



Application and development of real-world study on Chinese patent medicine



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ABSTRACT

Objective: This paper aims to summarize the development status and clinical application of Chinese patent medicine (CPM) in real-world study (RWS), and provide references for the use of real-world evidence (RWE) in the field of CPM.

Methods: By searching keywords, we searched relevant literature in CNKI, Wanfang Data, PubMed and other databases, and summarized the application and development of RWS in CPM field.

Results and conclusion: Currently, RWS has been frequently used in wide aspects of CPM field, mainly in observational study, including evaluation of effectiveness, safety and economics of CPM based on RWE. This paper reviews the applications above, which will help researchers to have an in-depth understanding of the development status and application characteristics of RWS in CPM field, and express views on the challenges and solutions facing the RWS of CPM, in order to guide and promote the development of the re-evaluation of CPM after marketing.

1. Background

Real-world study (RWS) has attracted increasing attention in the field of pharmaceutical research worldwide. RWS refers to the use of epidemiology, health statistics and other research methods in real clinical, community or family settings to obtain various data in an unbiased or less biased population to evaluate the impact of an intervention (including diagnosis, treatment, prognosis) or exposure on health outcomes.^{1–4} In the field of medicine research, randomized controlled trials (RCTs) are the main methods commonly used, but the strict experimental conditions make the research results lack practical application value and may be difficult to promote and apply in clinical practice.⁵ RWS collects and utilizes data from a variety of sources, such as electronic medical records, medical insurance claims data, drug-related data, and Centers for Disease

Control and Prevention (CDC) data (big data network). The main advantages of RWS include large research scale, abundant evidence resources, good external authenticity, and individualized program application, and closer to the actual clinical situation.^{6–8}

RWS was first introduced and practiced in the field of traditional Chinese medicine (TCM) in China.⁹ In December 2018, the World Federation of Chinese Medicine Societies established the professional committee for RWS.¹⁰ In October 2019, The Real-World Study Committee of the China Association of Traditional Chinese Medicine was established, which aims to build a key methodology system for RWS in Chinese medicine, and promote the standardization of research and rational application of real-world evidence (RWE).¹¹ In January 2020, a number of academic institutions, such as the China Association of Traditional Chinese Medicine, issued the Technical Guidelines for Real

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World Study on Chinese Patent Medicine (CPM) to better guide and promote the development of post-marketing re-evaluation of CPM.^{12,13} Since 2007, the number of RWS of Chinese medicine registered in China has shown a gradual upward trend.⁹ Compared with RCT, RWS is more in line with the basic characteristics of Chinese medicine, such as “dialectical treatment” and “holistic concept”, preserving the characteristics of treatment according to people, places and times, which is of great significance to the research of Chinese medicine.^{8,14} Professor Liu Baoyan's team proposed a scientific research paradigm of integration of TCM clinical research and the RWE, suggesting segmented and progressive clinical research, and combining qualitative research with quantitative research.¹⁵ CPM is an important intervention measure in TCM. In order to promote rational drug use, improve medical quality, ensure patient's medication safety and improve resource utilization, RWS can provide strong evidence for post-marketing re-evaluation of CPM, including the clinical effectiveness, safety and economic evaluation.¹³ The multi-dimensional analysis results of RWS based on big data can provide new opinions for the clinical evaluation of CPM to make up for the shortcomings of RCT and small sample trials. It can be said that RWS is an important supplement to RCT. In particular, RWS has unique advantages in conducting clinical research for special populations, which is fits the characteristics of combining traditional research methods with modern scientific methods in TCM studies.

In this paper, through keyword retrieval, relevant literature was searched in CNKI, Wanfang Data, PubMed and other databases, we reviewed and summarized the application and development of RWS in the field of CPM, including observational studies based on RWE, specifically the effectiveness, safety and economic evaluation studies, as well as challenges and solutions.

