

Books
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Julio Moizeszowicz: Psychodynamic Psychopharmacology 4 editions

Hector Warnes' comment on the four edition

FIRST EDITION 1982

Professor Moizeszowicz attempts to integrate the multiple factors implicated in pharmacotherapeutics ranging from the specific ones (pharmacodynamics, pharmacokinetics, biotransformation, neurotransmitters, neuromodulators, neuropeptides, optimal dosing and others) and the non-specific factors which likewise are of paramount importance (the doctor-patient relationship, the placebo effect, the setting, the ongoing psychotherapeutic approach, the expectations of the doctor, of the patient and of the family, socio-cultural factors and last but not least, the impact of marketing). The book includes an appendix of the principal biochemical essays in psychiatry and a Vademecum, or handbook. It has 288 pages and is divided in eight chapters as follows:

The first chapter is on the General Principles of Treatment with Psychotropic Drugs. It has 65 pages and covers clinical issues, such as the clinical history oriented towards the prescription of a psychotropic drug, which includes 12 items to be asked during the interview before the prescription is given: previous use of psychotropic drugs, side effects, medical illnesses, current treatments and so on. Moizeszowicz deals with pharmacology in the proper sense of the word as a hard science in its complexity of absorption, metabolism and excretion of the drug. He covers true neurotransmitters, putative and autoreceptors or presynaptic receptors and sorts out their specific functions and site of major concentration in the brain. Among the neurotransmitters, Moizeszowicz includes catecholamines, acetylcholine, serotonin, histamine, gamma aminobutyric acid, glutamic acid and glycine, the latter has inhibitory action on muscular spasticity and is antagonized by strychnine. The most important neuro-modulators are the prostaglandins, each acting on different organs. Prostaglandin E inhibits the liberation of noradrenaline and facilitates the transmission of pain. Its action is antagonized by acetylsalicylic

acid and others. Moizeszowicz showed us an impressive bibliography and many figures on the biochemistry of each precursor, which are of great clarity. Further Moizeszowicz writes on neuropeptides and neurohormones, making the point that ACTH (adrenocorticotrophic hormone), which was thought to be present in the anterior-pituitary gland but later it was discovered to be present in the hypothalamus as well, shall stimulate the production of the following seven neuropeptides and neurohormones: melanocyte stimulating hormone, CLIP (corticotrophin lobular intermediate peptide), lipotrophin, beta-endorphins, methionine-enkephalin, methionine-leucine and opiate peptides (endorphins and lipotrophins). What follows is a dense section on the mechanism of action of psychotropic drugs, its adverse effects and the psycho-neurochemistry of affective disorder. In 1960, it was observed that hypertensive patients treated with reserpine showed symptoms of depression because reserpine depletes the intracellular deposits of catecholamines and would induce psychomotor retardation in experimental animals. These findings were corroborated by clinical observations and led Schildkraut to formulate his hypothesis which later on he himself called 'reductionist' when he understood that there were 'alterations of the metabolism of indolamines and other neurotransmitters as well as physiological and psychological factors' (cited by Moizeszowicz from Schildkraut on page 44). In the section on the psycho-neurochemistry of schizophrenic disorders, a didactic elaboration of the trans-methylation hypothesis first postulated by Axelrod in the 1950s is elaborated.

The section on the evaluation of the effectiveness of psychotropic drugs is very interesting, not only because of the use of rating scales and clinical parameters, which are applied to behavior, neurological, autonomic-vegetative nervous system profiles and the various psycho-physiological, sensorial, psychomotor, visual and intellectual performance, vigilance and attention tests. Moizeszowicz introduces us to two instruments he used in Germany during his early training in research: the rotor pursuit and the visual psychomotor coordination tests. He classifies the psychotropic drugs into antipsychotics, anti-parkinsonian, tranquilizers, hypnotics, antidepressants, anti-manic, stimulants (analeptics, awakening drugs, stimulants of neuronal metabolism, vasodilators and stimulants of memory) and finally the group of psychotomimetics or psychodysleptics.

