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## Psychiatric nosological historiography - Part II: psychopharmacology and somatogenic perspectives

*Historiografia nosológica psiquiátrica - Parte II: psicofarmacologia e perspectivas somatogênicas*

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### ABSTRACT:

**Introduction:** The history of psychiatry encompasses the evolving concepts about the relationship between body and mind and also of the definition of normality, which depend on the knowledge and customs of different times and places. For a better understanding of this journey, this study privileged the presentation of the main influential figures on the construction of psychiatric nosology and classifications mainly unfolded on a descriptive or causal basis, from psychics or somatics driving, since the Western Renaissance. This article, the second in a two-part series, mainly discusses the importance of psychopharmacology for a better understanding of mental disorders and their classifications. Part one is a preamble to the historical development of the new nosography and psychopharmacology. **Method:** Narrative review based on secondary sources. **Results:** The current article illustrates how the understanding of the pathophysiological mechanisms underlying mental illness improves, mainly employing the psychopharmacology that may lead to the reclassification of certain mental disorders. This natural reductionism view of the sciences must be in cooperation with an integrative understanding of the human being, as is customary in the humanities. **Conclusion:** The study of psychiatric nosohistoriography helps to understand the conceptual evolution of mental illnesses and the most recent importance of psychopharmacology for this.

**Keywords:** classification, psychiatry, psychopharmacology, neurosciences, nosology, taxonomy, history of medicine

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**RESUMO:**

**Introdução:** A história da psiquiatria abrange a evolução dos conceitos sobre a relação entre corpo e mente e também da definição de normalidade, que dependem dos conhecimentos e costumes de diferentes épocas e lugares. Para uma melhor compreensão deste percurso, este estudo privilegiou a apresentação das principais figuras influentes na construção da nosologia e das classificações psiquiátricas desdobradas sobretudo numa base descritiva ou causal, a partir da condução psíquica ou somática, desde o Renascimento Ocidental. Este artigo, o segundo de uma série de duas partes, discute principalmente a importância da psicofarmacologia para uma melhor compreensão dos transtornos mentais e suas classificações. A primeira parte é um preâmbulo ao desenvolvimento histórico da nova nosografia e da psicofarmacologia. **Método:** Revisão narrativa baseada em fontes secundárias. **Resultados:** O presente artigo ilustra como melhora a compreensão dos mecanismos fisiopatológicos subjacentes à doença mental, empregando principalmente a psicofarmacologia que pode levar à reclassificação de certos transtornos mentais. Esta visão reducionista natural das ciências deve estar em cooperação com uma compreensão integrativa do ser humano, como é habitual nas humanidades. **Conclusão:** O estudo da noso-historiografia psiquiátrica ajuda a compreender a evolução conceitual das doenças mentais e a importância mais recente da psicofarmacologia para isso.

**Palavras-chave:** classificação, psiquiatria, psicofarmacologia, neurociências, nosologia, taxonomia, história da medicina

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**RESUMEN:**

**Introducción:** La historia de la psiquiatría abarca la evolución de conceptos sobre la relación entre cuerpo y mente y también de la definición de normalidad, que dependen de los conocimientos y costumbres de diferentes épocas y lugares. Para una mejor comprensión de este recorrido, este estudio privilegió la presentación de las principales figuras influyentes en la construcción de la nosología psiquiátrica y de las clasificaciones desplegadas principalmente sobre una base descriptiva o causal, desde la conducción psíquica o somática, desde el Renacimiento occidental. Este artículo, el segundo de una serie de dos partes, analiza principalmente la importancia de la psicofarmacología para una mejor

comprensión de los trastornos mentales y sus clasificaciones. La primera parte es un preámbulo del desarrollo histórico de la nueva nosografía y psicofarmacología. **Método:** Revisión narrativa basada en fuentes secundarias. **Resultados:** El presente artículo ilustra cómo mejora la comprensión de los mecanismos fisiopatológicos que subyacen a las enfermedades mentales, empleando principalmente la psicofarmacología que puede conducir a la reclasificación de ciertos trastornos mentales. Esta visión reduccionista natural de las ciencias debe ir en cooperación con una comprensión integradora del ser humano, como es habitual en las humanidades. **Conclusión:** El estudio de la nosohistoriografía psiquiátrica ayuda a comprender la evolución conceptual de las enfermedades mentales y la importancia más reciente de la psicofarmacología para ésta.

