Drug discovery and mental illness
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Mental disorders are among the most disabling of all diseases. Effective well-documented medications have been available for many decades. Yet, limited understanding of the pathophysiology of mental disorders has impeded the development of novel treatments. Drug discovery must move toward a new mechanism-based paradigm using the tools of contemporary genetic and molecular medicine. At the same time, this new paradigm must be matched by an equivalent effort to modernize established approaches to clinical trials methodology.

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Traditional measures of disease burden, such as prevalence and mortality, have vastly underestimated the personal, societal, and economic burdens of mental illnesses, which are more often disabling than lethal. The highly regarded World Health Organization (WHO)–World Bank study of the Global Burden of Disease defines the “disability-adjusted life year” (DALY) as healthy years of life lost to (i) premature death, or (ii) disability. As a cause of DALYs, depression ranks second only to heart disease in established market economies, and fourth overall. Realization of the need for treatments and, ultimately, for tested approaches to prevention has grown in response to the recognition of this high degree of burden.

Approaches to drug discovery

The textbook approach to drug discovery moves in logical order from the bench to the bedside to the clinic to the community in sequentially ordered steps: molecular targets are defined through basic research; biochemical assays are used to screen for lead compounds; animal studies establish pharmacokinetic and pharmacodynamic parameters; and toxicology studies assess safety and risk. All these lead to human clinical trials in a multiphased developmental process that has been well documented. Though widely held as the ideal for basic, translational, and clinical research, the textbook approach has not characterized drug development in mental health. Rather, there have been three major discovery paradigms.

Serendipity, the completely fortuitous discovery of therapeutic effects, is the typical pattern for drug discovery. In the early 1950s, for example, chlorpromazine was synthesized by Charpentier at Rhone-Poulenc. The surgeon Henri Laborit used the compound to induce a state of “artificial hibernation” and in 1952 forecast its potential for use in psychiatry. In that year, benefits were identi-
fied in single cases and as monotherapy in open case series of patients diagnosed with bipolar illness and psychosis. Study of the drug expanded to other countries and the first controlled trial was carried out in England and published in 1954.

The discovery of imipramine followed roughly the same sort of path. The drug was developed by Geigy in Switzerland in the 1940s as a possible antihistamine. No particular advantage was observed and the drug was “shelved.” It was tried in schizophrenia in 1955 and failed, though in retrospective analysis, certain mood-elevating effects were observed. It was then pursued in depression and issued in the late 1950s, but not without significant difficulty in acceptance both within the company and the community.

A related approach to drug development is represented by the well-known phenomenon of compounds in search of a disease. That is, drugs with suspected central nervous system (CNS) activity are studied in various clinical populations until a therapeutic signal is detected. The late 1950s experiences of Nathan Kline and others with the application of antituberculosis drugs in the mood and anxiety disorders are illustrative of this approach to drug development.

Once a successful drug is developed, compounds with similar structures and activities (so-called “me-too” compounds) are tested for the purpose of identifying specific comparative advantages.

**Gaps in the discovery process**

Though the serendipitous, nonlinear approach to drug development has produced a number of important and even revolutionary changes in our approaches to the care of people with mental illnesses, there are very serious gaps in our treatment armamentarium.

Heart disease, the most disabling of illnesses, has at least 15 distinct classes of drugs available for use in treatment, most having been developed in the last decades. In depression, we have only a handful based on monoamine-elevating mechanisms of monoamine oxidase inhibition, serotonin, or norepinephrine uptake inhibitors. In schizophrenia, there are even fewer approaches characterized as dopamine receptor antagonists or some mixture of other actions (atypicals). In bipolar disorder, we have three: lithium, anticonvulsants, and atypical antipsychotics. The number of distinct classes of treatment for mental disorders has not increased appreciably since the 1950s.

Clearly, we are dealing with a very complex system, and the complexity seems to be increasing as our knowledge increases. The order of complexity in the CNS goes from $10^2$ (the number of neurotransmitters) to $10^{12}$ (the number of synapses). In addition, data from imaging and from neuropsychology show that the pathology of mental disorders is widely distributed through the CNS. Genetic studies have shown that these diseases are polygenic with multiple biochemical pathways that may contribute to the expression of a single disease. Environmental factors may contribute to as much as half the variance in disease expression. Coupled with a system of diagnostic classification that is often ambiguous and incomplete, our challenge is formidable indeed.

**New opportunities**

More than ever before we now have the opportunity to revolutionize drug discovery for the mental illnesses.

With discoveries in molecular biology, genomics, proteomics, bioinformatics, and automation, we have the tools we need to move to a whole new approach to drug discovery. Experiments or procedures that took years now take hours as information produced through robot technology and combinatorial chemistry is fed to supercomputers for processing and comparison to established informatics resources. Laboratories in the private sector and the public sector have revolutionized their methodologies to search for promising compounds. Using genomics and proteomics, it will be possible to produce mechanism-based classifications of clinical patient populations and disease targets for therapeutic or prophylactic intervention for these new compounds. All this will move us from an approach based on serendipity to one based on rationality.

The therapeutics of the future will be expected to identify specific molecular targets with minimal side effects in genetically defined clinical populations. Our current approaches are largely still broad targets with high side effect burdens in ill-defined patient populations. An increasingly important piece of this puzzle will be the growing importance of biomarkers and surrogate markers using brain imaging and other technologies for lead compound identification and optimization, and proof of principle. Some very promising approaches have begun to appear in the literature, particularly in the area of Alzheimer disease.
After drug discovery

Like the drugs we use, the methods we use to study them in human clinical trials were established for the most part in the 1940s and 1950s with the first modern randomized controlled trial, the Medical Research Council (MRC) trial of streptomycin. Yet nearly everything we do in clinical trials in depression minimizes treatment response, enhances placebo response, and, in the case of combination treatment approaches, inflates the value of active psychosocial comparators. There are many factors that contribute to this.

