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Research Progress in Concentration Monitoring of Antipsychotic Drugs

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Abstract

Objective: To explore the drug concentration detection of antipsychotic drugs in the treatment of schizophrenia and other psychiatric diseases. **Methods:** Collecting the research results of relevant references in recent years, and summarizing the development and existing problems of the detection of psychotropic drugs in recent years from the perspective of drug detection methods, multidisciplinary integration, and interdisciplinary cooperation, so as to provide a reference for the follow-up monitoring of antipsychotic drugs. **Results:** It was found that the individual differences in pharmacokinetics of these drugs were large, and the side effects and toxic reactions were not easily distinguished from the aggravation of the symptoms of the disease itself. **Conclusion:** Through the analysis of the collected literature, we can understand the research progress of antipsychotic drug concentration monitoring, and provide strong evidence for the realization of clinical individualized precise treatment.

Keywords

Antipsychotic Drugs, Therapeutic Drug Monitoring, Blood Drug Concentration, Pharmacokinetics, Genomics, Precision Treatment

1. Introduction

Therapeutic drug monitoring (TDM) is a new branch of clinical pharmacy. It is guided by the principle of pharmacokinetics and uses quantitative pharmacological models to measure the drug concentration in patients, evaluate the efficacy or determine the drug administration plan, so as to individualize the drug delivery plan, improve the drug treatment level, and achieve clinical safe, effective and rational drug use (Zhang, 2020). Antipsychotic drugs are mainly used to treat various mental diseases, such as schizophrenia, depression, bipolar disord-

er, organic mental disorder, senile dementia, etc. The clinical application of antipsychotics has the following characteristics: individual differences in pharmacokinetics are obvious, and the blood drug concentrations at the same dose can vary greatly; Joint use of drugs that may have interactions; Lack of concise efficacy indicators, and efficacy indicators are easily affected by doctors' subjective factors, and side effects and toxic reactions are not easily distinguished from the aggravation of the symptoms of the disease itself. The blood drug concentration is related to the curative effect and toxic side effects, too high or too low curative effect is not good. Psychiatric patients usually have a long course of disease and need long-term drug treatment. Through TDM, drug accumulation and poisoning can be avoided, and problems such as drug compliance and tolerance can be found in time to ensure the safety and effectiveness of drug treatment (Lu et al., 2020). The traditional drug treatment mode follows the group and experience treatment of drugs; Clinicians select the corresponding treatment drugs through clinical diagnosis, auxiliary examination results and their own clinical experience. This model ignores the individual differences in drug efficacy and fails to maximize the efficacy of drugs, avoid the toxic and side effects of drugs and guide patients to use drugs accurately (Yu et al., 2020). Therefore, the monitoring of therapeutic drugs for psychotropic drugs is an important means to adjust the dosage of drugs, optimize the treatment plan, improve the treatment effect, reduce adverse reactions and avoid drug poisoning. From the perspective of drug detection methods, multidisciplinary integration and interdisciplinary cooperation, this paper summarizes the development and existing problems of drug detection in psychiatric treatment in recent years, so as to provide reference for the follow-up development of antipsychotics TDM. The research results are now summarized as follows.

2. Progress in TDM Methodology

There are many methods for TDM detection; At present, the two most widely used methods are chromatography and immunoassay (Wang et al., 2017). See **Figure 1** for details.

2.1. Chromatography

High performance liquid chromatography (HPLC)is a branch of chromatography, which uses liquid as the mobile phase and adopts high-pressure infusion system to pump the mobile phase such as single solvent with different polarity or mixed solvent and buffer solution with different proportions into the chromatographic column with fixed phase. After the components in the column are separated, they enter the detector for detection, so as to realize the analysis of samples (Dong et al., 2021). This is the most widely used analysis method in TDM at present. It is generally ultraviolet detector or diode array detector, which has good detection stability and relatively low maintenance cost; However, biological sample pretreatment is required before separation, which is time-consuming,

