WITHDRAWN: Post-marketing Centralized Monitoring of clinical safety of Naoxintong Capsules in 7345 patients

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Abstract

Background: Naoxintong Capsules (NXT), a type of preparation for long-term oral administration in the clinic, is mainly used for preventing and treating cardiovascular and cerebrovascular diseases such as coronary heart disease, angina pectoris, and stroke. However, currently, there are no reliable clinical data on NXT safety assessment.

Aim: To evaluate the frequency and categories of the adverse drug reaction (ADR) of NXT in clinical application in China and analyze the factors related to ADR incidence.

Methods: A total of 7345 inpatients and outpatients from 14 hospitals in China who were orally administrated with NXT between January 2018 and December 2018 were followed up at least once. The monitored items mainly included gender, age, nationality, BMI, personal drug and food allergy history and family allergy history, patients' disease types, NXT medication, and the occurrence, characteristics, and recovery of ADR. Univariate and multivariate logistic regression were used to analyze the influencing factors of ADR.

Results: The incidence of ADR was 3.44‰, and gastrointestinal system damage was the most common adverse reaction. All ADRs were mild or moderate. Most ADRs (86.36%) occurred within 4 weeks after administration, while in 81.82% of patients who continuously took NXT, ADRs improved or were fully resolved. There were no indicators related to the significant increase of ADR risk.

Conclusion: NXT was well tolerated in the general population. The hospital centralized monitoring research method, which was established based on data from the Hospital Information System and Web-tracking follow-up system, is necessary to carry out the safety research study for post-marketing of traditional Chinese medicines.

Trial registration: This protocol has international registration in the China Clinical Trials Registration Center through international registration (No. ChiCTR-OPC-17013912) on December 14, 2017.

1. Introduction

Naoxintong capsule (NXT) is the national basic drug catalog variety [1] that is listed in Pharmacopoeia of the People's Republic of China (2020 Edition)[2]. This preparation consists of 16 traditional Chinese medicines involving *Astragali radix, Salviae miltiorrhizae radix et rhizome, Paeoniae radix rubra, Chuanxiong rhizome, Persicae semen, Carthami flos, Myrrha, Spatholobi caulis, Achyranthis bidentatae radix, Cinnamomi ramulus, Mori ramulus, Pheretima*, *Scorpio* (toxic traditional Chinese medicine), *Hirudo* (toxic traditional Chinese medicine), *Angelicae sinensis radix*, and *Olibanum*. NXT, whose annual sales exceed 1 billion, can replenish qi, activate blood circulation, remove blood stasis, and dredge collaterals. Clinically, it is required to be orally taken for a long period, mainly to prevent and treat cardiovascular and cerebrovascular diseases such as coronary heart disease, angina pectoris, and stroke [3–4]. Over recent years, clinical research has attracted increasing attention, and great progress has been made in material

and pharmacological experimental research. Due to its beneficial clinical effect, the application of NXT has been popularized [5–7]. However, as a long-term orally administrated medicine, the relevant ADRs and influencing factors are still unclear. There is also a lack of evidence-based safety guidance in clinic.

Over recent years, an increasing number of reports on NXT clinical adverse reactions/events (ADRs/ADEs), involving general damage, central and peripheral nervous system damage, hepatobiliary system damage, have appeared [8–10]. Yet, most of these related studies on clinical safety are case-based reports or literature studies. Therefore, in this study, we evaluated the post-marketing safety of NXT in the real world by using the centralized monitoring system in hospitals, thus providing safety evidence for NXT clinical application.

2. Methods

2.1 Study Design

This prospective, multi-center, large sample observational cohort study was conducted in three comprehensive traditional Chinese medicine hospitals in Henan Province, China, and one tertiary-level and 10 primary-level medical and health institutions in Shanghai. The selection of monitoring hospitals was as follows: first, we selected hospitals with relatively high sales of NXT in various regions of China, and then finally determined the monitoring hospitals based on the scientific research capabilities of each hospital and the willingness to participate in project cooperation. Based on the Hospital Information System (HIS) data, the active monitoring research model of adverse reactions after the listing of drugs in the real world was adopted.

This study was funded by the Ministry of Science and Technology of the People's Republic of China (Ministry of Science and Technology of the People's Republic of China, No. 2015ZX0950104-001-007) and approved by the China Clinical Trials Registration Center through international registration (No. ChiCTR-OPC-17013912).

2.2 Study Population

All inpatients and outpatients who were orally administrated with NXT in 14 surveillance hospitals, including 3 comprehensive traditional Chinese medicine hospitals in Henan Province, and 11 tertiary and primary medical and health institutions in Shanghai, between January 2018 and December 2018 were included in the study (see Fig. 1 and Table 1 for details).

