Editorial

Future paths in psychopharmacology

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Drug development in psychiatry is gradually moving from serendipity to personalized medicine. Some promising paths will be reviewed in this issue.

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Since the 1950s the discovery of psychotropic compounds, mostly based on serendipity, has dramatically changed the lives of millions of people suffering from severe mental disorders. However, important questions remain regarding the lack of or insufficient effectiveness of psychotropic drugs in at least one third of cases, and there are also risks associated with their use, such as the serious metabolic effects associated with antipsychotics and some antidepressants. An increased time to response or remission is associated with suffering as well as an increased risk of morbidity and mortality.

The improvement in our knowledge of the brain circuitry dysfunction associated with severe psychiatric disorders will lead to the identification of reliable biological markers (for review see refs 1-3) which are key elements on the path to personalized medicine. Former US President Obama provided a persuasive definition of personalized medicine in 2015: "Getting the right treatment at the right time to the right person." Indeed, there is significant interindividual variability in psychotropic drug response, dosage, and adverse effect profile. Improving the benefit:risk ratio of a given compound in a given patient, using a more biologically informed selection of psychopharmacologic agents, particularly through genotyping, has become a reality in clinical psychiatry. For example, in this issue, Gurwitz (p 131) has reported on the expression levels of certain microRNAs, which deserve further exploration as tentative diagnostic biomarkers for neuropsychiatric disorders and as promising drug targets for the development of future treatments. However, the classical aspects of precision medicine linking genotypes to diagnosis and treatment remain a difficult point in psychiatry. In contrast to somatic diseases such as diabetes mellitus or cardiovascular diseases, diagnosis may fluctuate between anxiety, depression, and even bipolar disorders or psychotic disorders as a function of time, and treatment has to be tailored accordingly. With the advent of reprogramming technologies and the recent developments in induced pluripotent stem cell differentiation into defined neural cultures and 3-dimensional cerebral organoids, a new era of preclinical disease modeling has just begun. It has the potential to assist drug discovery in psychiatry and to help overcome the challenges encountered with the current classifications used in psychiatry (see also Rossetti et al in this issue, p 203).

Since the 1980s, fewer than 40 drugs have been registered for psychiatry. The pharmaceutical industry is constantly cutting research into psychiatric medicines, and the drug development pipeline for psychiatric drugs is almost empty. In this respect, psychiatrists have reanalyzed the psychoactive properties of old illicit drugs such as psychedelic drugs or 3,4-methylenedioxy-lethamphetamine (MDMA). The key target for psychedelic drugs is the serotonin 5-HT2A receptor where they act as agonists (See article by Nutt in this issue, p 139). MDMA is a serotonin-releasing agent.

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Future paths in psychopharmacology - *Thibaut*

Recently the European Medicines Agency approved psilocybin for a phase 3 study in treatment resistant-depression and the Food and Drug Administration for post-traumatic stress disorder with MDMA. A single IV dose of ketamine could produce an improvement in mood lasting up to 4 days. Suicidal ideas may also improve dramatically after a single dose of ketamine. Its active enantiomer, s-ketamine (given intranasally) may be licensed soon. However, in many cases, depressive symptoms and suicidal ideas relapse within several weeks or months. Ketamine is thought to act as a glutamate antagonist of the NMDA receptors. However, the legal status of these powerful mind-altering compounds remains a challenge, as all psychedelics and MDMA were listed in the UN Conventions as Schedule 1 drugs. Schedule 1 drugs are defined as having no accepted medical use and significant potential for harm and dependence.

The current research on vaccine to treat substance disorders is another interesting pathway. A vaccine would induce antibodies which may compete with the drug, decrease the drug's ability to cross the blood-brain barrier and therefore reduce the reward associated with drug intake.[4]

Schulz, in the State of the art article in this issue, (p 119) has reviewed new areas that could be of interest to improve the management of psychiatric disorders. ■

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