**Palabras clave:** clasificación, psiquiatría, psicofarmacología, neurociencias, nosología, taxonomía, historia de la medicina

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## Introduction

This work has a line of thought about the history of psychiatric nosography that covers the periods of Ancient History until the Enlightenment, passing through the development of Psychiatry in the 19th and early 20th centuries, reaching the time of the new psychopharmacology. However, the second part of this publication aims to highlight the achievements that

are reaching the 21st century, with emphasis on the current state of nosography and its perspectives. We emphasize the role of therapies such as psychopharmacology as a means to better understand the pathogenesis of some mental disorders and consequently potentially provide the somatogenic basis of psychiatric nosography.

### **Psychomedication vs. mental illnesses classifications?**

This section begins equating the relationship between treatment, mainly by psychotropic drugs, and understanding the pathogenesis of mental illnesses with repercussions on their classification.

Restraints, convulsive therapy/electroconvulsive therapy and lobotomies continued to be widely used until the 1970s, consequently, etiological theories coexisted to explain human behavior, from genetic and organic predisposition to psychological stressors, in the biopsychosocial model [1]. By way of illustration in this stormy therapeutic journey with more recent attempts, we name below some of the precursors of new therapies for mental disorders as follows. Julius Wagner-Jauregg (1857–1940) attempted, in 1917, the inoculation of malaria parasites to cause fever which proved successful in the case of paralytic dementia; Manfred Sakel (1900-1957), neurophysiologist and psychiatrist, in 1927, was the discoverer of insulin shock therapy for schizophrenics and other mental patients; Ugo Cerletti (1877-1963), psychiatrist and neurologist at the University of Rome La Sapienza, discovered the method of electroconvulsive therapy applied in clinical psychiatry; António Egas Moniz (1874–1955), professor of Neurology at the University of Lisbon, introduced the distressing frontal lobotomy for refractory cases of psychosis [2, 3].

However, the main somatogenic treatment for mental illness was established with the first psychotropic drugs in the mid-twentieth century. Fortunately, new acquisitions were emerging in the development of highly effective and safe antidepressants, antipsychotics, stimulants and relaxants, as follows [2, 4].

Lithium carbonate's ability to stabilize mood swings in bipolar disorder was demonstrated by Australian psychiatrist John Cade in 1948. Thus, this was the first effective medication for the treatment of mental illnesses. However, lithium as a psychopharmaceutical has been known since ancient times as the consumption of water from certain sources was recommended for the treatment of melancholy. The fathers of American neurology

indicated the use of it in the form of lithium bromide: Silas Weir Mitchell (1829-1914), proposed it as an anticonvulsant and hypnotic and, later, for the treatment of 'general nervousness', and William Alexander Hammond (1828- 1900) becomes the first physician to prescribe this form for the treatment of 'mania' [5]. Consequently, the specificity of lithium in the treatment of mood disorders has provided empirical support for the Kraepelinian opposition between schizophrenia and bipolar disorder.

In 1952, the first clinical trial of the first antipsychotic, chlorpromazine, was conducted by Jean Delay (1907–1987) who coined the word 'psychopharmacology' and proposed the new name of the neuroleptic drug. Chemical therapy of the phenothiazine core has led to the creation of several compounds with comparable properties, such as thioridazine, fluphenazine, and trifluoperazine. Others, such as haloperidol belonging to the butyrophenone group, developed by Paul Jansen in 1958 in Belgium, proved to be equally effective.