2. Observational studies of CPM based on RWE

Observational studies based on RWE mostly come from patient registration information, hospital databases, patient health records, medical insurance databases, which can objectively and truly reflect the clinical application and progress of CPM. With the assistance of increasingly refined big data processing tools, the using rules of CPM obtained by analyzing large-scale RWE are more suitable for the physiological and pathological diversity of the human body and the complexity of lesions. Until December 2022, observational studies on CPM with the key word of “real world” have been searched from CNKI, Wanfang Data, and PubMed databases, and finally 102 published articles have been obtained with years ranging from 2011 to 2022 (Fig. 1). It can be seen that the number of observational RWS articles published about CPM shows an overall upward trend yearly under a slight fluctuation. Among them, the publication of relevant research results after 2020 has increased significantly compared with previous years, which is closely

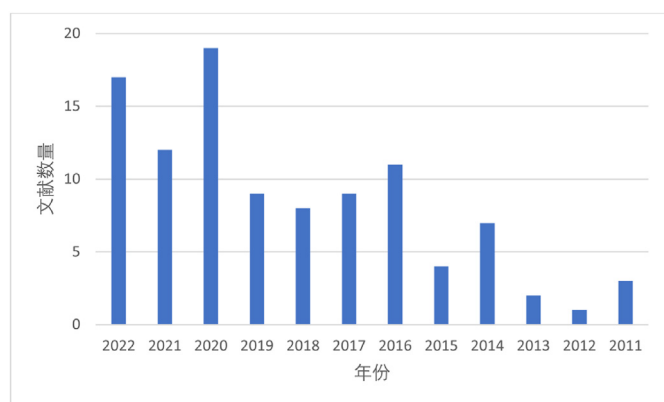


Fig. 1. Observational studies of CPM based on RWE published from 2011 to 2022.

related to the increasing attention of professionals to RWS of CPM and the improvement of relevant systems. Some articles published in core journals or SCI journals provide valuable research results and reference methods, which have guiding significance for the subsequent observational RWS of CPM.

Observational studies can objectively obtain the using rules and medication characteristics of CPM from massive real-world data. Some studies mainly summarize the types and principles of medication. For example, Li XT et al conducted a RWS on the application of CPM during hospitalization in 796 patients with cerebral infarction, and found that the combined application of CPM, such as those activating blood circulation, removing blood stasis, invigorating qi, and regulating qi, was more common.¹⁶ Patients with cerebral infarction often have hypertension, anemia, coronary heart disease and other diseases during hospitalization, and the pharmacological effects of the combination are often suitable for these comorbid diseases and the combination of drugs presents a specific rule, which provides a reference and basis for follow-up research and clinical rational drug use.¹⁶ In addition, Tang B et al conducted RWS for 628 cases of cervical radiculopathy (CR) using CPM, it was found that the top two CPM were Yu Xue Bi capsules and Jingshu granules, which further confirmed that the treatment of CR patients with CPM is based on blood circulation and stasis, communication and pain relief as the basic treatment.¹⁷ Some studies analyze the rules and characteristics of medication for a particular drug. For example, Teng Y et al analyzed the information of 12 385 patients using Qingkailing injection in 16 medical centers, and obtained the drug characteristics in the real world, among which the patients who used this drug were mostly middle-aged and elderly people. In the cases, the recommended dose and indications of the drug are not in accordance with the drug instruction, the combination drug phenomenon is common and there exists a risk of adverse reactions, and the results of RWS can provide the basis and evidence support for the clinical re-evaluation of Qingkailing injection after marketing.¹⁸ Zhao FY et al analyzed the treatment information of 823 patients with urinary tract obstruction (UTO) from 16 medical centers in detail, and finally concluded that UTO caused by inflammatory response is a precise target for the treatment of Honeysuckle Miyanning tablets.¹⁹ The researchers also analyzed the characteristics of the combination of Honeysuckle Miyanning tablets for the treatment of UTO, and concluded that 91.7% of the combination drugs were antibiotics when combined with western drugs, and 48.48% of the combined drugs were Chinese patent medicine heat-clearing agents when combined with CPM.¹⁹ Such studies are helpful to observe the rules of using CPM in a real-world environment, which effectively makes up for the disadvantage that RCT results are difficult to generalize and apply to clinical practice.