Following the sample size requirements defined by the "Guidelines for Key Drug Monitoring of Manufacturers", the number of cases included in statistical analysis should generally be ≥ 3,000 [11]. A total of 7345 cases were included in this study, and 6399 cases were finally used for statistical analysis.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria were the following: all cases that were followed up for 3 times with a maximum monitoring time of 90 days. Cases with adverse reactions/events that occurred after NXT use were considered valid cases.

Dropout criteria were the following: patients who visited once but did not return for follow-up monitoring.

Exclusion criteria were the following: cases in the patient enrollment system, for which the information was not consistent with the data extracted by the HIS.

2.4 Database Information

The database covers two aspects of hospital centralized monitoring data and hospital HIS data. The centralized monitoring data of the hospital include the report data of the Monitoring Information Form A and B. Form A mainly involves patient demographic information, personal allergy history, allergic disease history, family allergy history, indication information, NXT usage information, and administration status, etc. (see Appendix 1). Table B mainly relates to NXT ADRs/ADEs category, past and family ADRs/ADEs status, ADRs/ADEs process description and treatment status, NXT usage conditions, ADRs/ADEs results, and conversion Return (see Appendix 2). The hospital HIS data accurately store the clinical actual electronic medical record information of the patients in the clinic, and include medical record home page information in the medical record management system (patient clinic/hospital number, gender, age, ethnicity, height, weight, working conditions, living area, personal history, family history, allergy history, diagnosis, treatment category, treatment course, treatment results, hospitalization days and frequency, etc.), information related to hospitalization course in the electronic medical record system (admission record, discharge summary, information related to vital signs in the medical workstation (body temperature, pulse, fluid intake and output, blood pressure, etc.), hospitalization course record), inpatient medical order information in the drug management system (drug name/specification/manufacturer, usage and dosage, frequency of administration, route of administration, start and end dates of medication, information on the execution of medical orders and information on patient medication, etc.), inspection related information in inspection system (names and results of inspection items, normal reference values of biochemical indicators, inspection report results, etc.).

2.5 Data source, Collection, and Quality Control

The data collection method is shown in Fig. 2. In this study, the active follow-up monitoring by third-party pharmacists was conducted three times to obtain information on ADRs/ADEs, and the monitoring form was filled out. All patients who used NXT were actively monitored and/or were followed up by the pharmacist via telephone for 3 times. The follow up data were reported to the Patient Enrollment Registration System on the Web network, including patient medical record number, name, gender, age, visit time, outpatient or inpatient service, usage and dosage of NXT, as well as the number of prescriptions, visit times, and the occurrence of ADRs/ADEs, and other information. Monitoring Information Table A was also filled out (see Appendix 1). Pharmacists registered patients by using the Patient Enrollment Registration System at each visit and/or telephone follow-up, eliminated duplications, and kept track of patient identification. At the first visit, the pharmacist filled in the Monitoring

Information Form A, which they actively tracked and monitored. They also cooperated with the follow-up three times in the monitoring period, and completed the telephone follow-up on the 15th – 18th day, 45th – 48th day and 90th – 93rd day after patients took the medicine, respectively. Among those who were discharged from the hospital with NCT, the two-way contact information was kept between pharmacists and patients, and the patient was kept informed of the course of treatment and the time of next visit. If there were any medication related problems, pharmacists were contacted or the patient was sent directly to outpatient clinic, and was then followed up by pharmacists.

The monitoring period was terminated for the patients without ADRs/ADEs. If ADRs/ADEs occurred during the monitoring period, due to which monitoring needed to be stopped, the monitoring of the patient was finished by tracking the patient to recovery or improvement. At the same time, the Monitoring Information Form B (see Appendix 2) and ADRs/ADEs Report Form were filed and reported to the National Adverse Drug Reaction Monitoring System (http://www.adrs.org.cn/). If ADRs/ADEs occurred during the monitoring period, and mild symptoms did not affect the follow-up of continuous use of the medicine until the end of 3 months, the monitoring could be finished. At the same time, Monitoring Information Form B and ADRs/ADEs Report Form were filled and reported.