Equally impactful was the pioneering development of antidepressants. In 1957, the first of them, the tricyclic, imipramine, was discovered, which undermined the classic differentiation of psychoanalytic origin between psychotic and neurotic depressions and called into question the notion that these modalities would be treated exclusively with psychotherapy.

The first modern anxiolytic to be commercialized was meprobamate, in 1955, however, it shared many of the limitations and risks of barbiturates, being an alternative to it, chlordiazepoxide which was the first benzodiazepine synthesized (1960) followed by diazepam, flurazepam and clonazepam, which became the medication of choice for anxiety disorders.

Thus, in the early 1960s, the basic psychiatric therapeutic arsenal had already been outlined and the clinical conditions previously regarded as intractable proved to be largely manageable. Therefore, the social, conceptual and scientific repercussions of these events were immense, the greatest being social, and psychiatric deinstitutionalization [2, 4].

Consequently, the neurosciences were also radically affected by the fruits of the Golden Age of psychopharmacology unfolding in the dopaminergic hypothesis of schizophrenia and the catecholamine hypothesis of affective disorders.

The dopamine hypothesis of schizophrenia originated in the work of Arvid Carlsson and others on the mechanism of action of antipsychotics which is based on the idea that schizophrenia may be related to a relative excess of DA [dopamine]-dependent neural activity [6].

On the other hand, in 1965, independently J.J. Schildkraut and Bunney & John Davis published papers proposing a so-called "catecholamine hypothesis of affective disorders", linking depression and deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain [6].

### **The new nosography and psychopharmacology for the 21st century Classifications**

Only in its sixth version (1948) the International Classification of Diseases (ICD), was expanded to also apply to morbidity and inclusion of a new grouping of 'Mental, psychoneurotic and personality disorders that included 26 categories, which were divided into three broad clusters: psychoses, psychoneurotic disorders, and disorders of character, behavior, and intelligence [7]. However, for most of the 20th century, psychoanalytically oriented psychiatry was dominant in the USA and organicity fell into disuse. As a result, in 1952 the American Psychiatric Association (APA), directed by neuropsychiatrist George Raines, published its first Diagnostic and Statistical Manual of Mental Disorders (DSM), later revised into DSM-II (1968), DSM-III (1980) and its revised form DSM-III-R (1987), DSM-IV (1994) and its revised DSM-IV-TR (2000) and DSM-V (2013) [8].

The main objective of the creation of the DSM was to create a common reference for mental disorders dominated by a national institution of the hegemonic country. As for the DSM III (1980), coordinated by Robert Leopold Spitzer (1932-2015), there was an attempt to recall the ideas of the European masters of the late 19th century and the beginning of the 20th, especially Emil Kraepelin. Thus, DSM-III began with the main categories of psychiatric illness as articulated by European psychiatrists from the late 18th century onwards, developing operationalized criteria for these categories, often relying substantially on earlier sets of criteria, including 'Schneiderian' symptoms of schizophrenia. However, the introduced 'bipolar disorder' is distinct from unipolarity and comes from Karl Leonhard (1948), and in this edition, numerous other new diagnoses were added such as attention deficit disorder, post-traumatic stress disorder, and a new anxiety disorder [8]. From DSM-V, these classifications became predominantly Descriptive, with Emphasis on symptoms more



than a course, Categorical with dimensional features, Operationalized and nomothetic (laws or generalizations that apply to all people) [9].

Revisions of the manual since then follow this line and this new dominant paradigm of psychiatry became neurobiological, replacing the psychoanalytical one, but it was heavily criticized by both psychists and somaticists. The first is for excluding a psychological understanding for psychiatric diagnoses and sticking to operational criteria, and the other for the still lack of biological basis. These constraints conducted the building on one side psychodynamic and idiographic (uniqueness) perspectives by means e.g. the Psychodynamic Diagnostic Manual (PDM, 1st ed. 2006, and the other side, by transdiagnostic approaches, e.g. Research Domain Criteria (RDoCs) (2013) constructed by USA National Institute of Mental Health. The first was Descriptive and Aetiological, Categorical with dimensional features (more dimensional than DSM), Phenomenological and Idiographic. On the contrary, the second is predominantly Aetiological, dimensional and Nomothetic [9].