It is noteworthy that in the chapter on Stimulants, Moizeszowicz starts off by quoting Freud's 1930 paper on Civilization and its Discontents, vol. XXI of the Standard Edition: " We

are threatened by suffering from three directions: from our own body, which is doomed to decay and dissolution and which cannot even do without pain and anxiety as warning signals; from the external world, which may rage against us with overwhelming and merciless forces of destruction; and finally from our relations to other men...An unrestricted satisfaction of every need presents itself as the most enticing method of conducting one's life, but it means putting enjoyment before caution, and soon brings its own punishment" (p.77). Freud then turns to chemical intoxication to overcome displeasure or psychic pain and adds "there must be substances in the chemistry of our own bodies which have similar effects, for we know at least one pathological state, mania, in which a condition similar to intoxication arises without the administration of an intoxicating drug" (p. 78). (In German the word Rausch means intoxication, exhilaration and ecstasy).

We are forever trying to keep misery at bay: "for one knows that, with the help of these downer of cares one can at any time withdraw from the pressure of reality and find refuge in a world of one's own with better conditions of sensibility" (p.78). Starting with alcoholic beverages up to the use of cocaine that Freud knew very well because, in the late 1800s, he wrote an important paper on the subject and he himself had a period of dependence on this drug.

The stimulants are classified into stimulants of alertness and wakefulness, of psychomotor activity, of neuronal metabolism and of memory. In the latter, the author listed three hormones related to memory: ACTH, MSH and vasopressin adding clarifying figures on the metabolism of choline and the mechanism of action of the cholinesterase inhibitors.

SECOND EDITION, 1988

The second edition of Psychopharmacology Psychodynamics contained a preface by Dr. Ricardo Avenburg, a prominent psychoanalyst and the introduction was written by the author himself. It was increased considerably in size to 670 pages with fourteen chapters. New chapters include psychopharmacology in Pediatrics, in Geriatrics, in Alcoholism, in childhood Epilepsy, in Attention Deficit Disorders, in adult Epilepsy, in Parkinson's Disease, each new chapter with the collaboration of Herbert Chappa, Hector Wainsburg, Fernando A. Alvarez and Oscar Gershanik. This second edition was expanded in its bibliography and the latest advances in the

discovery of new psychotropic compounds. On the cover there is an intriguing painting by Laszlo Moholy-Nagy (1925).

In the introduction, the author recognized the changes in the field in the last 6 years since the publication of the first edition, namely, drug-interactions, introduction of the DSM-III-R, multi-axial classification, significant advances of the neurosciences, molecular biology and the new era of molecules designed to target only certain receptors. In 'General Principles' I shall cite page 19, which reads: "these trophic pituitary hormones are under the control of a releasing hormone and an inhibitory one the actions of which are added up algebraically along with psychological factors (mediated by neurotransmitters, neuromodulators, etc) and its hormonal activation with its positive or negative feedback leading finally to an organismic response". Further, in the same chapter, page 31, I shall cite the crucial concept of excitation or inhibition of firing of certain neuronal groups, which allow movement of Na or Cl in or out of the cell: "The transmission would be mediated in the first place by neurotransmitters (first messenger) and by AMPc called second messenger. This second messenger would activate the enzyme adenylcyclase which would transform the energy stored in ATP to AMP to be finally stored in the form of information in a third messenger, the protein kinases". On page 32, of the third edition of his book, the author present an excellent diagram elaborating on these three messengers, which would facilitate ionic and enzymatic intracellular transduction, based on the studies of Nyman and Nestler.

I must underline the many excellent figures, which are highly didactic including comparing predictive factors of outcome of treatment. A letter from a patient was also transcribed regarding the side effects of the medication he had personally experienced. In this long letter, the patient raises key questions which we must always have in mind.