Combination medicine is often the key research content in the real-world application of CPM. By analyzing the electronic medical data of 49 597 patients treated with compound Kushen injection from 22 medical centers, Zhang Y et al found that the most common clinical combination drugs of compound Kushen injection included 5-HT receptor blocking drugs, hepatoprotective drugs, antibiotic drugs, antitumor chemotherapy drugs, immunomodulatory drugs, glucocorticoid drugs, analgesics and proton pump inhibitors, providing reference for the subsequent clinical rational drug use.²⁰ Similarly, in RWS of injectable Xueshuantong, it was found to be commonly used in combination with lipid modulators, antiplatelet drugs and cerebrovascular drugs.²¹ In addition, Wang ZY et al screened 216 juvenile patients from the patient information of 25 medical centers using Maixuekang capsules, and summarized the using rules. The researchers found that Maixuekang Capsule is used in combination with drugs with similar pharmacological effects in juvenile patients, including blood stasis activating agents, antibiotics, anti-viral drugs, anti-peptic ulcer drugs, and anti-tumor drugs.²² Besides, Sun LX et al collected information on 16 856 elderly patients who used Suxiao Jiuxin pills from 37 medical centers, and found that the commonly combined western drugs were vasodilators (78.39%), and the commonly combined CPMs were blood-activating and stasis-dissolving drugs (82.04%), which meet the treatment guidelines for coronary

heart disease, providing diagnostic and treating viewpoints for expanding the awareness of the clinical application of Suxiao Jiuxin pills.²³ While improving clinical effectiveness, the safety of drug combination is a warning and consideration for clinicians.

Some RWE can be compared with the drug instructions to find using difference. For example, Ai YN et al obtained information of 1459 patients to analyze the clinical application of Danshen Ligustrazine injection compared with the drug instruction.²⁴ They found that the drug was generally used beyond the instruction, and the information for the frequency of use, course of treatment, and medication of the elderly and children are lacking.²⁴ Xue CM et al conducted a study on the prescription information of 12 465 cases of Pudilan anti-inflammatory oral liquid from 6 medical centers. They found that the dose of the drug for children was basically the same as that of adults, which may have potential safety risks, and found a common off-label indication phenomenon.²⁵ These studies also prove that RWS can provide a reliable data reference for the regulatory application of pharmaceutical products. In summary, RWS can truly reflect the using rules and application characteristics of CPM, provide real basis and guidance for subsequent drug treatment, and optimize the use of drug schemes. In addition, observational studies also focus on the evaluation of the effectiveness, safety and economics of CPM, which are described in detail below.

3. Studies on the effectiveness of CPM based on RWE

In recent years, the use of RWE to evaluate the effectiveness of drugs has become a hot issue in the field of drug research and development. Traditional RCTs focus on the study of drug efficacy, but drug effectiveness research is often more applicable to actual clinical needs, resulting in a series of effectiveness-related RWSs, the results of which have better external authenticity and are conducive to wider application in clinical settings.

For example, Zhang Q et al retrospectively collected 555 patients' data with variceal bleeding to analyze whether CPM adjuvants are effective in preventing variceal rebleeding.²⁶ The results showed that standard treatment with CPM could significantly reduce the incidence of variceal rebleeding and delay the time of rebleeding ($p < 0.05$).²⁶ Additionally, Ma XF et al collected and analyzed data of 5000 patients who had taken Jianguyabao series of CPM, and found that hypertension was effectively controlled after taking Jianguyabao series of CPM, which confirmed that these drugs had a certain positive impact on the blood pressure progression of hypertensive patients, which provided strong evidence for their stable effectiveness.⁵ Meng FC et al observed the therapeutic effect of Lingze tablet in 603 patients with benign prostatic hyperplasia, and found that after 30, 60, and 90 days of treatment with Lingze tablets alone and in combination, the international prostate symptom score and quality of life score were significantly improved compared with those before treatment ($P < 0.01$).²⁷ Furthermore, Xu Y et al made a meta-analysis of 43 studies on the effectiveness of CPM in the treatment of non-alcoholic fatty liver disease (NAFLD) based on RWE, and found that CPM assisted treatment of NAFLD can play a positive and effective intervention role, benefiting patients.²⁸ Moreover, studies have shown that Daning tablet combined with western medicine can significantly improve the clinical effective rate of NAFLD.²⁸ Some RWS also used propensity scores to balance the confounding real-world influences between the observational and control groups. For example, Pan L et al evaluated the difference between the efficacy of Danshen ligustrazine injection in patients with orthopedic diseases and those without it based on the information of 1370 patients. In order to reduce the impact of confounding factors in the real world, researchers used the propensity score matching method.²⁹ The results showed that the therapeutic effect of Danshen ligustrazine injection in promoting blood circulation and removing blood stasis in patients with orthopaedic diseases was better than that of patients without using Salvia ligustrazine injection ($P < 0.05$), which is consistent with the results of clinical reports.²⁹ Some researchers have explored the long-term effectiveness of certain CPM in