Patient selection

Subject selection often is limited by censoring the severity distribution through entry criteria where exclusions often require elimination of patients who are suicidal or psychotic, or have a variety of common comorbidities, such as physical illness, substance abuse, or personality disorder. Since these are typically associated with severity, elimination leads to preferential recruitment of less severely ill subjects. Similarly, many studies have long no-treatment periods for observation and diagnostic purposes. Clinicians are not likely to withhold treatment from severely ill patients in whom immediate treatment is seen as an absolute necessity. Thus, only those patients who can tolerate a long no-treatment period are recruited. These patients are likely to be less severely ill. It has long been observed that severity and placebo response are inversely related.

If advertising is used as the primary source of recruitment, a group of high-likelihood placebo responders, the “worried well,” are often the ones recruited. If, on the other hand, the recruitment is largely from active clinic or practice populations, there is likely to be preferential treatment of nonresponders under the justification that it is inappropriate to “rock the boat” for patients that are doing well by switching to a new treatment.

Study operations

In large, multiple-site studies, recruitment is often set as a horse-race with enrollment concluded when the overall study sample is achieved. Payment to sites is largely on a per-patient basis. Therefore, as the study recruitment goal appears closer, there is a financial incentive to enroll subjects while enrollment is still possible. Over time, that could lead to a drift in criteria: mild symptoms are seen as more serious, and borderline eligibility gets to be considered acceptable. This erosion of severity promotes placebo responder recruitment.

In combination treatment studies, operational concerns minimize differences between pharmacological and psychosocial treatments. Typically, the approach to pharmacotherapy is rigid with fixed dosing and short duration—an approach uncharacteristic of clinical practice. Clinicians in the pharmacotherapy arm must behave robotically and in a manner unlike the way they generally work. Training and supervision are minimal. Those doing the psychosocial treatment, on the other hand, are typically highly selected, well-paid, well-trained, and closely supervised. We therefore commonly encounter trials in which expertly done psychotherapy beats poorly done pharmacotherapy, and cannot separate the operational aspects from the true clinical effect of the different treatment approaches.

Outcome measures

In psychiatry trials in general, and in depression trials in particular, there is a tradition of using too many measures, most of which are rating scales or self-report forms of dubious validity and notorious unreliability. Measures are selected because they have worked in the past, and are therefore uninformed by contemporary science and knowledge of etiology or pathophysiology. There are few examples of composite, event-based measures, such as are typically used in cardiovascular trials (major adverse cardiac events, MACE), in mental health. We need to have more. Treatments may be having effects that our measures are incapable of capturing.

Analysis

The preferred approaches to statistical analysis of trials data, such as “intent to treat” or “last observation carried forward,” may reward placebo response. Newer approaches such as mixed-effects modeling and survival models may provide crisper alternatives for the identification of treatment effects. And, of course, statisticians continually remind us that effect size estimation, not statistical significance, should be the criterion applied to all trials.
Conclusion

Clinical trials often fail because we feel constrained to follow the classic approaches to clinical trials methodology. New science and new treatments should be subjected to a methodology that is appropriate and built upon the best of our current knowledge. There is a pressing need to reengineer the standard approaches to clinical trials in the mental disorders.

We also need to remember that discovery and development are the beginning and midpoint of treatment development, not the end. Traditional models have limited generalizability, restricted outcome measures, and leave substantial amounts of nonresponse, residual symptomatology, and associated disability. New pragmatic trials, based on approaches articulated by Peto and colleagues, are expanding our vision with respect to treatment assessment in our field.

Finally, we need to remember that mental disorders are complex, chronic, and often recurring. Medications are important and necessary, but they do not constitute the total approach to long-term care necessary for people with these serious conditions. In the US and elsewhere, we learned a sad lesson and incurred great suffering in the rush to “deinstitutionalize” people hospitalized for care of mental illnesses, but provided with little post-hospital care beyond drugs. As recently articulated in the UK with respect to schizophrenia: “… The management of schizophrenia involves a comprehensive package of care, […] drug therapy currently accounts for less than 5% of the total health care costs for schizophrenia.”

El descubrimiento de fármacos y la enfermedad mental

Los trastornos mentales están entre las más incapacitantes de todas las enfermedades. Durante muchas décadas se ha dispuesto de medicamentos efectivos, bien documentados. Sin embargo la comprensión limitada de la fisiopatología de los trastornos mentales ha impedido el desarrollo de nuevos tratamientos. El descubrimiento de fármacos debe trasladarse hacia un nuevo paradigma basado en el mecanismo que utilice las herramientas de la genética y la medicina molecular contemporáneas. Al mismo tiempo, este nuevo paradigma debe acompañarse de un esfuerzo equivalente para modernizar las aproximaciones que se han establecido para la metodología de los ensayos clínicos.

Découvertes médicamenteuses et maladies mentales

Les troubles mentaux font partie des maladies les plus handicapantes. Bien que des médicaments dont l’efficacité a été prouvée soient disponibles depuis des dizaines d’années, le développement de nouveaux traitements a été généré par la compréhension limitée de la physiopathologie des troubles mentaux. La découverte médicamenteuse doit s’orienter vers un nouveau modèle basé sur les mécanismes qui utilise les outils contemporains de la génétique et de la médecine moléculaire. En même temps, ce nouveau modèle doit être assorti d’un effort équivalent pour moderniser les approches existantes de la méthodologie des études cliniques.

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