It must be pointed out that in more than 90% of the book, the author does not deal with psychodynamics per se as the second title of the book would suggest, at least in the sense of a conjoint treatment of psychotherapy and pharmacotherapy and its interaction in the form of facilitation or hindrance. We know for sure that an excess of tranquilizing drugs put the unconscious (in Freud's conception) to rest. Other times, the depressive episode leads to stagnation of the psychoanalytic or psychotherapeutic process and the antidepressant drug would instill new life in the therapeutic relationship. Further, casualties are seen with the use of abreaction or catharsis in latent or former psychotic patients. It means that some defenses against

primitive anxieties are not to be tampered with. There are criteria for selection in psychoanalysis, in psychoanalytic psychotherapy, in cognitive behavioural therapy, in Gestalt therapy and so on. In fact each school of psychotherapy put more emphasis on either the interpersonal, the intrapsychic and within the latter the cognitive, the vicissitudes of transference upheavals, the past, the present or the future, the emotional, the somatic (such as the method of autogenic training of Schultz and Lütke), biofeedback, relaxation training, Yoga, etc). Unless the patient is carefully evaluated for each potential psychotherapeutic approach, the fall out rate increases significantly. We have not reached that level of sophistication as yet. However, we are more accurate should we be good psychopathologists to select patients for particular psychoneuropharmacological interventions, at least in the short term.

THIRD EDITION 1994

The third edition III (1994 and 1996) is vastly expanded in scope and much updated. The sub-title has been changed to 'New clinical-therapeutic approaches' and was written with the collaboration of prominent psychiatrists and one neurologist, who wrote the chapter on Pharmacology of Parkinson's Disease.

On page 3 and 4, the authors listed the collaborators to this Third Edition of 833 pages, comprising 15 chapters, including chapters on psychopharmacology in children and adolescents, geriatrics, panic disorder, obsessive compulsive disorder, bulimia, emergencies, Day-Hospital and addictions.

In the first chapter, the author has clarified the difference between the medical model and the current model of illness (e.g., as shown in tuberculosis). We would be naive to subscribe to the strict medical model in view of epigenetic and environmental factors, which have become more and more the center of attention.

The medical model in the classical view states:

1. There is a known etiology
2. There is a clear discontinuity or break with normality
3. There are defined symptoms of illness
4. Once the noxa or pathogen which is causing the illness is identified the external environment has little influence on the course of the disease.

The author discusses each of the above points, demonstrating its anachronism. Once more it is worth citing Freud, the visionary, as the author does on page 19: "...But here we are concerned with therapy only in so far as it works by psychological means; and for the time being we have no other. The future may teach us to exercise a direct influence, by means of particular chemical substances, on the amounts of energy and their distribution in the mental apparatus. It may be that there are other still undreamt-of possibilities of therapy. But for the moment we have nothing better at our disposal than the technique of psychoanalysis, and for that reason, in spite of its limitations, it should not be despised" (p. 182 of an Outline of Psychoanalysis. The Standard Edition vol. XXIII. 1937-1939).

On page 45, of the Introduction to the Psychopharmacological treatment, the author writes: "The amphetamines or their derivatives can be trans-methylated by the enzyme N-methyl-transferase. In addition, the amphetamines cause the release of catecholamines and the inhibition of MAO, creating the conditions for the formation of psychotomimetic molecules which would explain the amphetamine psychosis". Further, the author graphically shows how metabolic errors would result in increases of the following psychotomimetics:

3-4-dimetoxifenyletilamine,

N,N-dimetyltryptamine,

bufotenine (O-phosphoryl-4-.hydroxy.-N,N-dimetyl tryptamine) and

3,5 methoxy-N, N-dimetyltryptamine.

It would be beyond the scope of this review to cite the finest details on the function and locus of serotonin receptors and on the deviation of the various metabolic pathways (its synthesis and degradation) of L-tryptophan. On page 52, the author presents a revision of neuro-peptides and hormones, including those produced by the gut. On page 55, we have a pictures of the characteristics and function of 9 major receptors. Moizeszowicz advances on the theory of the oncogene, which are found in chromosomes and are activated by c-fos and c-jun: "An oncogene fos combines with the action of RNA messenger is translocated and transformed in the cytoplasm in a protein fos which modifies genetic expression" (p. 56).

