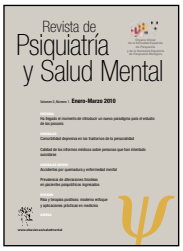
Rev Psiquiatr Salud Ment (Barc.) 2011;**4(1)**:5–8

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental



EDITORIAL

Commentary: the current state of psychopharmacology and psychiatry

Comentario: el estado actual de la psicofarmacología y la psiquiatría

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Modern clinical psychiatry has come to be dominated by psychopharmacology at many levels over the past several decades, following an era of psychodynamic hegemony in many countries. The inauguration of an important international psychiatric journal, the Spanish *Revista de Psiquiatria y Salud Mental*, provides an opportunity to consider the current state of psychiatry in relation to psychopharmacology.

Modern psychopharmacology can be dated from the reintroduction of lithium carbonate (used previously to treat gout) into clinical medicine for the treatment and prevention of mania by John Cade in Melbourne in 1949, or initial discoveries of antimanic and antipsychotic effects of chlorpromazine in Paris by Pierre Deniker and others in 1952.[1] The neuroleptic-antipsychotic agent chlorpromazine and its many chemical analogues arising in the 1950s and 1960s, derived from antihistaminic-sedative agents known from the late 1800s. It represented a major contribution of chemical and pharmaceutical technology but also of clinical serendipity. Its discovery led to the eventual development of the antidepressants, starting with imipramine in the late 1950s, and of the second-generation ("atypical") antipsychotic agents, starting with clozapine in 1960. Both differed from the tricyclic neuroleptics by having a seven-membered central ring which radically changed the stereochemistry and actions of these agents from mainly dopamine D_2 receptor antagonists with abundant adverse neurological effects, to a weak dopamine antagonist-potent antiserotonergic agent (clozapine) or to inhibitors of neuronal transport of norepinephrine or serotonin (tricyclic antidepressants).[1,2]

These largely accidental, though perceptive, clinical discoveries strongly encouraged a generation of basic and applied research aimed at clarifying the actions of the new drugs and guiding development of new and hopefully improved treatments. Moreover, an associated core concept of biological research was that the opposite of the pharmacodynamic actions of antipsychotic, antimanic, or antidepressant drugs might provide clues to the pathophysiology, if not the etiology, of the still-idiopathic major psychiatric disorders. This questionable strategy is consistent with the history of biomedical research in psychiatry over the past two centuries, which has been marked by waves of efforts to apply currently innovative technical developments from biology and general medicine to psychiatry.[3] In the case of psychopharmacology, hope emerged that a narrow range of identified drug actions were both necessary and sufficient to account for their effects and for further innovation. This view led to extraordinary advances in understanding the basic neurobiology of cerebral, chemical synaptic neurotransmission,[4] as well as

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supporting growing efficiency in the narrow identification of more new compounds with actions similar to older agents.[1,2]

This seemingly plausible, highly attractive, even compelling, process, carried out over several decades, encouraged a rationally closed circle whose origins are often overlooked. It has been marked, for example, by considering virtually only antidopaminergic agents as potential treatments for psychotic disorders or mania, and of amine-potentiating agents as possible antidepressants. Although the chemistry involved has become increasingly diverse, the basic drug-actions have remained similar to those of agents known by 1960. It can be argued that true innovation has been stifled by such closed and circular thinking, certainly for drug-development, but also for biological hypothesizing as the two lines of investigation became increasingly intertwined. The result has been a marked fall-off in true innovation over the past decade, despite massive investments in research and development and introduction of powerful new research and screening technologies.[5] That is, very few newer psychotropic agents represent novel mechanisms of action, and candidates that do have often failed in the clinic. Moreover, the developmental costs involved have become huge, especially for clinical trials, which increasingly often fail to show clear efficacy of new agents.[1,2,5] In addition, there are parallels in frankly disappointing advances in biological understanding of potential pathophysiology, let alone etiology, of major psychiatric disorders, or in the application of new biological principles to direct development of improved or more rational treatments.[6-9]

This scientific process is severely limited by the lack of plausible clues to coherent biological bases of the idiopathic major psychiatric syndromes. Despite their seeming plausibility and productivity in so many aspects of modern medicine, confidence in the hope that biological approaches will contribute to fundamental understanding of major psychiatric disorders seems to require an act of faith. Without a tissue pathology or coherent pathophysiology to guide both basic, etiology-oriented, research or to promote a rational experimental therapeutics, psychiatry continues to await unanticipated discoveries and the impact of the sort of serendipity that led to the discovery of virtually all classes of modern psychotropic drugs by 1960.[1,2] Increasingly sophisticated knowledge of drug-actions appears to be the street-light under which one elects to look for lost keys, even though there is little reason that this approach—however attractive and plausible—will prove superior to any other.

To put it succinctly, psychopharmacology may have been and continue to be overvalued, not only as a route to biological understanding of still-idiopathic disorders, but even as a satisfactory basis for advancing clinical treatment. Ready, world-wide availability of a growing range of medicinal treatments for most major psychiatric disorders has had an enormous impact on the conceptualization and practice of clinical psychiatry—much of it favorable or even revolutionary, but some of it questionable or even counter-productive. Biological theorizing based on the actions of psychotropic drugs exerts simultaneous stimulating and constraining effects on biomedical research in psychiatry, and in addition, has a major impact on psychiatric therapeutics and clinical practice.