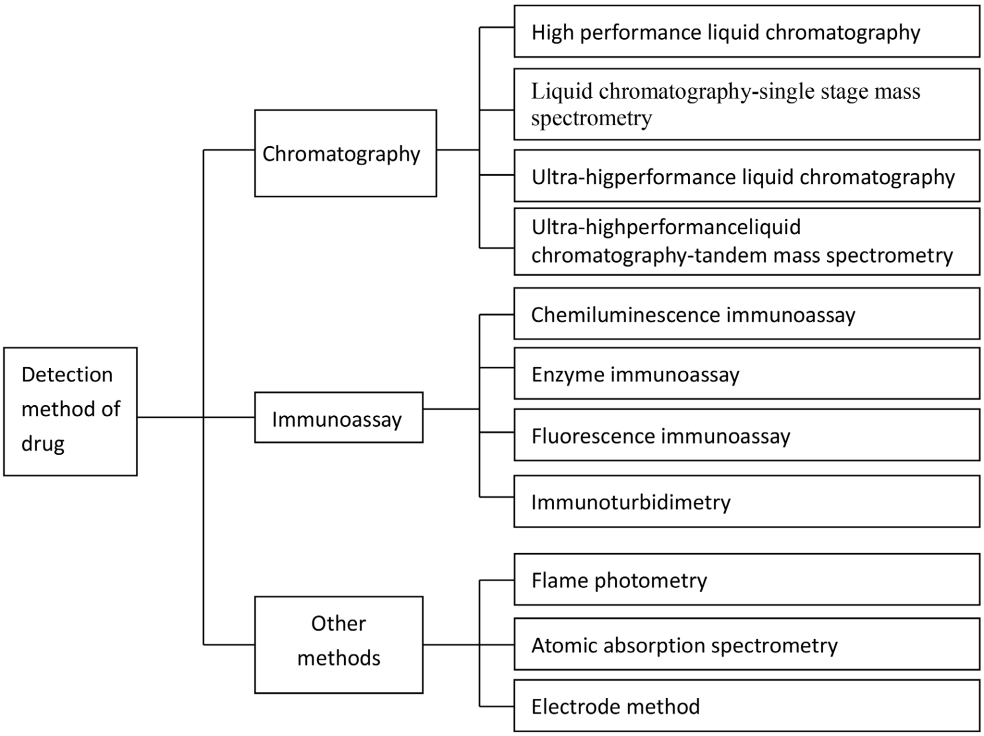

Figure 1. Method of drug concentration detection.

low automation, and poor specificity and sensitivity. HPLC can be combined with mass spectrometry to further expand the scope of application and improve the sensitivity, accuracy and selectivity of detection.

Liquid chromatography-single-stage mass spectrometry (LC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS). It is an analytical method based on liquid chromatography as separation system and mass spectrometry as detection system. Combining the high separation ability of chromatography for complex samples with the advantages of high selectivity, high sensitivity and the ability to provide relative molecular weight and structural information of mass spectrometry, it has been widely used in the field of drug analysis (Li et al., 2021b). Tandem mass spectrometry has higher sensitivity, accuracy and selectivity than single-stage mass spectrometry; It can analyze multiple drugs at the same time; These excellent properties make LC-MS/MS more and more used in TDM, which will gradually become the mainstream technology. The disadvantages are high instrument cost, high maintenance cost, high requirements for personnel and environment, and relatively poor stability; The main problems for quantitative analysis are ion inhibition effect and lack of appropriate calibration materials (Li et al., 2021a).

Ultra-high performance liquid chromatography (UPLC) uses column fillers with particles smaller than 2 μm and can withstand high pressure. Compared with HPLC, UPLC has the advantages of faster analysis speed, better signal-to-noise ratio, better peak width and separation, higher column efficiency, richer peak information, smaller sample size and less solvent consumption. However, UPLC

also has the disadvantages of higher pretreatment requirements and more complex operation (Wang & Zhao, 2017).