cancer patients. For example, Wang L et al performed RWS on 614 patients diagnosed with stage II-III non-small-cell lung cancer (NSCLC) to determine the effect of Huisheng oral liquid on the 2-year survival rate of patients.³¹ Results showed that 2-year survival rates were significantly improved in patients treated with Huisheng Oral liquid for ≥ 3 months ($P < 0.05$), and the 2-year survival rate tended to increase with the extension of treatment time.³⁰ In addition, Bao HX et al analyzed the influence of Zilongjin tablets on the long-term postoperative effectiveness of 1256 patients with lung tumor based on electronic medical record data, and found that the drug could improve the quality of life of patients to a certain extent and have a positive impact on the postoperative follow-up treatment, and patients showed high voluntary selectivity for Zilongjin tablets and a tendency to stick to medication.³¹ Another RWS on Zilongjin tablets included 2553 patients with lung cancer and analyzed the drug effect on survival of these patients. The results showed that the mean survival time of patients using Zilongjin tablets was significantly higher than that of patients without Zilongjin tablets (35.9 months vs 25.0 months, $P < 0.001$). The use of Zilongjin tablets was an independent protective factor for lung cancer patients ($P < 0.001$).³²

RWS of CPM and RCT are mutually complementary. The former provides research evidence of high patient compliance, large sample size, long follow-up time, low data input cost, and more relaxed screening conditions for research objects. It is more suitable for the effectiveness evaluation of drugs after marketing, and provides a more comprehensive reference for the drug use plan of clinicians.

4. Studies on the safety of CPM based on RWE

In the pre-marketing clinical research and development process of CPM, traditional RCTs are commonly used. Nevertheless, RCTS cannot make individualized judgment on the medication of some special groups (such as pregnant women, children, and the elderly), which will increase the risk of adverse drug reactions.³³ Safety research is a key evaluation index affecting the post-marketing application and development of CPM, and RWS can help and improve the scientificity and rationality of the safety evaluation of CPM. Drug safety studies become the most widely used direction of RWS in the field of CPM. The safety evaluation of CPM usually uses hospital information system (HIS) data as the information source, and the trends of adverse reactions are found out through data mining in massive clinical drug information.³⁴ Since 2007, the safety studies of registered RWS of CPM cover a wide range, such as "Hospital Centralized Monitoring Study of Adverse Reactions of Kuaiwei Tablets", "Hospital Centralized Monitoring Study of Adverse Reactions of Yangxinshi Tablets", "Centralized Monitoring Study of Adverse Reactions of Wuling Capsules", "Centralized Monitoring of Clinical Safety in Hospitals after the Marketing of Naoxintong Capsules", and "Centralized Monitoring of Clinical Safety of Yunnan Baiyao capsules".⁹

Data from RWS tend to provide a clearer picture of the incidence of adverse effects and identify associated risk factors. For example, Li Y et al collected the information of patients who used Danhong injection in 18 hospitals in the past 8 years, evaluated its safety, and found that the number of adverse reactions reported to the drug has increased in recent years.³⁵ And they found that the risk factors influencing adverse reactions include infusion speed, connective tissue disease, and comorbidity index.³⁵ For example, Shenmai injection, Diemailing Kudiezi injection, and Dengzhanxixin injection were all re-evaluated by the safety of large sample sizes of RWS, and the incidence of adverse reactions was 1.5‰, 0.99‰ and 0.39‰, respectively, which proves the good safety of these CPM.^{36–38} Some of the adverse effects shown by RWE may provide additional data on drug instructions. For example, Guo X et al mined and analyzed the signals of adverse reactions of Danshen Chuanxiongzine injection, and 17 of the 18 adverse reaction signals detected were not included in the instructions.³⁹ Some studies stratify high-risk groups, focusing on special population. For example, Jiang J et al summarized the characteristics of adverse reactions of Shuxuetong injection in 14 640 elderly people, and found that the adverse reactions

were mainly allergies, and when administering drugs to the elderly with chronic renal failure, more serious consideration should be given to the dosage and combination of drugs.⁴⁰