For several decades there have been drugs to treat a wide range of severe mental illnesses, including the psychoses, bipolar and depressive disorders, and the various anxiety and addiction syndromes. Drugs approved for clinical use and commercial marketing generally have met conventionally accepted criteria of efficacy. These typically include being statistically superior to an inactive placebo in at least some randomized, controlled clinical trials, and of being apparently similar in beneficial effects to agents already accepted into broad clinical use. However, there are major limitations in this evidence. Many drug-candidates out-perform a placebo inconsistently, and may yield marginal palliative effects on some symptoms. These benefits may be statistically acceptable, but quite limited in effect-size or miss clinically important aspects of illness, including cognition, function, and excess mortality. Developing evidence of long-term, prophylactic effectiveness is even more challenging than demonstrating short-term efficacy in acute phases of illnesses that are increasingly recognized as recurrent or chronic. There has been a tendency to accept as such evidence, results of trials which involve discontinuation of ongoing treatments followed by clinical relapse. Such trials often involve carefully selected and not necessarily representative patient-subjects barely recovering from an acute illness. Moreover, many trials seem not to consider repeated demonstrations with virtually all types of psychotropic drugs that discontinuation, especially rapidly, is followed by early and excessive risk of recurrences or relapses,[10–12], raising both clinical-scientific and ethical questions.[1]

Establishing a rational, evidence-based therapeutics,[13] at least for psychiatry, remains a distant hope since it is difficult to rank available drugs within a class by efficacy. That is, the confidence intervals of improvement ratings or "responder" rates (proportions of patients showing partial symptomatic improvement in time-limited trials) generally overlap, even in many of the rare, head-to-head comparisons for antidepressant,[14–16] antipsychotic,[17] and antimanic drugs.[18] In part, this impasse may reflect the considerable limitations of the methods of clinical trials as applied to psychiatric disorders, with almost exclusive reliance on highly subjective symptom-ratings—themselves a rather narrow view of the clinical impact of psychiatric disorders. In addition, there is abundant heterogeneity of even carefully applied diagnoses based on modern nosological systems, which remain descriptive and phenomenological, and have variable predictive value.[19,20] Additional heterogeneity of diagnoses and clinical ratings can be expected to arise from the recently popular trend toward involving multiple international sites in drug trials.[21] This seemingly efficient trend has been encouraging by involvement of less costly, but less developed and remote areas with uncertain generalizability to major clinical markets. In developed countries, there is increased reliance on contract research organizations (CROs) to manage trials within clinical practices, typically with few patients per site and relatively mild illnesses. Alternatively, many academic or specialty sites tend to

collect increasingly complex and atypical patients who have failed previous treatments.[22] All of these trends may increase heterogeneity and inconsistency in trial outcomes with declining drug-placebo contrasts, and decrease generalizability. In turn, these outcomes probably arise from tendencies of heterogeneous observations to regress toward average outcomes.[23,24] Of note, the problem of psychiatric diagnosis and categorization is not only a major problem for experimental therapeutics, but also for most forms of psychiatric research, including elusive means of identifying relatively homogenous "phenotypes" for genetic and other types of studies.

The lack of clear separation, by efficacy, among individual drugs for most types of psychotropics include conducting more head-to-head trials rather than comparing outcomes across trials, and perhaps considering characteristics of subgroups representing the most versus least responsive or tolerant patients. Both suggestions have met with strong industrial reluctance. It is unlikely to be in a manufacturer's self-interest to subject its product to comparison trials aimed at identifying the better drug. Similarly, many corporate leaders appear to prefer broad marketing opportunities with drugs that may have measurable, though not necessarily optimal, benefits in broad categories of patients with heterogeneous disorders. However, a growing number of marketing experts perceive the value of distinguishing their products from other very similar drugs, as by demonstrating superior efficacy or tolerability in particular clinical subgroups.

Finally, though it is painful to consider, the advent of modern medicinal treatments for most severe mental illnesses has interacted in complex ways with clinical practices and with the economics of contemporary systems of clinical care. Rapid categorization, even superficially into insecure diagnostic groups, followed by prescription-writing, avoidance of concern about comprehensive care, and very limited after-care can be economically attractive, but risk encouraging relatively mindless and minimalist clinical practices.[1,25] Although the serious limitations of the "biopsychosocial" movement as a basis for improved diagnosis or as a research method have been pointed out,[26] there are abundant clinical reasons for more comprehensive approaches to patients with typically complex, and life-altering major psychiatric disorders of unknown cause. In short, it would be a tragedy if simplicity, efficiency, and cost-savings were to continue giving clinical psychopharmacology undue influence, even as the advances of the past two centuries in psychopathology and psychosocial approaches were forgotten.

Funding

Supported, in part, by a grant from the Bruce J. Anderson Foundation and by the McLean Private Donors Psychopharmacology Research Fund.

Conflict of interest

The authors declare no conflict of interest.

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