PSYCHIATRIC DRUG THERAPY: CRISIS OF INNOVATION

A significant number of people (about 1 in 5 in the U.S.A.) take medication for psychiatric disorders. Numerous antidepressants, antipsychotic and hypnotic drugs, hide two serious shortcomings: firstly, many of the drugs vary only minimally in their pharmacology, and are called, in pharmaceutical jargon, "me too" drugs. Secondly, there is little pharmacological difference between the six antidepressants "inhibitors of serotonin reuptake", and the same occurs when comparing the ten antipsychotics known as "atypical".

Moreover, with new drugs, tolerance and security are given priority, at the expense of their clinical efficacy. The number of therapeutic failures with newer medications for schizophrenia, depression and bipolar disorder, is significantly high, and intolerance due to their adverse effects is higher than preclinical studies and subsequent promotion had shown.

Since the golden age of psychiatric drugs, in the 1950s, when the first neuroleptics [(1)] and antidepressant [(2)] freed patients from “incarceration” in Mental Institutions, and humanized the treatment of the mentally ill, critical analyses of subsequent innovations have been very disappointing. The acceptance of new drugs is partly due to the trivialization of diagnoses that have ma**d**e drugs out to be “effective”, when, in reality, this is not the case.

After a series of unsuccessful clinical trials in which new potential antidepressants and antipsychotic hardly showed greater efficacy than that achieved in the study groups treated with a placebo, pharmaceutical companies appear to have reached the conclusion that the development of new psychoactive drugs is , from a financial standpoint, too risky. This trend was exemplified during the 2011 scientific meeting of the American Society for Clinical Pharmacology and Therapeutics, where only 13 of the 300 abstracts presented were related to psychopharmacology, and none had anything to do with new psychotropic drugs. Pharmacological research money is now spent on looking into other diseases such as cancer, diabetes and heart diseases, where the biochemical markers are better defined than those of mental illness.

It should be noted that the new psychotropic drugs (antidepressants, antipsychotics and anxiolytics) share the same molecular targets as their prototypes of the mid-1950s.

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Consider two examples: the newer antipsychotics block dopamine receptors, the same mechanism of action as the first antipsychotic neuroleptic, Chlorpromazine, synthesized in 1950. This was introduced into therapeutics as a "major tranquilizer" (as it was then called) and was discovered fortuitously by *Henry Laborit*, a French anesthetist, born in Hanoi, in what was then North Vietnam*;* another example: most recent antidepressants increase synaptic concentrations of neurotransmitters (serotonin, dopamine, norepinephrine), the same mechanism of action as the first antidepressants, called tricyclics.

A critical analysis suggests that there has been no real psychopharmacological innovation in recent decades. At the risk of generalizing, it can be said that new psychotropic medications are safer and better tolerated, but not more effective.

One cause of this rather disappointing situation is the difficulty of studying the brain. It is the only organ where it is not possible to perform biopsies in the hope of finding new drug targets.

Moreover, the biochemical mechanisms of mental illness are inferred from the action that psychoactive drugs exert on neurotransmission. The obvious question is: are these changes in brain concentrations of certain neurotransmitters the main cause, or just one of the consequences of the change (or changes) that define the disease? It is conceivable that increasingly sophisticated brain imaging techniques, along with indispensable studies in animal models, will bear fruit in the next few years. In part, this has already happened in the recent past. Two antipsychotics (also prescribed in depressive and bipolar disease), Quetiapine [(3)] (Seroquel ®) and Aipiprazole [(4)] (Abiliy ®), are pharmaceutical “blockbusters”. Their copyright protection has expired, but, so far, no similar drug has been able to oust them from their privileged position.

According to some experts, the Pharmaceutical Industry’s lack of interest in research on the brain is a mistake.

Consider the paradigm of ketamine [(5, 6)] (sold illegally as "Special K"), an anesthetic which has proven to be a powerful antidepressant. Ketamine acts upon a cerebral target which is different from that acted upon by currently available antidepressants. Ketamine blocks the NMDA receptor [N-Methyl-D-Aspartate] whose physiological ligand is the amino-acid glutamate, an important neurotransmitter linked to important functions such

as learning and memory, and, in view of this pharmacological finding, is also associated with depressive illness.

A clinical study has shown that many patients diagnosed with multi-drug refractory depression, experienced a rapid resolution of their symptoms after prolonged infusion (several hours) of Ketamine. Particularly striking was the rapid response, especially when compared to the several weeks that are usually necessary when current-day antidepressants are used. This is due to the fact that the NMDA receptor is "fast acting". This receptor is truly fascinating. The modulator, as mentioned before, is glutamate. If the activation of this receptor is of low intensity, it can trigger a psychosis, but an excessive activation leads to neuronal apoptosis.

It is impossible to predict whether Ketamine will become an antidepressant medication. At present, the pharmaceutical industry does not seem to be particularly interested.

Major research projects, such as the Brain Activity Map, with gene sequencing technology, can help identify brain circuits and genes that are linked to various psychiatric disorders, allowing the discovery of new drug targets. This will enable us to interact with them, and develop new psychiatric drugs.

Bear in mind that Regulatory Bodies authorize new drugs based on short-term trials, and only post-marketing studies (Phase IV) define the safety of long-term medications. This is particularly important with respect to substances that interact with new drug targets for which there are no pharmacological predecessors, and our technical knowledge about them is limited.

Mental illness is a source of great personal suffering and social marginalization, as well as being a great economic burden for Healthcare Services. The treatment of these diseases requires research, as well as medical and financial risk-taking. This has happened in the past. And it worked!.

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