The method Ultra-high performance liquid chromatography combined with tandem mass spectrometry (UPLC-MS/MS) has higher ionization efficiency and reduced matrix effect. In recent years, the UPLC-MS/MS method has gradually entered clinical practice, especially in the multi-drug analysis for TDM, which can achieve simultaneous analysis of multiple compounds in a short time. UPLC-MS/MS has gradually become the core technology of drug analysis because of its fast analysis speed, high sensitivity and good specificity (Fan et al., 2021), and is a new direction of the development of therapeutic drug monitoring methods.

2.2. Immunoassay

Immunoassay does not require deproteinization of serum samples, and has the advantage of fast and simple, which has been developed rapidly in clinical application. Its advantages include: 1) short test period; 2) The sample demand is small, and cannot be extracted, with a high degree of automation; 3) With reagent box, easy to operate; 4) It has appropriate sensitivity, accuracy, specificity and precision. Therefore, the use of immunoassay for TDM can meet the characteristics of large batches of clinical samples and timely monitoring, and help clinical rapid analysis of a large number of samples. However, immunoassay also has some disadvantages: 1) Currently, there are limited kinds of drugs with test kits on the market, which limits its application scope; 2) The kit is expensive and currently depends on imports, with low cost-effectiveness; 3) It may cross-react with the active drug metabolites, thus interfering with the determination; 4) It is necessary to develop a corresponding kit for each drug, which is not applicable to new drug research. Therefore, immunoassay is difficult to completely replace chromatography in TDM application (Wang et al., 2017); The commonly used immunoassay methods are as follows.

Chemiluminescence immunoassay (LIA) uses a chemiluminescent reagent to label antigen or antibody, and then measure the luminous intensity after the antigen-antibody immune reaction, and then measure the concentration of the detected drug. Chemiluminescence immunoassay has both the high sensitivity of chemiluminescence and the high selectivity of immunoassay.

Enzyme immunoassay (EIA) uses enzyme to label antigen or antibody, and uses enzyme to efficiently and specifically catalyze reaction to produce photometric changes, so as to quantitatively detect drug concentration. The method has the advantages of high sensitivity, strong specificity, rapidity, stability of enzyme marker, automation, low requirements for instrument and operation, but the preservation conditions of reagent enzyme are high.

Fluorescence immunoassay (FIA) uses fluoresce in to label drug molecules or antibodies. After antigen-antibody competitive binding reaction, the fluorescence polarization or fluorescence signal intensity is measured to determine the drug

concentration.

Immunoturbidimetry uses the complex formed after antigen-antibody binding to precipitate in a specific system and form turbidity changes to determine the drug concentration. It is simple, fast and easy to realize automation, and can be detected on the biochemical analyzer (Wang & Zhao, 2017).

2.3. Other Methods

Other detection methods include lithium carbonate flame photometry, atomic absorption spectrometry, electrode method, etc.

TDM chromatography has a low degree of automatic detection, high skill requirements for operators, expensive instruments, more expensive tandem mass spectrometry, and high instrument maintenance costs. Some small and medium-sized hospitals have no conditions to purchase a chromatograph and choose to use the immunoturbidimetry of the existing automatic biochemical analyzer in the laboratory to detect the drug concentration. The immunoturbidimetric method may cross react with the metabolites of the active drug and interfere with the determination. The stability period of the reagent after bottle opening is short; The instructions indicate that the reagent is stable for one month, but some of them are out of control after less than half a month; Re-calibration requires multiple calibration points, and the loss is large. The amount of specimens is small, and the reagent may not be used up within the stable period; The reagent price is also high, and can't afford the management costs of calibration, indoor quality control, etc. The above reasons lead to the failure of TDM to be carried out on a large scale. Lu Haoyang and others investigated the implementation of psychiatric treatment drug monitoring in South China and its surrounding areas; Among the 69 surveyed hospitals, 39 hospitals had carried out TDM; Among the 39 hospitals carrying out psychiatric TDM, the methods mainly used were high performance liquid chromatography (35.0%) and liquid-mass combination (25.0%); The number of TDM projects ranged from 1 to 37, among which 8 hospitals carried out only 1 project (20.5%), and 53.9% of the surveyed hospitals carried out no more than 5 projects; Most of the surveyed hospitals carried out no more than 20 items (82.1%), and only one surveyed hospital carried out more than 30 items (2.6%) (Lu et al., 2020).