Within one month after monitoring, the HIS data were extracted, and valid fields were set for information collection and mining, and the centralized monitoring ADRs/ADEs database of NXT clinical safety hospital was established with the integration of monitoring table data and other information. A scientific and standardized quality control system was established to ensure the controllability of the whole research and the quality of monitoring data, which mainly included data quality control during and after monitoring. At the same time, the dynamic quality control method was used in the monitoring research process. Three-level quality control was established in this study, including first-level quality control in each monitoring hospital, second-level quality control in sub-centers, and third-level quality control in the project monitoring unit, thus forming the quality control system that could be used to ensure the quality of centralized monitoring research in hospitals. A database was established by using EpiData data management software. Two persons recorded the monitoring information table separately and used the computer to carry out synchronous entry consistency check and logical error detection. Errors and inconsistencies were immediately corrected according to the monitoring table. After the data were verified and corrected by computer, 2.5% of the sample size monitoring table was randomly selected, and all the fields in the monitoring table were manually checked with the database. The main field error item is required to be 0, and the secondary field error is within 0.3%. Otherwise, it is necessary to re-enter all data. Outpatient and inpatient medical record data of the electronic information system of each research hospital were directly imported, and the data were reviewed in detail. The questionable parts were confirmed by the data export summary and were then reviewed again. After the data were checked and standardized again, the database was locked under the supervision of statisticians and researchers.

2.6 Statistical Analysis

Descriptive statistics on the types and outcomes of adverse reactions related to NXT, the demographic characteristics of the monitored objects, count data such as baseline variables, and categorical variables

are described by frequency (%). Logistic regression analysis was used to explore the risk factors of ADRs, including variables such as BMI, personal drug/food allergy history, disease allergy history, family allergy history, whether this was the first medication that was used, and the first medication dose. SPSS 23.0 software package was used for data analysis. A p value < 0.05 was considered to be statistically significant.

3. Results

3.1 The General Situation of the Monitoring Hospitals

This clinical safety research on NXT was carried out across 14 monitoring hospitals across two provinces and cities and included 7345 monitoring cases. According to the monitoring inclusion/shedding/elimination standard, 936 cases were untraced on account of loss of communication with the patients. Ten cases were excluded due to inconsistent information between the patient enrollment registration system and HIS extraction data. According to the research plan, cases that were monitored at least once and up to four times were considered effective cases; the longest monitoring time was 90 days. Among the 14 monitoring hospitals, 3 were tertiary Chinese medicine hospitals, with 4909 cases (76.72%) monitored; 1490 cases (23.28%) were monitored in 10 primary medical institutions. The total number of ADRs/ADEs cases was 24. All ADRs/ADEs cases were found in tertiary hospitals, while no ADRs/ADEs cases were found in primary medical institutions during the monitoring period (Table 1).

Table 1
Performance of centralized monitoring in NXT monitoring hospital

Research hospital	Cases	ADRs/ADEs
Shanghai Pudong Hospital	590	5
Datuan Community Health Service Center	310	0
Laogang Community Health Service Center	63	0
Liuzao Community Health Service Center	211	0
Luchao Port Community Health Service Center	87	0
Nicheng Community Health Service Center	284	0
Shuyuan Community Health Service Center	101	0
Wanxiang Community Health Service Center	73	0
Xuanqiao Community Health Service Center	135	0
Zhou Pu Community Health Service Center	64	0
Zhuqiao Community Health Service Center	162	0
The First Affiliated Hospital of Henan University of Traditional Chinese Medicine	1450	6
The Second Affiliated Hospital of Henan University of Traditional Chinese Medicine	1062	1
Zhengzhou Traditional Chinese Medicine Hospital	1807	12
Total	**6399**	**24**

3.2 Baseline Characteristics

The demographic characteristics of the monitored subjects mainly included gender, age, ethnicity, body mass index (BMI), personal drug and food allergy history, family allergy history, and disease types of NXT users. The baseline characteristics of the study population are shown in Table 2. There was a slight difference between male and female patients; there were 5081 patients (79.40%) aged ≥ 60 years and 3153 patients (49.27%) with BMI exceeding the normal standard. There were 344 patients (5.38%) with a history of allergy to medicines and foods, and only 9 patients (0.14%) with a family history of allergy, and 52 (0.81%) with a history of allergic diseases.

There were 3632 patients (56.76%) who were administrated with NXT for the first time and 2532 patients (39.57%) who previously received NXT (6 patients had ADR at one point; gastrointestinal system damage was found in 4 patients, skin and its accessories damage, and sympathetic parasympathetic nervous system damage in 1 patient. Besides, 4 patients continued to use NXT with ADR until we performed this clinical safety monitoring study).

NXT is mostly prescribed according to the instructions. All patients took the drug orally, and the most common dose was 2–4 capsules each time (6152 cases, 96.14%); a few patients (69 cases, 1.08%) exceeded recommended dosage (using up to 9 capsules each time). The most frequent use was 3 times a day (5953 cases, 93.03%). The results of centralized hospital monitoring in real-world showed that NXT was used for 9636 indications (the same patient could have multiple indications), including 357 different indications. Cerebrovascular disease was the most common indication (26.13%), followed by coronary heart disease (22.60%).

