many older neuroleptics with
predictable acute movements disorders and later tardive dyskinesia). The decade also brought some appreciation
for both theoretical and practical limitations of newer agents, in that none was free of important clinical risks of
adverse effects and “side-effect burden,” and most were developed by very limited and essentially circular
reasoning based on partial understanding of drug-actions and rather compulsive repetition, often with marketing
success and clinical value but little theoretical progress. There was rising interest in effectiveness (real clinical
value in realistic circumstances) versus simple efficacy (beating placebo, usually short-term). Technological
advances that became prominent in the decade included computerized molecular design, high-throughput
chemical synthesis, and automated screening for drug-actions at molecular targets, often in increasingly
computer-controlled, robotic laboratories.

The 2000s, up to the present era, have brought increased interest in developing an “evidence-based psychiatry”
(EBP) that relies heavily on pooling findings from seemingly well-designed RCTs, often by the methods of meta-
analysis, as means of evaluating relative efficacy and tolerability of specific agents within a class. There has also
been an associated increase in proposed “treatment-algorithms,” though with very limited research support, versus
“expert opinions.” Less attractive aspects of the field have included insufficient interest in many important but
relatively neglected clinical problem-areas (e.g., pediatric and geriatric disorders, suicide and other forms of
mortality, dementia, brain injuries, addictions, and many others). Drug-based treatment has also interacted with
rising pressure from insurance-supported medical practice, to emphasize managed-care, cost-containment, and the
like. The result of these movements appears to include a tendency to seek increasingly “efficient” (brief,
relatively inexpensive, and technically-based) approaches to complex human conditions, and to de-emphasize
what the mental-health professions had learned over the past century about patient-centered diagnosis, descriptive
psychopathology, and psychological approaches to comprehensive clinical care. One can argue that these trends
(perhaps including some “dumbing-down of psychiatry) are strongly driven by seemingly opposite, but highly
cooperative economic factors, including the enormous profit motive in marketing psychotropic drug products, and
the wish to contain costs but also maximize profits by insurance companies that at best, pay much less for mental
health care than many other treatments. Despite strenuous and sometimes brilliant applications of the technical
advances of functional brain imaging and molecular genetics, the biological bases for most major mental illnesses
remain elusive. Without them, it is very difficult to develop truly innovative and rational new treatments based on
knowledge of psychiatric disorders, including their pathophysiology or even etiology. A final major trend in the
pharmaceutical industry in recent years, and particularly worrisome for psychopharmacology, is rapidly rising
investment in research and development costs, against fewer new products reaching patients or the market.

Currently, clinical selection among available psychotropic agents seems less than entirely rational. Much of the
appeal of particular agents appears to lie in their safety, tolerability and acceptability to patients, as well as
simplicity and efficiency of use by clinicians (saving time, effort, and costs)—all strongly encouraged by both the
pharmaceutical and health-insurance industries. Another trend is to over-generalize the use of familiar terms and
concepts, such as “major depression,” and “bipolar disorder,” as happened earlier with “schizophrenia,” thus
including ever-larger proportions of potential patients, despite variable or weak evidence to support such
practices, as well as a general exaggeration of the clinical effectiveness of most drug-based psychiatric treatments.
One example is the enormous popularity of antidepressants in the US to treat patients diagnosed with bipolar
disorders (itself a modern fad-diagnosis), despite a lack of evidence of their efficacy, effectiveness, or safety in
such patients. Another example is using anticonvulsants as mood-stabilizers, based on a putative, but unproved,
analogy between epilepsy and bipolar disorder. Yet another recently emerging trend is use of what is politely
termed “polytherapy,” but often seems to be a “shot-gun” approach to keep adding more and more varied
medicines (the “allopathic compulsion”) when response and even diagnosis remains elusive, despite lack of
scientific evidence of the efficacy or safety of the practice.

Efforts to develop an evidence-based psychiatry (EBP) is laudable, but is being pursued with information that is
severely limited and may even be fundamentally flawed and misleading. Notably, most examples of meta-
analyses that seek to differentiate among particular agents in a given class are simply not up to the task. Instead,
we are left with the impression that specific drugs within a class are all “similar in efficacy,” with additional
biases introduced by the well-known phenomenon that “the sponsor’s product always looks superior.” Such
conclusions for antidepressants, antipsychotics, and mood-stabilizers, may be attractive for mass-marketing, but seem less than helpful clinically. Reasons for such limitations include high levels of variance within even seemingly well-designed RCTs, in large part probably owing to reliance on multiple collaborating sites per trial (sometimes several dozen, and in different regions or often even countries), across which diagnostic and assessment standardization is simply not realistic. This circumstance leads to averaged values of outcomes from meta-analyses that are heavily regressed-to-means, with large confidence intervals, such that distinctions among specific treatments, let alone among subgroups or individual patients, are virtually impossible. Placebo-responses appear to be even more influenced by lack of control of diagnosis and assessment, and by large site-counts, than are active agents, in turn, leading to larger “placebo responses” and growing risk that drug-placebo differentiation is increasingly difficult, as has been noted in recent years among several types of psychotropic drugs. Moreover, though most severe psychiatric disorders are recurrent or chronic, methods of testing for long-term prophylactic or protective effects are difficult, expensive, and remain severely limited.

An additional consideration is that the great bulk of support, design, and conduct, and analysis, and reporting of modern RCTs is now provided by the pharmaceutical industry. The representativeness of the findings of such trials can be questioned, especially since most patient-subjects are highly selected, often atypical, uncommonly co-morbid, and usually not severely ill, lest their recruitment and retention be impeded by their own refusal to participate, by increasingly ethically-sensitive human studies review committees (IRBs), or by the impact of severe illness itself. Most of the findings obtained from RCTs are presented in a highly controlled manner, typically with emphasis on findings that seem favorable for mass-marketing. It is nearly impossible to gain access to data pertaining to subgroups that may do especially well or especially poorly with a given treatment, let alone data at the individual-subject level (even though such analyses might well lead to distinctions among seemingly similar drugs, potentially favoring marketing aims as well as clinical applications), we may be limited to coarse, over-generalized impressions that are inadequate to guide rational assessment of differential clinical effectiveness or safety and to serve as a basis for EBP.

A related, major challenge is to encourage thoughtful and critical balance to the growing tendencies toward rapid but relatively simplistic diagnostic assessment, overly technically-oriented and frankly simplistic treatments, and a risk that “curiosity” may be sacrificed in the process, particularly in the service of “efficiency and cost-containment,” which seem to be major current considerations in the development of public and clinical policy. Overall, it remains important to maintain a critical and circumspect view of modern clinical psychopharmacology. It has brought about revolutionary changes and improvements in the treatment of many psychiatric patients since the 1950s, but some aspects of the impact of psychopharmacology are less attractive at both the level of clinical care and for efforts to advance theoretical psychiatry. Moreover, the rate of innovation and introduction of novel and superior drugs appears to be slowing substantially.

References & Recommended Reading


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