In chapter two, Moizeszowicz going beyond the DSM III, points out that a complete diagnosis should include (p. 69):

1. A phenomenological or symptomatic description
2. Major intra-psychic conflicts

3. A structural analysis
4. Bioelectrical studies
5. Neurochemical studies
6. Psychopharmacotherapeutic indications.

In the chapter on antidepressants, the author cites Akiskal (1985) on the etiopathogenic factors in depressive disorders, such as biological stress, psychosocial stress, life history, genetic vulnerabilities and personality profile, including character and temperament (p.255). Based on the work of Gold, Goodwin and Chrousos, the author presents a clarifying diagram on the differences between stress and depression (p.268). Apart from the clinical difference, the two share the same physiological response of hypercortisolemia, hyperactivity of the locus coeruleus, immuno-suppression with the difference that the stress response has a counter-regulatory mechanism which limits its chronicity unlike the depressive response. The frequency of sub-affective dysthymia and the overlapping of dysthymia, major depression and recurrent depression are dealt with very clearly (p. 334 - 335). We have to be alert to the presence of double or triple depression. The diagnostic validation of sub-affective dysthymia is confirmed with the presence of a family history of depression, unipolar or bipolar affective disorders, the hypomanic response to antidepressant therapy, a short REM latency period and a non-suppressing dexamethasone test. Atypical depressions are presented in a diagram following the criteria of Nies and Robinson, cited by the author (p. 332). It comprises, in short, the following items: interpersonal reactions, course of the illness, psychopathological symptoms and autonomic or vegetative symptoms, which usually are atypical (Liebowitz, cited on page 33, enumerates these as hypersomnia, hyperorexia, weight gain, evening worsening, fatigue and interpersonal hypersensitivity).

New rating scales and biochemical measures of plasma concentration of psychotropic drugs are added to this expanding field. Once more, I must express my admiration for the excellent figures which make the book easy to read and understand. I particularly recommend the chapter where the topic of atypical depression and the chapter on Geriatrics are elaborated in depth. Regarding the latter topic Moizeszowicz in a masterful way reminds us of the key issues in a psychogeriatric history, which also includes rating scales, neurological, cardiological, and endocrine examinations, as well as biochemical measures, MRI, CT, EEG, and so on. Of course, one cannot ignore that drug metabolism, or pharmacokinetics, are altered in the geriatric patient.

The involucional neurochemical changes cited by the author are the following: a) a reduction of dopamine receptors, b) a reduction of muscarine receptors, c) an increase of the benzodiazepine receptors and d) an increase of the enzyme MAO_B. On page 524, a diagram on involucional pharmacokinetic changes are presented in terms of absorption, distribution, elimination and neurochemical alterations, including a decrease of acetylcholine, tyrosine hydroxylase and DOPA decarboxylase. The figures used by the author, based on original studies, are of great value, particularly in regard with his update on the dementias. The diagrams on the histopathology of degenerative dementias and of the deposit of the protein beta-amyloid are indeed outstanding. The author cites the work of Tanaka et al. regarding the differential expression of three types of Amyloid Precursor Protein (in chromosome 21) found in the brain and non-neural tissues. The protein B amyloid A4 is the product of degradation by an enzyme of the Amyloid Precursor Protein. The normal versus the abnormal degradation of beta amyloid involves the activation of proteases and are of paramount importance in the development of dementia of the Alzheimer type. The bibliography in this latest volume has grown exponentially with the advances in the field.

FOURTH EDITION 2000

The fourth edition of Psychopharmacology-Psychodynamics published by Paidos in 1998 and reprinted in the year 2000 has increased significantly in size and academic content. Prof. Moizeszowics has enlisted 12 collaborators, each highly qualified in the respective field of their contribution to this volume of 1248 pages, divided in 19 chapters. The subtitle of the book has changed to "Therapeutical and Psychoneurobiological Strategies".