RDoCs emphasize the underlying biological mechanisms and symptom spectrums that underpin psychiatric nosology. Besides, Michelini et al. [10] argue that another initiative of the Hierarchical Taxonomy of Psychopathology (HiTOP), a hierarchical classification that conceptualizes psychopathology as a set of dimensions organized into increasingly broad transdiagnostic spectrums, is committed to the same objectives as the RDoC, which is a research framework linked to the Neurosciences. Both were developed to overcome the limitations that currently plague psychiatry. It should be clarified that HiTOP was developed by a consortium of scientists who study psychiatric nosology, and in this system, they incorporated the most common forms of psychopathology, as well as a series of rare conditions.

However, DSM-5 emphasized the potential value of neuroscience for diagnostic validation, but a translational view is at the core of RDoC. DSM criteria can be replicated by several professionals, and psychiatric nosology by DSM III to V was predominantly descriptive with an emphasis on symptoms rather than course, categorical with dimensional features, operationalized and nomothetic [9]. Thus, biological psychiatry seems to have prevailed, and the launch of the DSM-V in 2013, although based on a wide range of literature reviews, commissioned research and expert consensus, generated much controversy, due to its medical/biological bias

and for expanding the scope of psychiatric disorders which reduces the range of normality.

Regarding the ICD 10th edition, it included a chapter on mental and behavioral disorders that was heavily influenced by the DSM, but this system is used in multiple contexts by health professionals and non-specialists around the world, in addition to being coordinated and released by an international institution. ICD-11 has also devoted considerable effort to exploring and expanding the relevant evidence base that reinforces its use in global practice, and clinical utility in different countries, which ensures that it will be an essential tool for global mental health. This version of the ICD has built on the key strengths embodied in the DSM and the RDoC, with the chapter on mental, behavioral and neurodevelopmental disorders representing an important step forward for the field of global mental health in general and services and research, in low and middle income contexts in particular [[11](#)].

There is still a main problem in psychiatry and to a lesser extent in the system classifications in medicine as a whole of the 20th century, as most mental disorders are not within the concept of disease entities or clusters of disease entities that are etiopathogenetically explainable, but maybe some would already be as major depression and schizophrenia. However, many others would be clinical syndromes or just aggregations of clinical symptoms and signs. Besides, some supposed disorders should better be classified as simple as nondiseases without fulfilling any criterion of pathogenicity as stated by Hucklenbroich [[12](#)].

### **The proximity of the soul, mind and the brain**

On the evolving classifications, there is still a dualist struggle that would say that the psyche and soma are separate but equally real, while a reductionist would try to explain the psyche as a result of somatic causal processes, such as biochemical interactions. The biomedical model brings some specific ways of understanding health, illness and disease that can always be reduced to a physical, biological disease, which concerns purely the physical body, seen as analyzable. This is a mechanistic view of biology, in which the parts are not changed by context and therefore can be studied in isolation. The mechanistic view, along with the dualism that separates the body from the mind, is deeply rooted in Western culture, mainly because of the influential work of René Descartes [[13](#)].