At present, only some immunological detection methods have approved supporting detection systems and kits, but most of the drug concentration detection methods of TDM projects belong to high performance liquid chromatography, liquid chromatography-tandem mass spectrometry and other technologies, which are self-built methods (LDT). The data shows that the test results of different test methods for the same test item are significantly different, and the test results of different laboratories for the same method are also significantly different. The reasons are as follows: 1) The TDM test results have not yet realized the traceability of the quantity value; 2) The detection method has not been standardized; 3) The coverage of EQA plan is insufficient; 4) TDM laboratory has insufficient

awareness of participating in EQA program; 5) TDM standardization is still in its infancy. These problems restrict the clinical application of TDM and the development of related research work (Guo et al., 2021). Although some people have compared different methods of various antipsychotic drugs, the results have good correlation and no significant difference (Zhang et al., 2022; Zhao et al., 2022), but there is no traceable reference material or exchange of certified reference materials for accuracy verification, which may lead to abnormal deviation of TDM results, causing clinical misreading and wrong guidance of drug dosage. Chen Yang, Yang Aijuan and Ma Wei reported that the low concentration of clozapine was 56% detected by high performance liquid chromatography system, and only 18.89% of patients' blood concentration was within the treatment window (Chen et al., 2022).

3. Multi-Disciplinary Integration of TDM and the Development Direction of Precision Therapy

Clinically, individualized differences in drug response are very common. For example, patients have the same diagnosis and general condition, the same drug administration and the blood drug concentration are all within the therapeutic range, however, the efficacy and toxic side effects may be completely different; And some patients showed inadequate administration, while others showed serious adverse reactions. Conventional TDM cannot well explain and solve these problems, while the emergence of pharmacogenomics has brought more in-depth explanation and prospective guidance for individual differences in clinical drug use (Wang et al., 2017). Drug genomics is to assess the risk of adverse drug reactions and guide clinical individualized drug use by detecting gene sequences, establishing the relationship between gene sequence differences and drug effects, studying gene characteristics that affect individual differences in pharmacokinetics, and the diversity of drug effects caused by gene polymorphisms. Pharmacokinetics is mainly to study the dynamic changes of drug disposal in the body, including the absorption, distribution, biochemical conversion and excretion of drugs in the body, especially the law of the change of blood drug concentration with time. In recent years, pharmacogenomic and pharmacokinetic detection of TDM fusion drugs in psychiatric department has attracted more attention and become an emerging development direction.

The differences in the blood concentration of psychotropic drugs within and between individuals (such as the differences in pharmacokinetics) are mainly due to the differences in the activity of drug metabolic enzymes. Cytochrome P450 (CYP450) superfamily is involved in the metabolism of psychotropic drugs in the genomes of psychotropic drugs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5. Many CYP genes are very prone to mutation, and the genetic polymorphism of CYP enzyme is the main reason for the large difference in blood drug concentration between individuals, which makes the determination of blood drug concentration particularly impor-