The first chapter has changed its name from the one used in previous editions (General Principles of Treatment with Psychotropic drugs) to Introduction to Psychopharmacology and Psychoneurobiology. The author, in his introduction to the book, reminds us that the old concept of psychotropic drugs (labeled as chemical 'straight jackets'), with advancing research beyond neurotransmitters, has been transformed to involve the domains of molecular and genetic psycho-neurobiology and the human genome. Moizeszowicz also elaborates in his introduction on the role of the family of CYP450 enzymes, which could, as genetically determined inhibit or stimulate the effect of pharmacological agents. Many side effects are due to drug interactions are

set of by polypharmacy. The wealth of information and the bibliography has increased substantially with new chapters on Premenstrual disorders, Pregnancy and Puerperium written by Liliana Fernandez, Julio Moizeszowicz and yriam Monczor and an excellent new chapter written by Pablo V. Gejman on Epidemiological and Molecular Principles of Genetics in Mental Illnesses. The author of these chapters as is the general trend in the many editions, subscribes to the principle of multi-factorial convergence of nature-nurture. The volume has been enriched by very good images of CT and MRI of bipolar disorders during 20 and 15 years of follow-up. Further images of trichotillomania, self-aggression and the SPECT of a patient of 18 with schizoaffective disorder who showed left temporal hypo-perfusion are revealing. Another patient, who was a cocaine addict for 15 years showed in a SPECT with frontal orbital hypo-perfusion and thinning of the posterior parietal cerebral cortex. The SPECT of another patient of 45 years who consumed cocaine for 10 years, showed frontal and left temporal hypo-perfusion.

Another new chapter of high academic value is the one on Psycho-immuno-endocrinology and psycho-neuro-immuno-oncology written by Moizeszowicz and Sergio Guala. The authors cite Harvey Cushing, who in 1913, wrote on the difficulty of establishing which is the primary factor, the psychic or the endogenous dysequilibrium. It would appear that with modern technology we are coming to grips with this dichotomy. I shall cite Professor Moizeszowicz once more in an elucidating résumé: “The transduction which is the process of union of the neurotransmitter to a receptor (first messenger) has the objective of transmitting cyclic AMP, cyclic GMP, Ca, DAG, IP3 information (second messengers) which must phosphorylate a more complex protein kinase (third messengers) in order to transmit the message for storage in the neuron (factors of transcription or fourth messengers) which would result in signaling as a cellular response” (p.26). There is on page 28 an outstanding diagram on the mechanism of action of psychotropic drugs in the synapse, which points out to the importance of nitrous oxide and the activation of NMDA in the hippocampus, along with the role of Na, K, Ca and protein G in the postsynaptic neurons. Neurotransmitters, second messengers, protein kinases, ion channels and transcription factors (CREB, or cAMP response element binding protein) are responsible for memory, learning, and response to pharmacological and psychotherapeutic treatments. The interaction between genetic vulnerabilities, life events, stressors and current situation are pathogenic. The action potential are monitored with microelectrodes, which record the sequences of electro-chemical events

An outstanding diagram on page 56 shows us the difference between normal and pathological apoptosis. Pathological apoptosis involves a more severe dysfunction of immunity and of the blueprint of cellular response along with greater changes in the genotype

On page 57 of his introduction, the author elaborates on the issue of the efficacy of psychopharmacological treatment based on the regulation of genetic expression, i.e., the duration of the beneficial effects in the long run depend on long-term potentiation (LTP) in three key areas: “neuro-learning associated with memory, genetic transcription and Neuroplasticity.” Further the author points out that the oxidative phosphorylation is the vehicle of action of psychotropic drugs in long term use (LTP), of course, mediated by a particular genetic transcription. Antidepressant resistant or refractory patients are given another drug that would potentiate the effect of the antidepressant. On page 568, the author cites studies that have shown that lithium and T3, in combination with a known antidepressant, are useful in the treatment of refractory depressions. Finally, on page 1052, the author elaborates on the factors of neural growth and neural plasticity namely:

1. Phosphatidylserine
2. Acetyl-L-carnitine
3. Ganglioside (glial tissue secrete neurosteroids, N- acetylsphingosine or LIGA 4)
4. Antagonist of NMDA (Memantine)
5. Calcium antagonist (Nimodipine)
6. Nootropic agents (related to GABA, such as Piracetam and Aniracetam)
7. Idebenona (acts on the mitochondria with anti-oxidant properties and inhibits the synthesis of prostaglandins)
8. Biphemelane (increase cholinergic transmission)
9. Estrogens (increase the activity of the acetyltransferase and of the muscarine receptors)
10. Vitamine E (antioxidant that has been shown in animals to delay neuronal degeneration)
11. Anti-inflammatory drugs (aspirin, ibuprophen and prednisone which counter pro-inflammatory cytokines)
12. Neural Growth Factor (a beta polypeptide, neurotrophins, discovered by Levi-Montalcini).

I have also read updates of Psychopharmacology and Psychodynamics IV, published in 2002, 2003, 2004, 2005, 2006, 2007, 2008 and 2009, each volume of about 200 pages contains a wealth of information in this blossoming field and, most interesting, each volume has a final chapter with multiple-choice questions of great didactic value. Hopefully, I should be able to review these books at a later date. I understand that the different editions and the excellent figures shall be available free of charge in the Web in Power Point format.

I would like to underline the relative lack of real psychodynamic formulations of patients evaluated for or under psychopharmacological-psychotherapeutic approaches. Reading the updates from 2002 to 2009, this integration has been surmounted in this book, Psychopharmacology and Freudian Territory, written in collaboration with Mirta Moizeszowicz and published by Paidos in the year 2000. I shall be reviewing this outstanding book in the near future.

The role of psychotherapy to promote more beneficial outcomes than only with the use of psychotropic drugs has been established. I would add that the open ended interviews of patients provide a wealth of information (phenomenological and psychodynamic) that the structured interviews or the use of rating scales, do not.

In this regard, the outcome of patients treated only with drugs and those treated only with psychotherapy reach an unhappy conclusion because the statistical findings are not very encouraging (between 50 and 70 or at best 75% improvement rate in general with either mode of therapy). Strupp and Hadley singled out the specific versus non-specific factors in psychotherapy in a controlled study of outcome (Archives of General Psychiatry, 36(1): 125-136, 1979), not unlike the findings that in pharmacotherapy there are specific and non-specific factors at work. Luborsky L, Singer B and Luborsky L wrote of a comparative study of the various schools of psychotherapy and concluded that they all have approximately the same success rate (Archives of General Psychiatry 32: 995-1008, 1975). In 2008, Pollak DD and Kandel ER discovered that conditioning mice to associate specific noise with protection from harm (learned safety) produced a behavioural antidepressant effect comparable to that of medications (Neuron 60 (1): 149-161, 2008). Eric Kandel suggested that the structure of the cells may change as a result of learning and genetic changes. Those that were inactive or dormant interact with the environment in such a way that they become active. It was shown, in 1972, that the second messenger

molecule, cAMP, was also produced in *Aplysia* ganglia. It was found that serotonin is involved in the molecular basis of sensitization of the cAMP dependent protein kinase A. In turn, the potassium channel is regulated by the protein kinase A (PKA) whose nuclear target is the transcriptional control protein CREB (involved in long-term memory storage). The activation of CREB results in an increase number of synaptic connections. We are at the heart of the action of psychoneurotropic drugs, so well elaborated by Professor Moizeszowicz, which also leaves open the door for the deconditioning, counterconditioning and learning mechanisms of psychotherapy and insight-therapy.

Finally I would like to congratulate the author for the outstanding and most complete evaluation in the area of psycho-neuro-pharmacology

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