Due to the great increase in neurobiological knowledge in recent years and psychopathological disorders, a more holistic view of neurology and psychiatry is emerging and some achievements are presented by Steck [2]. Throughout history, neurologists and most psychiatrists have examined brain/mind function, but conflicting theories have often emerged as both areas are closely linked to some developments made by pioneers as follows. Hans Berger (1873–1941), became a professor of psychiatry at Jena, and is known as the first to record the electroencephalograms of human beings; Egas Moniz developed Cerebral Angiography; Imaging techniques were introduced into the clinic in the 1980s, and magnetic resonance imaging (MRI) assumed surprising importance in diagnostic medicine and more recently in basic research, mainly through functional magnetic resonance imaging (fMRI), in the early 1990s, the which is of paramount importance in basic research in cognitive neuroscience, in addition, in the last decade, fMRI dependent on the level of oxygen in the blood (BOLD) has been used to investigate the effect of diseases and pharmacological agents about brain activity. This last technique was first described by Seiji Ogawa, a Japanese biophysicist and neuroscientist, and research in cognitive neuroscience is changing and much is expected of it. Furthermore, this increasingly heralds a rapprochement between neurology and psychiatry [2]. Consequently, a new paradigm is being forged for psychiatry to be seen as a clinical neuroscience, and the RDoC project is proposing a consistent conceptual framework for this [14].

### **Advances in pharmacology**

In connection with the drive for pharmaceutical innovation, a new class of antidepressants called 'selective serotonin reuptake inhibitors (SSRIs)' was launched, the first being fluoxetine (1987) which is better tolerated and safer than previous antidepressants. In the antidepressant drug paradigms, dopamine and noradrenaline reuptake inhibitors (bupropion), selective serotonin and noradrenaline reuptake inhibitors ([SNRIs] (venlafaxine, duloxetine, milnacipran) or multimodal (vortioxetine) followed ease of use, tolerability and high safety margin which led to popularity among physicians and users [4].

Shortly afterwards, new antipsychotics were launched, the so-called 'atypical neuroleptics' with a more complex history since Hanns Hippius, in the 1960s, demonstrated that clozapine did not produce the extrapyramidal adverse effects of typical antipsychotics, but the Lancet magazine (1975) warned about the occurrence of 16 cases of patient with agranulocytosis, nine fatal. However, in 1988, Kane and his collaborators

considered that it was superior to chlorpromazine in the treatment of patients with refractory schizophrenia, did not produce extrapyramidal effects and could be used safely, provided that leucometry was monitored at regular intervals. Other so-called atypical antipsychotics, such as risperidone, olanzapine and quetiapine, followed one another, despite not having the much-feared side effect of agranulocytosis, they were not superior to conventional antipsychotics, except for clozapine [4].

Despite the undeniable qualities of SSRIs, it is estimated that 30% of depressed patients did not tolerate the remission of their symptoms even after four treatment attempts with drugs of different profiles [4].

The importance of this chapter of psychiatry is demonstrated by the notable Thomas Ban (1929-2022) who demonstrated an interest in questions of psychopathology, nosology and the history of psychopharmacology [15].

An evolving area is precision medicine, which has as its relevant focus pharmacogenomics, which studies the influence of genes on an individual's response to medications. This strand of research can classify patients into relevant diagnostic subgroups with the use of specific biomarkers that promote a better diagnosis and probably a better treatment [16].

In sum, a new era in Psychiatry still depends on clarifying, with stronger evidence than those already brought by psychopharmacology, the pathogenic mechanisms underlying mental disorders.

### **Summing up**

The field of neurosciences was also radically affected by the fruits of the golden age of psychopharmacology, with repercussions on the hypotheses dopaminergic of schizophrenia and monoaminergic depression.

However, even at the height of the medicalization of psychiatry in the 1980s and 1990s, it was recognized that unconscious dynamics affect the doctor-patient relationship and that interpersonal factors strongly influence whether patients feel helped by treatment. Thus, there was room for George L. Engel's formulation of the biopsychosocial model (1977), despite objections, as it is a general theory of illness and healing that encompasses all the scientific advances underlying modern medicine, while also highlighting that many conditions cannot be explained by detecting changes at the cellular or molecular level [13].

