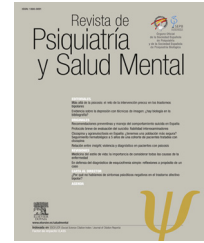




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EDITORIAL

Personalized medicine applied to mental health: Precision psychiatry[☆]

La medicina personalizada aplicada a la salud mental: la psiquiatría de precisión

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I remember it as if it were today, although many years have passed now. That skinny, simple woman, who had to leave school at the age of 12 to help her mother, who was supporting the family because the father had lost his job; those were hard times. An almost illiterate woman, yes, but intelligent. She presented rapid cycling bipolar disorder type II, with cycles that were very hard to stabilize. Until one day it happened. A year before, a new drug had been brought onto the market, it was only indicated for schizophrenia, although its mechanism of action suggested potential antidepressant effects. We started with a low dose, but noticed a change immediately. Six months later, the patient was able to remain stable for longer periods of time than ever in the past seven years. Then, after thanking me for having stabilized her after innumerable attempts with so many different medications, she asked me that question: "Thank you doctor, but why you did not give me those pills from the beginning?"

Personalized medicine tries to improve the diagnosis and the treatment of diseases through biomarkers that allow us to answer that woman's question. In fields like oncology, there is no doubt it is starting to bear fruit, and nowadays

it is much more important to know the genetic lineage of a neoplasm than its location. In psychiatry we still have subjective diagnoses, not completely reliable¹ and much less valid, and we still prescribe by trial and error: a drug that cures one patient does not work well with another, but there is no way of foreseeing what will happen before we try it. Our knowledge about the aetiopathogenesis of mental diseases, despite the remarkable progress made, continues to be "top to bottom" instead of being "from the bottom up", or what we popularly call "to begin building a house from the roof." The drugs available at the moment are not the result of the discovery of the pathophysiological basis of psychiatric disorders, but the fruit of precise and fortunate clinical observations; and from their mechanism of action we have deduced that something goes wrong in the brain with dopamine, serotonin or glutamate. But something is changing.

DSM-5 will be the last version of the mental disorders classification that does not include biomarkers.^{2,3} *Precision psychiatry* has come to stay; and although it may still be in stuttering phase, soon the discourse will be intelligible and clear, and nobody will be able to work denying the biological substrate of mental diseases. No more *prêt-à-porter*, everyone will have their own tailor and their custom-made suit. At the beginning, we will talk about psychiatry "stratification",⁴ that is to say, about a psychiatry that, without reaching an individual ultra-definition, would allow at least to define sub-groups or stratifications within the diagnose categories, and we will talk about the underlying

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symptomatic dimensions of the great syndromes. It happened in oncology, it has started to happen in neurology (only 10 years ago the diagnosis of multiple sclerosis was exclusively a clinical diagnosis, based on criteria that we, psychiatrists, still use), and it will start to happen in the field of mental diseases. An example: every day we are getting closer to foreseeing in a sensitive and specific way of the evolution towards psychosis in subjects at risk by combining clinical and genetic markers.

Of course, there will be barriers, particularly ideological and economic barriers. I am optimistic about the ideological barriers; and although the stigma of mental illness will still continue to exist for a long time, the increasing precision of psychiatry will manage to change those who still work with obsolete and messianic models, as happened, in its moment, with epilepsy, illness labelled for centuries as being "of the soul." I am more concerned about the economic barriers⁵: the price of biomarkers is rapidly going down, but they still continue to be unattainable for a large part of the world population. Neuroimaging tests, for instance, essential for the diagnosis of multiple sclerosis or Parkinson's disease, are still expensive and the prevalence of mental diseases is still too high to be able to say that those tests will soon be systematically used in clinical practice.

It is true that I still do not have the answer to the question my patient asked. Pharmacogenetics is growing and we currently have tests that allow us to better predict the tolerability of drugs (concrete cases: agranulocytosis to clozapine or Stevens–Johnson syndrome to carbamazepine), but there is still a long way to go regarding efficacy. An important aspect is that we have already come to the conclusion, not only scientifically, but also economically, that drugs provided in syndromic approaches will not take us far. The industry already accepts that it must stratify to discover new molecules with true added value over what already exists, which is mainly a generic market: we have a recent example with vortioxetine, which limits its market to depressed patients with neurocognitive dysfunction.^{6,7}

Precision *psychiatry* goes hand in hand with another psychiatry, its sister: *technological psychiatry*.⁸ Tertiarity in psychiatry is a reality,⁹ and stimulation techniques will start to be generalized as they become less invasive and less expensive. Based on the advances in neuroimaging that will allow to identify, as is already happening, dysfunctional circuits (the neuronal network by default, for example), which will become therapeutic targets.¹⁰ Some low-cost technologies, such as smart phone applications, are already being commercialized in the field of the mental health. Soon, the typical image of the psychiatry office with a table and 4 chairs will disappear, and those professionals who do not embrace the increasing use of technology in psychiatry will fall behind their colleagues.

It would make me very happy to work one day, not too far in the future, with tools that allow me to select from the very beginning the right treatment for a patient. To date, it is certain that the sensitivity and specificity of the

available biomarkers (genetic, biochemical, electrophysiological, imaging technologies or simply clinical biomarkers) are insufficient. But we are getting closer. The *Food and Drug Administration* has already approved the first electrophysiological diagnostic system for attention deficit hyperactivity disorder, and we assist an authentic emergence of small companies of entrepreneurs (*start-ups*) who investigate ways to validate the diagnosis and to predict the best treatment for mentally ill patients. These are exciting times. Do not let them pass you by.

Conflict of interests

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