tant (Hiemke et al., 2022). Drug metabolism enzymes, especially CYP isozymes, have genetic variation; Fast metabolizers (EM) are wild-type with 2 active alleles; slow metabolizers (PM) lack functional alleles; And moderate metabolizers (IM) may be heterozygotes, carrying 1 active allele and 1 inactive allele, or may also carry 2 low active alleles. Ultrafast metabolizers (UM) carry highly active alleles or polyploid functional alleles. The gene polymorphism of drug metabolizing enzymes has important clinical significance; On the one hand, slow metabolizers may have unexpected adverse reactions or even toxic reactions due to the increase of blood drug concentration; On the other hand, people with ultrafast metabolism will be ineffective in treatment because they are lower than the effective treatment concentration (Hiemke et al., 2022). Changes in the concentration of psychotropic drugs caused by gene polymorphisms are common in clinical practice. CYP1A2 (-163C > A) type A/C is related to the decrease of blood concentration of clozapine, and type A/A is related to the decrease of blood concentration of olanzapine (Liu et al., 2020). The polymorphism of cytochrome P450 2D6*10 (CYP2D6*10) gene has an effect on the blood concentration of risperidone. There is a statistically significant difference in the blood concentration of risperidone, 9-OH risperidone and 9-OH risperidone/risperidone ratio among different genotypes; The blood risperidone concentration of T/T genotype patients was significantly higher than that of C/T and C/C genotype patients, while the blood 9-OH risperidone concentration and 9-OH risperidone/risperidone ratio were significantly lower than those of C/T and C/C genotype patients (Lu et al., 2021).

In the treatment of mental diseases, multi-drug combination therapy is often used; When the drugs used in combination are inhibitors or inducers of drug metabolism enzymes, and the drugs used in combination are the substrates of inhibited or induced enzymes, pharmacokinetic drug interactions may occur. Dose adjustment should be conducted under the guidance of TDM to avoid treatment failure, tolerance reduction or poisoning due to pharmacokinetic drug interaction (Hiemke et al., 2011). For example, escitalopram is a CYP2D6 enzyme inhibitor, and a small part is metabolized by CYP2D6; Risperidone, clozapine and propranolol are the substrates of CYP2D6 enzyme, and the combined application may affect the blood concentration of drugs metabolized by CYP2D6; Omeprazole, a CYP2C19 enzyme inhibitor, will increase the blood concentration of escitalopram when used in combination. For the combined application of drugs with interaction, the blood drug concentration should be well monitored (Zhong et al., 2022).

In pharmacogenomics, in addition to the correlation between metabolic enzyme gene polymorphism and psychotropic drug concentration, there are also the polymorphism of ATP-binding cassette B subfamily member 1 transporter group (ABCB1), receptor gene polymorphism, drug response risk gene such as human leukocyte antigen HLA-B*1502, which are related to adverse effects of psychotropic drugs (Lin, 2017); The phenotypes of metabolic enzymes, receptors, transporters, etc. of the test subjects are known by detecting the gene muta-

tions of the test subjects. Through the influence of different phenotypes on pharmacokinetics and pharmacodynamics, some drug efficacy and adverse reaction risks are predicted (Jiang et al., 2022). However, there are still many patients who can not benefit from gene testing; The possible reason is that the relationship between known gene status and drug treatment effect and adverse reactions is not completely clear or there are unknown interference factors (Wang et al., 2022).

4. Cross-Professional Cooperation Situation

TDM implementation mainly includes application, sample collection, laboratory testing, result interpretation, adjustment of treatment plan, and other links, which requires the cooperation of clinicians, nurses, laboratory technicians, and clinical pharmacists.

Clinicians prescribe application forms for drug concentration or gene testing according to the needs of diagnosis or treatment, but most doctors do not understand pharmacokinetics, so pharmacists are required to help interpret TDM reports and provide suggestions for adjusting medication regimen based on TDM monitoring results (Liu et al., 2021); For the TDM results that exceed the laboratory warning concentration, the pharmacists first determine whether there are pharmacokinetic abnormalities, and if not, adjust the dosage appropriately, If yes, further investigate the metabolic enzyme of the drug, and analyze whether there is a combination of enzyme inducers or inhibitors in combination with the patient's medication situation; If there is no combination of enzyme inducers or inhibitors, further investigate the patient's medication compliance or whether there is a missing or wrong medication; If the cause of abnormal results is still not found after the above factors are excluded, the medication compliance should be checked to determine whether the metabolic enzyme and transporter gene polymorphism of patients need to be measured (Xie et al., 2020), and the results and clinical significance of pharmacogenomics detection should be interpreted to propose guidance and develop customized treatment plans (Zhou, 2022).

