

Precise treatments for schizophrenia: where is the way forward?

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Schizophrenia is a kind of chronic mental disorder that leads to disability, and it is characterized by the incoordination of perception, mind, emotion and behaviour, and the disconnection between mental activities and reality. It is recurrent and hard to cure. Schizophrenia has caused both agony to patients and their families, and heavy economic burden to their families and society. The appearance of chlorpromazine, the first antipsychotic drug in the 1950s, brought about a revolutionary change in the treatment of schizophrenia. Even though the first-generation antipsychotic drug's effectiveness for schizophrenia (especially the positive symptoms) was absolutely positive, it did not cause significant improvement in negative symptoms or cognitive impairment. Furthermore, these drugs could cause a variety of adverse reactions, such as extrapyramidal side effects, oversedation and so on. Therefore, a number of second-generation antipsychotic drugs gradually appeared on the market in the 1970s. Compared to the first-generation drugs, they were less likely to cause those side effects. In the meantime, some randomised controlled trials reported that the effectiveness of the second-generation antipsychotic drugs during the acute stage treatment of schizophrenia was significantly better than that of the first generation. Hence, a lot of hope was put into the second-generation antipsychotic drugs within the field of clinical psychiatry. However, as the drugs became more widely used, it was found that their long-term effect did not reach the expected level in many

clinical observations and studies. In order to eliminate the pharmaceutical companies' conflicts of interest in evidence-based medical studies, the National Institute of Mental Health granted a total of US\$40 million funding to carry out the Clinical Anti-psychotic Trials of Intervention Effectiveness (CATIE) study in 57 centres of 24 states in the USA in 2005.¹ According to the results of CATIE, there were no differences in the effectiveness of the second-generation antipsychotic drugs and perphenazine, the first-generation antipsychotic drug, after 18 months of follow-up.² Similarly, cooperating with the Shanghai Center for Disease Control, our team conducted a 24-month clinical follow-up study, which was based on the 'real world' situation among the schizophrenia population in Shanghai. The results have shown that seven widely used first-generation antipsychotic drugs, namely perphenazine, chlorpromazine, aripiprazole, olanzapine, quetiapine, risperidone and clozapine, and second-generation antipsychotic drugs have equivalent effectiveness, and the differences in the severity of disease, remission rate, medication compliance and social function are not significant.³ Health economics data indicate that the global sales of antipsychotic drugs has increased drastically from around US\$800 million in 1993 to US\$25 billion in 2015. The main driver for this increase is the success of second-generation antipsychotic drugs; however, the huge amount of medical resources occupied by the second-generation antipsychotic drugs does not match their effectiveness. In the past 20 years, the application of first-generation antipsychotic drugs in the field of clinical psychiatry has decreased on purpose due to a variety of factors, while the second-generation

antipsychotic drugs have started occupying a number of medical resources. Furthermore, the secondary diseases caused by their metabolic disturbance side effects aggravate the disease burden of patients' families and the society, which alone should warrant reconsideration of these drugs.^{4 5} Therefore, a new way of thinking is needed in treatment studies for schizophrenia.

How does one choose the strategy of medication treatment? At the beginning of 2015, former American President Obama mentioned the idea of precise medicine in the new year's State of the Union speech, and announced the launch of the Precise Medicine Project. Precise medicine is referred to as making the most reasonable treatment and prevention plan by taking patients' different genetic information, conditions of disease, lifestyles and environments into account.⁶ One of the important contributions of the Human Genome Project, which was finished in 2003, is the deepening of the understanding about the relationship between genetic mutation and disease. Precise examination is both the foundation of precise medicine and an important method of achieving precise treatments. In recent years, precise studies about the effectiveness of antipsychotic drugs mostly focus on two factors: (1) precise studies that were based on the pathological mechanism hypothesis. Even though epidemiological data have shown that heritability of schizophrenia is as high as 80%, there have rarely been any breakthroughs in molecular genetic research since the past few decades. Therefore, even when multiple studies point out that the neurotrophic factor family, dopamine receptor system, 5-serotonin receptor system and G protein signalling pathway are probably related to the effectiveness of antipsychotic drugs, studies on precise treatments based on molecular targets are still having trouble making progress because, usually, it is hard to reproduce the results, and the sensitivity and specificity are not high.⁷⁻⁹ (2) The other factor is the precise studies that are based on drug metabolism pathways. Antipsychotic drugs' metabolism

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relies on the catalysis of a variety of drug-metabolising enzymes. The cytochrome P450 enzyme system, which is located in the liver microsome, is the main enzyme system that catalyses the metabolism of drugs. Any factor that might affect the activity of drug-metabolising enzymes could probably lead to changes of antipsychotic drugs' metabolism, thereby affecting the blood concentration, which changes pharmacological and toxic effects.¹⁰ One of the important factors that influences the activity of P450 enzyme is genetic polymorphism. However, the genetic polymorphism of P450 enzyme is more revealed in detecting adverse reactions and preventing interactions of drugs. The gap between it and effectiveness is too large, and it is also limited by the blood–brain barrier. Hence, a number of future studies are needed to explore the feasibility and effectiveness of the precise treatments strategy with P450 enzyme gene as the target.

Comparing the characteristics of the first-generation and second-generation antipsychotic drugs, one can conclude that the biggest difference between them is in their adverse reactions. Based on the features of receptors, the pharmacological mechanism of the first-generation antipsychotic drugs is the antagonism of D2 dopamine receptor. Its common adverse reactions are extrapyramidal side effects, increasing prolactin and so on. The pharmacological mechanism of the second-generation antipsychotic drugs is the antagonism of 5-hydroxytryptamine 2A receptor/D2 dopamine receptor. Its common adverse reaction is metabolic disturbance, such as weight gain, blood sugar increase, hyperlipidaemia and so forth. The effectiveness of the first-generation and second-generation antipsychotic drugs is equivalent, but their adverse reactions are revealed in different aspects. Therefore, the precise prediction of antipsychotic drugs' adverse reaction is probably a feasible option for the current precise treatments for schizophrenia. For instance, a recent genome-wide association study that employs the research sample of CATIE points out that the weight gain caused by the second-generation antipsychotic

drugs is associated with the OGFRL1 gene.¹¹ According to a series of studies on patients with schizophrenia who take clozapine for a long term, we have found that the metabolism syndrome led by clozapine is related to the COMT gene, that the effect which BDNF gene has on this kind of adverse reaction has a sex difference, and that the C3 gene can effectively predict whether patients who take clozapine are suffering from hyperlipidaemia or not.^{12–14}

In conclusion, precise medicine combines the knowledge and technical system of modern medicine technology, and has revealed trends in the development of modern medicine: from simplicity to complexity and from complexity to precision. Due to the complexity of schizophrenia, patients need long-term medication treatments. Evidence-based medicine indicates that the effectiveness of different types of antipsychotic drugs is equivalent, and that the current technical methods cannot achieve precise treatments based on effective prediction at the moment. However, the adverse reactions of different types of antipsychotic drugs are clear. If we employ the current precise detection methods, we can choose medication for treatments based on patients' susceptibility to certain adverse reactions. This may offer new thinking about precise treatments for schizophrenia. There are a lot of efforts needed in researching precise treatments for schizophrenia, and these efforts need to be made by clinical doctors and researchers together. Only after we overcome all those difficulties can precise medicine have a bright future in the psychiatric field.

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