Moreover, Li XX et al analyzed and summarized the adverse reactions of Tanreqing injection in 13 061 elderly people, and found that the incidence of adverse reactions was 2.45%, and was significantly increased in those with a history of drug allergy, irregular infusion speed, combined use of antibacterial drugs, and not use sugar or salt as infusion interval ($P < 0.05$).⁴¹ Another study showed that the incidence of adverse reactions of Tanreqing injection in 6188 children was 3.07%, and the most common adverse reactions were skin and its appendages, all of which occurred within 24 h.⁴² The RWE can contribute to the clinical use of CPM in special populations. Some studies provided analyses based on RWE using a specific adverse reaction, such as abnormal liver function or allergic reactions. Researchers have conducted data mining and analysis of certain specific adverse reactions of some drugs, such as the suspected allergic reaction of Qingkailing injection in RWS, the abnormal changes of Xianping injection on aspartate aminotransferase (AST), and the abnormal liver function or allergic reaction caused by breviscapine injection, and obtained specific relevant influencing factors, which provide clues for clinical safe drug use.^{43–46} Meanwhile, Li YN et al analyzed the liver function of Xianlinggubao capsules and Cheng FJ et al analyzed the liver function of Mailuo Shutong pills, and found that these two drugs did not have a significant effect on liver function, which proved the safety of the drugs.^{47,48} Some researchers collected data from the National Adverse Drug Reaction Monitoring Center's Spontaneous Reporting System (SRS) for safety analysis. For example, Peng SY et al collected 2796 adverse reaction reports of Xianlinggubao preparations derived from SRS, and found that the incidence of serious adverse reactions of the drug was 2.68%, mainly manifested as abnormal liver function, and found that the drug has two peaks of adverse reactions within 2 days and ≥ 15 days of medication.⁴⁹ Through RWS, researchers present real drug safety data, which provides a reliable basis for subsequent medication strategies. In addition, the Center for Evidence-Based Medicine of Tianjin University of Chinese Medicine has created a safety monitoring system for TCM injections based on active acquisition to achieve efficient and low-cost full-cycle drug risk monitoring.⁵⁰ Nowadays, it has become a trend to conduct safety evaluation of CPM based on RWE, which can fully explore the adverse reaction signals, improve the safety evaluation system of CPM, and promote the development of CPM with high-quality evidence. In the future, more safety monitoring systems related to CPM can be established to achieve risk management and control of CPM throughout the life cycle.

5. Studies on the economics of CPM based on RWE

The research of CPM needs to continuously enrich the clinical economic evidence to achieve high-quality post-marketing re-evaluation of CPM, so as to adapt to clinical practice, promote rational drug use, improve pharmaceutical policies, and improve the efficiency of the use of pharmaceutical resources. The main sources of RWE include, but are not limited to, the in-hospital sales price of drugs, the average daily drug cost, the average treatment cost, and the proportion of medical insurance reimbursement.⁵¹ Commonly used evaluation methods in pharmacoeconomics include cost effectiveness analysis (CEA), cost utility analysis (CUA), cost benefit analysis (CBA), and cost minimization analysis (CMA). Some studies have suggested that the CUA method be used in the economic evaluation of CPM, and that quality-adjusted life years (QALY) and health utility values are regarded as crucial outcome indicators in the economic evaluation of CPM.¹³ However, currently in China, quality of life research and various sinicized health scales have not been maturely developed, and it is difficult to convert health outcomes into monetary efficiency indicators.⁵² Therefore, most of the economic evaluation research in the current stage is still based on the CEA method.