Table 2
Baseline characteristics of the study population

Patient characteristics	Patients, N = 6399
Gender	
males(cases)	3357(52.46)
females(cases)	3042(47.54)
Nation	
Han	6128(95.76)
National minority	263(4.11)
unspecified	8(0.13)
Age group(year)	
<60	1318(20.60)
≥ 60	5081(79.40)
BMI	
Lean	193(3.02)
Normal	3027(47.30)
Overweight	2371(37.05)
Fat	782(12.22)
unspecified	26(0.41)
Personal history of drug and food allergy	
not	6039(94.37)
exist	344(5.38)
unspecified	16(0.25)
Family allergy history	
not	6376(99.64)
exist	9(0.14)
unspecified	14(0.22)
Personal history of allergic diseases	
not	6329(98.91)
Unless otherwise stated, the data are all n(%)	

Patient characteristics	Patients, N = 6399
exist	52(0.81)
unspecified	18(0.28)
First use	
First use	3632(56.76)
Non-first use	2532(39.57)
unspecified	235(3.67)
Whether the single dosage exceeds the specification	
Yes	69(1.08)
No	6330(98.92)
Disease type	
cerebrovascular disease	2518(26.13)
coronary heart disease	2178(22.60)
high blood pressure	1041(10.80)
diabetes	423(4.39)
other	3219(36.07)
Unless otherwise stated, the data are all n(%)	

3.3 ADR/ADEs incident evaluation

A total of 6399 cases were collected in NXT's centralized monitoring study of ADRs/ADEs hospitals, and 24 cases of ADRs/ADEs were found during the centralized monitoring process. The three-level evaluation was carried out according to the scheme, and finally, the results of NXT's ADRs/ADEs causality evaluation were determined. According to the correlation evaluation method recommended by China Adverse Drug Reaction Monitoring Center, ADRs/ADEs were divided into six grades: "affirmative, probable, possible, possibly irrelevant, to be evaluated and impossible to evaluate". There were 22 cases that were judged as "affirmative, probable and possible", which were determined as NXT-related adverse reactions; the calculated incidence of adverse reactions was 3.44‰. The results of the relevance evaluation are shown in Table 3.

Table 3
ADRs/ADEs Correlation Evaluation Results

Relevance evaluation results	Cases(%)
affirmative	1(4.17)
probable	10(41.67)
possible	11(45.83)
possibly irrelevant	2(8.33)
to be evaluated	0(0.00)
impossible to evaluate	0(0.00)
Total	24(100.00)

3.4 Characteristics of ADRs

There were 22 ADRs cases of NXT, with 31 ADRs cases, involving 10 organs/systems, especially the gastrointestinal system, with 17 cases accounting for 54.84% (Table 4).

According to the severity of ADRs, standard ADRs were considered those where mild symptoms or signs could be perceived, and no drug withdrawal or special treatment was needed. Moderate ADRs meant that symptoms and signs could be tolerated and needed special treatment without affecting daily life. Severe symptoms and signs were unbearable and when they occurred, the treatment needed to be stopped so that ADRs could be specially treated, which also affected daily life. Statistical data show that among 22 cases of ADRs, there were 16 cases with moderate ADRs, accounting for 72.73%, followed by mild ADRs observed in 6 cases, which were perceptible symptoms and signs, and did not require suspension of drug intake or special treatment, accounting for 27.27%. There were no serious ADRs.

Table 4
ADR involving organ/system damage and clinical manifestations

Involvement of organ/system damage	Cases(%)	clinical manifestation(Cases)	Distribution of ADR severity(Cases)
Gastrointestinal system damage	17(54.84)	abdominalgia(5) feel sick(3) upset the stomach(2) Gastrointestinal flatulence(1) sour regurgitation(1) Stomach discomfort(1) Nonspecific abnormal appetite(1) dyspepsia(1) constipation(1) diarrhea(1)	mild(4), moderate(9)
Heart rate and arrhythmia	3(9.68)	palpitate(3)	moderate(3)
Central and peripheral nervous system damage	3(9.68)	dizzy(1) Local numbness(1) paresthesia(1)	mild(2), moderate(1)
Damage to skin and its accessories	2(6.45)	nettle rash(1) rash(1)	mild(1), moderate(1)
Nervous system disorder	2(6.45)	feel suffocated(1) sleep disorder(1)	moderate(2)
Extracardiac vascular damage	1(3.23)	ophthalmorrhagia(1)	moderate(1)
Systemic damage	1(3.23)	Have a fever(1)	moderate(1)
Sympathetic parasympathetic nervous system damage	1(3.23)	hidrosis(1)	moderate(1)
Systemic damage	1(3.23)	fatigue(1)	moderate(1)
Total	31(100.00)	—	moderate(1)