In addition to the biomedical model of mental illness based on biological aspects, others advocate that a phenomenon such as mental illness does not arise from physical properties [13]. However, psychiatry as a medical speciality is increasingly grounded in neuroscience and pharmaceutical research. Meanwhile, clinical psychologists have empirically validated the use of cognitive-behavioural therapy (CBT) primarily for depression and anxiety over analytical and dynamic therapies. Consequently, emotional complaints have been accurately diagnosed and then treated with even valid psychotherapies such as cognitive behavioral therapy considered the gold standard of them. Besides, as Stein et al. report [14] CBT is very consistent with a neurobiological model of mental disorders and consequently can be easily associated with neurobiological approaches, especially pharmacotherapy.

On the other hand, unrecognized or underestimated side effects of drug therapy have been revealed by increased suicidal behavior with the use of SSRIs, and some patients experience severe 'discontinuation syndromes' when stopping treatment. Furthermore, atypical neuroleptics have been linked to a 'metabolic syndrome' of weight gain, increased risk of diabetes and other medical complications. Anyway, in this eagerness to discover new drugs, there was an advance in the understanding of the etiology of psychiatric illnesses, in addition to the pressure for expensive psychiatric drugs for uses that are still not more effective than those already launched.

It is equally clear that we are not close to analyzing and treating human psychology in a reductionist way at the neural level, although psychopharmaceuticals, for example, target psychiatric phenomena as biochemical processes that have gone wrong [13]. Consequently, the biomedical model is still influential and entrenched in medicine, however, medicalization without deep intervention at the social and psychological level has not been successful in resolving many psychiatric conditions as certain genetic or other biological differences will be linked to psychological vulnerabilities [13].

Robust psychiatry of the future will certainly lay claim to a wide reach, from the cellular basis of behavior to individual psychology to family dynamics, and finally to the community and social phenomena that affect the human being.

We have seen that the biomedical model of disease is based on a dualistic and reductionist view of the human condition. In any case, an ecological

perspective in medicine seems to be needed that places much more emphasis on understanding human biology, including mental suffering, as genuinely interactive, and on investigating how biological processes are integrated into human context and lived experience [13].

Thus, psychiatry was remodelled inside medicine, and its specialists became differentiated clinicians for clinical diagnosis and management of patients with the help of psychopharmacology, adding the advantage of knowing the person behind the symptoms in alliance with psychotherapists. These special physicians may represent the pinnacle and model of communication skills in today's relevant narrative medicine. These specialists initiate an investigation of the patients from their highest level of complexity to contemplate the whole of being.

### **Study limitations**

This narrative review depends on the subjectivity of the authors, which predisposes it to bias. On the other hand, there are limitations of systematic reviews in this multivariate and long-trending field, which favored the narrative review due to its access to diverse sources of information to explore many understudied areas. Thus, this type of review contributes to a holistic approach with potential deeper insights into this subject, leading to a comprehensive understanding of the historical development of psychiatric nosology.

### **Conclusion**

As understanding of the pathophysiological mechanisms underlying mental illness improves, this may lead to the reclassification of certain disorders. Naturally, there may even be subtyping with more specific treatments e.g. Furthermore, a better understanding of pharmacogenetics may influence how disorders are classified based on genetic markers that affect response to medication. Of course, the diagnostic criteria can also be refined, e.g. if a subgroup of patients with distinct symptoms responds differently, this could be a subtype specific to the disorder. Thus, more insight into drug responses may influence how disorders are classified and therefore diagnosed and treated.

It is clear, therefore, that this tendency towards the etiological search for mental disorders to arrive at their nosography has not yet been fully achieved, but there is a perennial oscillation between different classification standards around the central philosophical questions of nosology. Consequently, the dominant psychiatric classification systems seek to

follow the same flow as that of medicine as a whole. This path goes through the ancient holistic approach to the whirlwind of today's medical discoveries, but this view was associated not only with the sciences, regarding its reductionistic approach, but also with an integrative understanding of the human being, as is customary in the humanities.

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