The most influential factor of blood drug concentration monitoring results lies in the process of sample collection and submission. Nurses are mainly responsible for the collection of blood samples in TDM. The different TDM monitoring drugs need different blood collection time point; If there is an error in the sampling process, it will have an important impact on the clinical reliability of TDM results, and may even mislead clinical decisions. Therefore, TDM sampling has high requirements for nurses. At present, there is less relevant education for clinical nurses, which leads to errors in TDM sampling (Li et al., 2021b). The blood sampling time for monitoring the blood concentration of antipsychotic drugs is before the next period of administration after the continuous administration of 3 to 5 half-lives and reaching the stable drug concentration (Wang et al., 2017). Hospitalized psychotic patients are usually given drugs twice a day: at 11: 00 noon and 8: 00 p.m. Some drugs are only taken once at night, or

the amount of drugs taken at noon is small, and the amount of drugs taken at night is large. The dosage forms of some drugs are also different, including conventional oral drugs, intravenous drugs, orally disintegrating tablets and sustained-release tablets. Pharmacists are required to determine the sampling time according to the requirements of TDM and the pharmacokinetic characteristics of different drugs, and help nurses formulate blood sampling plans.

The laboratory inspectors are skilled in experimental operation and have certain knowledge of indoor quality management and interlaboratory quality assessment; In addition, some of the immunoassay drug concentration tests can be conducted by the existing chemiluminescence instrument, automatic biochemical analyzer and other instruments in the laboratory; Therefore, most hospitals carry out drug concentration detection by medical laboratories, and only a few large hospital pharmacy departments have the conditions to carry out drug concentration detection. In the traditional TDM work mode, laboratory testing and clinical work are relatively independent, and it is impossible to use pharmacokinetic knowledge to manage the time information and pre-test quality of blood collection and administration, and it is also difficult to meet the requirements of China's TDM work specification (Zhang et al., 2019) and result interpretation (Miao et al., 2020). Sending reports directly to patients or clinicians will mislead treatment and cause a crisis of trust.

In recent years, more and more studies have shown that the maximum value of TDM can only be brought into play by the multi-disciplinary collaboration model led by pharmacists (Li et al., 2019). With patients and samples as the center and pharmacists monitoring sampling timing, interpreting TDM reports, and providing medication adjustment plan according to TDM monitoring results as the links, the interdisciplinary cooperation among pharmacists, physicians, nurses and laboratory professionals was realized. Finally, under the guidance of pharmacists, physicians develop a safe, reasonable, effective and economical drug treatment plan based on the comprehensive consideration of the drugs being taken by patients and individual genes, etc., and administer the right drugs in the right dose at the right time, so as to achieve the purpose of individualized precise treatment (Chen et al., 2017).

At present, only a few major hospitals have pharmaceutical talents who are well versed in TDM, pharmacogenomics, pharmacokinetics and other disciplines. Influenced by traditional medical education, pharmacists have little knowledge about the significance of new technology diagnosis, the relationship between biological targets and disease progression, personalized gene testing and blood drug concentration detection, and lack theoretical knowledge about pharmacogenomics and bioinformation analysis, which cannot meet the needs of precise drug use services (Zhang & Zhang, 2019).

5. Summary and Prospect

Monitoring the concentration of antipsychotic drugs is an important means to

adjust the drug dosage, optimize the treatment plan, improve the treatment effect, reduce adverse reactions, and avoid drug poisoning. With the integration of pharmacogenomics, pharmacokinetics and other related disciplines and technologies, TDM has great application potential and development prospects. However, as mentioned above, antipsychotic drug monitoring faces some problems, which hinder their further promotion and application. Antipsychotic drug monitoring needs more improvement and development, such as establishing a reference system, verifying the accuracy, reducing costs, and carrying out clinical pharmaceutical guidance, in order to have a wider clinical application.

6. Limitations of the Study

Due to the limited reference documents collected in this study, more complete conclusions cannot be obtained globally, so it has certain limitations.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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