Among the 22 ADR cases, 9 (45%) occurred within 1 day, 7 (30%) within 1 day to 1 week, 3 (10%) within 1 week to 4 weeks, and 3 (15%) over 4 weeks. Among them, in 2 cases, ADR occurred within 30 days after taking medicine, and the longest one occurred after six months (Table 5).

Table 5
Occurrence time of ADR

ADR	Occurrence time				Total
	≤ 1 day	1 day～1 week	1 week ~ 4 week	>4 week	
Cases	9	7	3	3	22
constituent ratio (%)	40.91	31.82	13.64	13.64	100.0

3.5 Treatment and the recovery of ADRs

Most NXT-related ADR could be cured or improved without treatment, and 5 patients (22.73%) continued to take medicine after being tolerated by patients without any treatment. Among them, 3 ADR cases developed organ/system damage and gastrointestinal system damage. After taking medicine for several days, 1 case recovered, and 2 cases improved. In addition, 2 patients felt dizzy and suffered itchy skin after taking medicine. ADR involved central and peripheral nervous system damage, skin, and accessories damage. Without treatment, ADRs did not improve. The treatment measures for adverse reactions mainly included drug withdrawal, symptomatic treatment, drug reduction/drug withdrawal, and drug withdrawal/symptomatic treatment, where the most commonly used treatment was: drug withdrawal (11 cases, 50.00%), drug reduction (3 cases, 13.64%), drug withdrawal + symptomatic treatment (2 cases, 9.09%), symptomatic treatment (1 case, 4.55%)(Table 6).

Among the ADR cases, 7 cases recovered, 13 improved, 2 patients continued to use the drug, and 1 case had sequelae that mainly manifested as indigestion and loss of appetite, which lasted for more than one year then gradually improved after the drug dose was reduced by half.

Table 6
Treatment of ADR

Treatment measures	Cases (%)	Return and Cases (%)
not	5(22.73)	Improve 2(9.09), recovere 1(4.55), Not getting better 2(9.09)
drug withdrawal	11(50.00)	improve 7(31.82), recovere 4(18.18)
symptomatic treatment	1(4.55)	improve 1(4.55)
drug reduction	3(13.64)	improve 2(9.09), recovere 1(4.55)
drug withdrawal + symptomatic treatment	2(9.09)	improve 1(4.55), recovere 1(4.55)
Total	22(100.00)	improve 13(59.09), recovere 7(31.82), Not getting better 2(9.09)

3.6 Analysis of risk factors for ADRs

For all cases with ADRs, the control group was screened by nested case-control study and matched by 1: 4 according to gender and age. There were 22 cases in the case group (10 males and 12 females with average age 71.38 ± 10.67 years), and 88 cases in the control group (40 males and 48 females with average age of 71.39 years). The distribution of sex and age was similar between the case group and the control group, and there was no significant difference between the two groups (P = 1.00, P = 0.408).

Univariate logistic regression analysis showed that none of the variables were significant for the adverse reactions induced by NXT and were all indistinctive (see Table 7).

Table 7
Univariate Logistic Regression Analysis

Factor	Coefficient	Standard Error	Wald X^2	OR(95%CI)	P
BMI					
Low body weight vs. Normal weight	-19.881	28420.722	0.000	0.000(0.000-)	0.999
Overweight vs. Normal weight	-0.089	0.480	0.035	0.915(0.357–2.341)	0.852
Personal history of drug and food allergy(Yes vs. No)	0.507	0.873	0.337	1.660(0.300-9.187)	0.562
History of allergic diseases(Yes vs. No)	22.636	40192.969	0.000	67669608865.239	1.000
Family allergy history(Yes vs. No)	22.636	40192.969	0.000	67669608865.239	1.000
First use(Yes vs. No)	0.267	0.480	0.308	1.306(0.509–3.348)	0.579
Whether the single dosage exceeds the specification(Yes vs. No)	-0.049	0.495	0.010	0.952(0.361–2.512)	0.921

4. Discussion

4.1 Hospital centralized monitoring method for clinical safety of oral Chinese patent medicine post-marketing

Currently, the subjects of clinical safety re-evaluation in Chinese patent medicine post-marketing in China are mainly Chinese medicine injections, while there are few re-evaluation studies on oral Chinese patent medicine. Literature analysis is the main resource for the safety of oral Chinese patent medicines. At

present, the major methods for clinical safety re-evaluation of Chinese patent medicine include large-scale centralized monitoring systems. Based on the experience of centralized monitoring of traditional Chinese medicine injections, safety monitoring studies have been carried out on a few large varieties of oral Chinese patent medicines over recent years [12–13].