Taking Qilong capsules as an example, the researchers used CEA to evaluate the economic effectiveness of Qilong capsules combined with

conventional treatment versus conventional treatment in ischemic stroke, and the cost parameters were taken from databases and previous literature. The effect parameter was set to the mean decline of the score in the National Institutes of Health Stroke Scale after treatment (NIHSS) derived from one prospective RWS. Finally, it was found that when the patient's willingness to pay was higher than 2811.36 yuan, the combined use of Qilong capsules to intervene in ischemic stroke was more economical than conventional treatment alone.⁵³ Also as a treatment for ischemic stroke, Tao LN et al conducted a CEA analysis on the economics of injectable salvianolic acids and butylphthalide sodium chloride injection based on real-world effect and cost data of 1036 ischemic stroke patients. It was found that the effect of injectable salvianolic acids was comparable to that of sodium chloride butylphthalide injection (effective rate 89.18% vs 88.80%, $p = 0.846$), the cost of injectable salvianolic acids is lower (cost 24 439.82 yuan vs 33 572.79 yuan, $p < 0.001$), and the treatment of ischemic stroke is more economical.⁵⁴ For another example, Tang XS et al conducted an economic evaluation of the top 10 TCM injections for blood circulation and stasis removal in hospitals in Shandong Province from 2016 to 2020, CEA was adopted and a decision tree model was established, and finally two optimal treatment options were obtained according to the patient's willingness to pay.⁵¹ When the willingness to pay value is less than 25 844.00 yuan, the optimal solution is injectable Xuesaitong (lyophilization), and when the willingness to pay value is greater than 25 844.00 yuan, the optimal solution is Kudiezi injection.⁵¹ Such CPM solutions designed according to specific conditions can recommend the optimal choice under different circumstances to ensure the maximum value of medical and health resources, and can also provide an effective basis for the adjustment of medical insurance catalogue and the decision of centralized procurement of related drugs. In addition, long-term real-world big data is conducive to better displaying the advantages of CPM in the prevention and treatment of major chronic diseases, which can make up for the shortcomings of the short pharmacoeconomic evaluation time of RCTs.⁵⁵

6. Challenges and countermeasures

The data of RWS of CPM are mainly based on centralized monitoring and medical records of hospitals, which has certain limitations. Firstly, the data sources did not have the randomization of RCTs, and no interventions were made during the studies, and the results were easily questioned by clinicians. However, one of the great advantages of RWS is that it can provide evidence of drug efficacy in a real healthcare setting, which is a powerful complement to RCT research. Secondly, a large number of high-dimensional clinical data requires corresponding manpower, financial resources and time for data collection, cleaning and analysis, and the data obtained are often highly heterogeneous. In this regard, the machine learning technology, which has received great attention in recent years, can be appropriately applied to the massive data cleaning and screening of RWS, and deal with a large number of confounding factors to reduce research bias and improve the accuracy of results. Moreover, in studies comparing between groups, the confounding factors of real-world data can be balanced by propensity score matching. In addition, the importance of RWE has not been fully recognized among TCM-related clinicians, which may cause missing or incomplete records of some data, resulting in losses to subsequent research data resources. Therefore, the concepts and operational procedures of RWS should be more widely disseminated and deeply learned among clinicians and healthcare policymakers, and promote the development of RWS across multiple disciplines. Another point is that CPM often works slowly, the follow-up period is relatively long, and it is difficult to obtain good patient adherence, which not only affects the reliability and accuracy of treatment effects, but also leads to the lack of some outcome indicators, reducing the quality and quantity of data sets. In this regard, in addition to the inclusion of a large number of multi-center real-world data on CPM, reasonable outcome indicators and appropriate observation and follow-up time should be formulated to

adapt to the CPM characteristics of focusing on internal factors, mild effects, and suitable for long-term use, so as to provide high-quality guidance and reference for subsequent research.

Summary

As a unique therapeutic drug in China, the effectiveness and safety of CPM have always been questioned. Nowadays, a large number of RWSs provide real and reliable research evidence for the clinical application status and effectiveness, safety and economic re-evaluation of CPM after marketing, and has become a key solution to the dilemma faced by CPM. This article reviews various aspects of RWS on CPM, focusing on the value, progress and challenges of RWS in the clinical application of CPM. Clinical evidence from the real world combines with epidemiology, statistics, artificial intelligence and other methods to improve the scientificity, innovation and applicability of research results, and modern medical methods are used to deeply study the using rules of CPM and post-marketing re-evaluation, which will enable RWS to play a greater role in the future clinical research of CPM.

Declaration of competing interest

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