NXT formula contains 16 traditional Chinese medicines, including leech and scorpion. Some researchers have suggested that leech and scorpion are common animal decoction pieces causing ADR [14]. Toxic elements contained in NXT may have potential safety hazards; thus, it is necessary to re-evaluate the drug after marketing. However, there is still no research report on the re-evaluation of NXT after marketing.

Herein, we reported a centralized monitoring study on the clinical safety of NXT after its marketing in hospitals. We adopted the third-party pharmacists as the monitoring subject and actively tracked and monitored the ADRs/ADEs collected by NXT for 3 months. With the help of the Web tracking and follow-up system, HIS cooperated in extracting and supplementing the monitoring information. To ensure the objectivity of the evaluation results of adverse reactions/events, the ADRs/ADEs found in the monitoring process were re-evaluated at three levels. Among them, the first-level evaluation included setting up ADRs/ADEs evaluation team in each monitoring research hospital to investigate the adverse events found in the monitoring process and making a preliminary evaluation (first-level evaluation). Secondary evaluation referred to the re-evaluation of ADRs/ADEs found in all monitoring hospitals by the ADRs/ADEs expert evaluation team, which is responsible for clinical monitoring. The three-level evaluation included medical experts, pharmaceutical experts, and related experts that evaluated all ADRs/ADEs and comprehensively analyzed the first-level evaluation results and the second-level evaluation results, thus finally determining the evaluation results. The evaluation standard adopts the internationally accepted MedDRA (The Medical Dictionary for Regulatory Activities) for standardizing the terms of ADR names in monitoring records and to classify the organ/system damage of adverse reactions. Strict quality control system and ADRs/ADEs three-level causal association evaluation method ensured the scientific and rigorous research.

4.2 ADRs of NXT

The incidence of NXT-related adverse reactions, which was 3.44‰, belonged to "occasional" level adverse reactions. Adverse reactions involved 10 organs/system damages, found in a total of 31 cases. The main clinical manifestations and involved system damages were gastrointestinal system (54.84%), including abdominal pain, nausea, heartburn, flatulence, acid regurgitation, stomach discomfort, nonspecific anorexia, indigestion, constipation, and diarrhea. Oral drugs pass through the blood circulation of the gastrointestinal tract, directly coming in contact with gastrointestinal cells, which may affect the function of the gastrointestinal system and cause adverse reactions [15]. Therefore, when clinically using NXT and other oral drugs, patients should be reminded to take them after meals according to the instructions to avoid or reduce gastrointestinal system damage. The severity of adverse reaction symptoms was found to be mild and moderate, and the prognosis was good after the treatment.

Similar to the descriptive analysis results of adverse reactions reported in NXT safety literature [16–17], adverse reactions mainly occurred within 1 day (40.91%) and 1 week (31.82%), and long-term medication (over 4 weeks) accounted for 13.64%. Previous studies [18] have shown that the adverse reaction time of oral drugs was related to the pharmacokinetic mechanisms. Adverse reactions occurred in 21 patients (95.45%) within 30 days. In this study, 250 patients were monitored within 30 days, and the incidence of adverse reactions was as high as 8.40% in patients who used NXT within 30 days. Therefore, it is necessary to pay more attention to short-term adverse reactions in patients who used NXT. Long-term monitoring can help to discover the clinical safety effect of long-term medication. At present, there is no literature on the influencing factors of NXT adverse reactions, and our multivariate logistic regression results revealed no significant influencing factors. In this study, there were 22 cases with adverse reactions in NXT clinical safety monitoring, where four patients had ADR before and continued to take medicine until NXT clinical safety monitoring was carried out. Therefore, this study found that 18 patients (4.96‰) experienced ADR when using NXT for the first time, and four patients (1.58‰) experienced ADR when using NXT for successive times. However, univariate logistic regression showed that the ADR of NXT used for the first time was 1.306 times higher compared to using NXT for successive times. Also, the incidence of adverse reactions of NXT used for the first time was relatively high; thus, more attention should be paid to the patients using NXT for the first time.

4.3 Differences between oral Chinese patent medicine and the Chinese medicine injection

Centralized monitoring research in hospitals is a mature real-world research method, which has been successfully applied in clinical safety re-evaluation of Chinese medicine injection post-marketing [19–20]. In this study, we established a centralized hospital monitoring method for oral Chinese patent medicines. By the demonstration of the NXT safety study, the different characteristics from traditional Chinese medicine injections were shown in monitoring objects, monitoring hospitals, sample size, monitoring period, and follow-up. Compared with traditional Chinese medicine injection, the different implementation points mainly manifested in the following three aspects:

First, the traditional data collection method was improved and perfected. A simple, cheap, and feasible web-based follow-up system for hospitalization and outpatient service was designed to ensure the long-term monitoring effect, which is consistent with the internationally common practice [21–23]. This ensures the timeliness and accuracy of out-of-hospital data collection and evaluation of long-term oral drugs and facilitates the follow-up and maintenance of patients. Telephone follow-up and medication follow-up were used to reduce the occurrence of lost follow-up, and standard terms and SOP were formulated to improve the response rate of patients during follow-up, to comprehensively improve the quality of follow-up and maintenance, and ensure the truthfulness and accuracy of the study.

Second, the establishment of stricter quality control system specifications. The three-level quality control method adopted in this study was successfully applied to the post-marketing safety monitoring of traditional Chinese medicine injections [21]. We designed a more strict and precise quality control process

according to the characteristics of oral drugs and previous experience. To strengthen the overall research quality control, in the pre-monitoring research scheme design stage, the research hospitals, researchers, and research cases were respectively formulated with selection methods, training methods, case inclusion/shedding/elimination standards, and detailed researcher manuals, which were formulated to ensure the smooth implementation of the research process. As a result, a strict and perfect quality control system was established during and after the monitoring, and a three-level quality control system was implemented during the monitoring and cooperated with the supervision during the monitoring process. After the monitoring, the data were recorded by two people, and the man-machine combination was used to check the data for multiple rounds to ensure the overall research quality of the clinical safety of oral drugs in a hospital centralized monitoring during the organization and implementation stage and the data management stage and to ensure the scientific and objective research results. Using HIS data warehouse technology to collect the monitoring information is a more comprehensive approach. Because of its complex source, HIS data contain a lot of semi-structured or even unstructured information, and there are some irregular or missing data [24]. In this study, HIS data warehouse technology was adopted, and the data from various hospitals could be processed by hierarchical and standardized methods [25]. According to the establishment mode of the data warehouse, the data were extracted, cleaned, and integrated by the combination of computer and manpower, and finally, the HIS real-world data warehouse that met the research needs was formed.

4.4 Limitations of this study

This research on centralized monitoring of clinical safety in hospitals was affected by objective factors such as sample size of monitored cases, monitoring time, monitoring area, etc., which requires close cooperation and support of relevant state departments, pharmaceutical manufacturers, and research institutions before it can be successfully implemented. Future hospital centralized monitoring research should continue to expand the sample size, investigate other possible related factors, further obtain ADR damage types and serious ADR damage types, deeply study the possible ADR occurrence mechanism from toxicology, and find ways to prevent ADR occurrence. The monitoring hospitals came from two regions, Henan Province and Shanghai, China. Henan Province is located in central China, and Shanghai is located in East China. The distribution of monitoring hospitals was relatively concentrated and did not reach national coverage. In the clinical safety research, the case review method was not used to study ADR, which may be related to HIS data mining. In addition, the informationization level of monitoring in this research was limited, which consumes research manpower. Due to the lack of outpatient HIS information, much information was missing. In the future, a daily monitoring and reporting system for outpatient service can be established, and doctors can be trained to complete, standardize and accurately fill in electronic medical record information, thus improving HIS information data. HIS data can be used to obtain the ADR results of drugs and bring them into the comprehensive evaluation research to obtain more objective, comprehensive, and scientific conclusions.

5. Conclusion

The hospital centralized monitoring research method of NXT's post-marketing clinical safety based on HIS data and Web tracking, and follow-up system is a necessary means to carry out the post-marketing safety research for oral Chinese patent medicines. The incidence of NXT-related adverse reactions was 3.44‰, which belongs to the "occasional" level, mainly involving gastrointestinal system damage. Most ADR occurred within 1 day or 1 week. The severity was mainly mild and moderate, and the prognosis was generally good after symptomatic treatment such as drug withdrawal or reduction.

Declarations

Competing interests: The authors declare that they have no competing interests.

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Availability of data and materials

The data generated and analyzed during the current research are not public, but some of the analyzed data can be obtained from the corresponding author upon reasonable request.

Authors' contributions

C-XL, XL, TX and BZ were participated in this study as clinical pharmacists and all data were collected by them and C-XL wrote the manuscript. Y-H C, Y-T J, HZ and BZ performed the analysis of the data. XL, C-XL and Y-H C were major contributors in writing the manuscript. C-XL and XL were major contributors in the data quality control. X-LL and J-F T designed this research and were corresponding authors of this article. All authors reviewed the manuscript.

Ethics approval and consent to participate

This is a prospective observational study. No medical intervention was conducted on the observed objects. This protocol has international registration in China clinical trial registration center (ChiCTR-OPC-17013912).

Consent for publication

There was no individual person's data in this research.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Geographic distribution map of hospitals centralized monitoring.

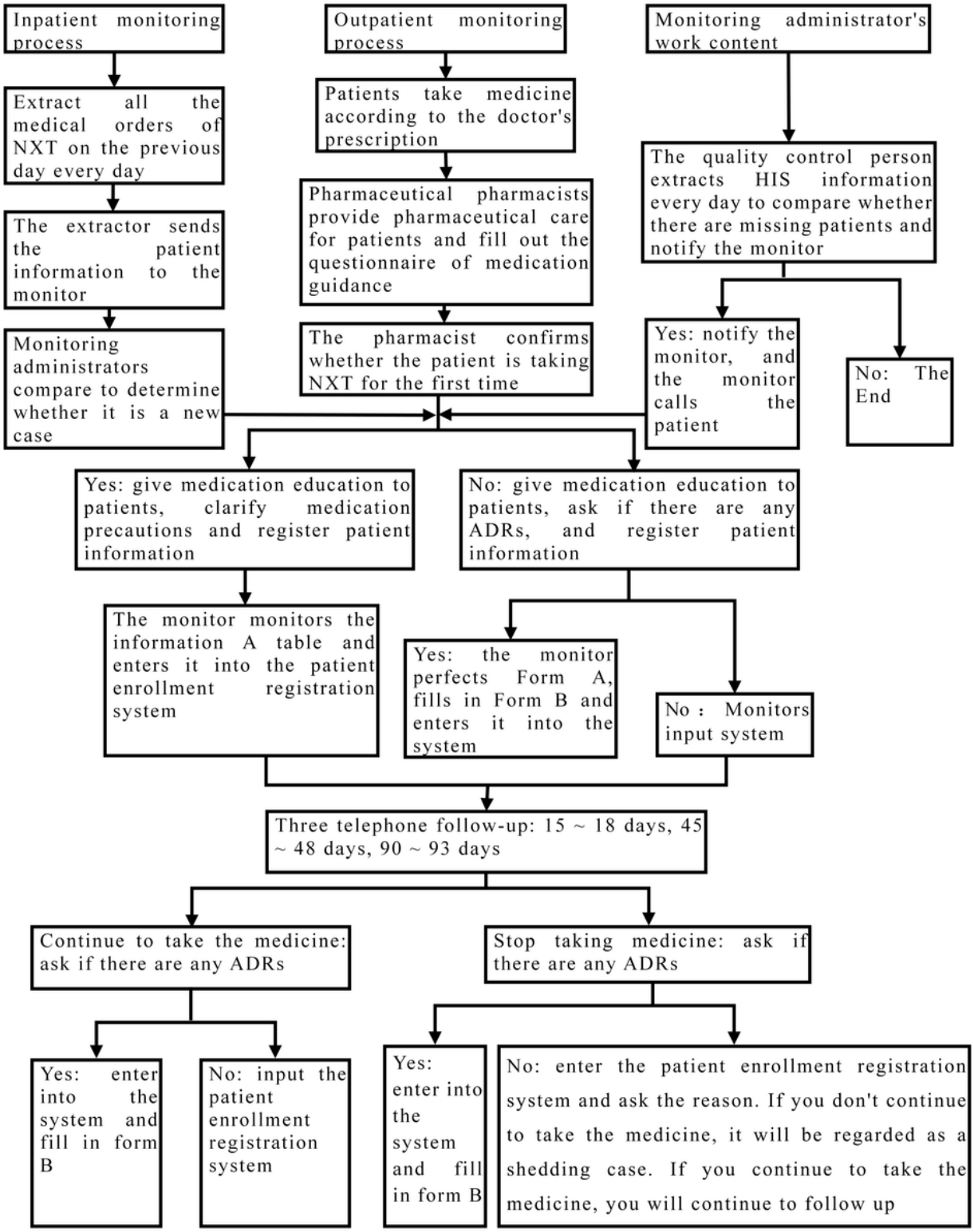

Figure 2

Flow chart of data monitoring and collection.