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Psychological Status of Volunteers in a Phase I Clinical Trial Assessed by Symptom Checklist 90 (SCL-90) and Eysenck Personality Questionnaire (EPQ)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Yudong Wei
AEFG 1,2 Haiyan Li
BCD 3 Huali Wang
BC 1 Shuang Zhang
AEF 4 Yumei Sun

1 Drug Clinical Trial Center, Peking University Third Hospital, Beijing, P.R. China
2 Department of Cardiology, Peking University Third Hospital, Beijing, P.R. China
3 Peking University Sixth Hospital, Institute of Mental Health, Beijing, P.R. China
4 Peking University School of Nursing, Beijing, P.R. China

Corresponding Authors: Yudong Wei, e-mail: weiyudong@bjmu.edu.cn, Yumei Sun e-mail: sym8022@bjmu.edu.cn
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Background: The psychological status of volunteers was investigated to provide a theoretical method for Phase I clinical trial management and result analysis.

Material/Methods: The Symptom Checklist 90 (SCL-90) and Eysenck Personality Questionnaire (EPQ) were used to assess the psychological status 200 healthy Chinese volunteers.

Results: SCL-90 results indicate that the average value of positive factors is 10.32±14.26 by self-assessment of healthy volunteers, somatization factor is 1.13±0.13, compulsive symptom factor is 1.29±0.27, interpersonal sensitivity factor is 1.31±0.21, depression factor is 1.26±0.33, anxiety factor is 1.21±0.21, hostility factor is 1.08±0.26, phobia factor is 1.05±0.18, paranoid factor is 1.12±0.23, and psychotic symptom factor is 1.17±0.26.

Conclusions: Compared to the norm in China, the score of each factor of healthy volunteers was relatively low, with a statistically significant difference (P<0.001). EPQ results show that P score was 4.59±2.33, E score is 13.13±4.32, N score was 6.89±5.26, and L score was 13.21±4.25 for the 200 healthy volunteers. Compared to the norm in China, the P and N scores were lower, and the E and L scores were higher, with a statistically significant difference (P<0.001).

MeSH Keywords: Adaptation, Psychological • Clinical Trial, Phase I • Questionnaires

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Background

Clinical research is a key step for clinical application of a new drug from the laboratory. In China, clinical trials and bioequivalence tests are usually referred to as clinical studies [1]. The time and money cost of a clinical study is extremely high. According to statistics from the Pharmaceutical Research and Manufacturers of America (phRMA), the average cost of developing a new drug in the United States is currently between 0.8 and 1 billion dollars, the average time needed is 10–15 years, and more than 70% of the cost and time is spent on clinical research [2].

A clinical trial can be divided into 4 phases in most of countries in the world, and the basic standards and technical requirements of each phase in a clinical trial are strictly regulated [3]. The phase I clinical trial, which is also called the clinical pharmacology and toxicology phase, aims at the new drugs which have already passed the assessment of pre-clinical safety and efficiency [4].

During phase I, the tolerance of volunteers to new drugs is investigated to propose a preliminary safe and efficient drug administration protocol, which is used to guide the next stage of clinical trials. The pharmacokinetics of drugs, such as absorption, distribution, metabolism, excretion, and other pharmacokinetics, are studied *in vivo*. A good protocol and well-organized program can ensure a high-quality clinical trial and allow the study to proceed smoothly. The establishment of standard methods with high sensitivity and specificity, small error, good evaluation system, and, most importantly, qualified and healthy volunteers, help assure successful completion of a clinical trial. Normally, only healthy volunteers are involved in phase I clinical trials. Prior to a clinical trial, a professional and comprehensive risk assessment for healthy volunteers will significantly reduce the interference of clinical research results caused by the volunteers themselves. Therefore, the evaluation of all the factors related to volunteers is particularly important at the initial stage of phase I clinical trials. Currently, only physical health of volunteers is assessed before clinical trials, and there is little to no attention to their psychological health. In an actual clinical trial, the emotional characteristics and personality of healthy volunteers are related not only to volunteer compliance, but also to adverse events, and can even affect the blood parameters in pharmacokinetics, and eventually influence the final results of drug clinical trials [5–12]. In the present study, the emotional and personality characteristics of healthy volunteers in phase I clinical trials were investigated to understand these volunteer characteristics. Our study provides a theoretical foundation for the management, quality control, and results analysis of future clinical studies.

Material and Methods

Research objectives

A convenience sampling method was applied to screen the healthy volunteers who were registered in the phase I database of qualified units for drug clinical trials in a Beijing upper first-class hospital. We randomly selected 200 volunteers by database administrator according to the registration number. Inclusion criteria were: age 18 years or above, able to communicate or write i Chinese language, and voluntary participation.

Methods

Two questionnaires were used in this study: the Symptom Checklist 90 (SCL-90) and the Eysenck Personality Questionnaire (EPQ).

Symptom Checklist 90 (SCL-90)

SCL-90 consists of 90 items, including a very broad area of psychiatric symptomatology ranging from feeling, emotion, thinking, consciousness, behaviors and living habits, interpersonal relationships, diet, and sleep. Ten factors are used to reflect the psychological symptoms in 10 aspects. The results of this questionnaire explain the number of positive items for primary basis (with a score of no less than 2) and score of each factor. The greater the number of positive items, the higher the score for each factor, with a higher score indicating worse psychological health. When a score is greater than 2 (beyond the normal average number), there might be some psychological problems in that aspect. The questionnaire is a classic self-assessed list. According to the Degrogatis report, the validity coefficient of various symptoms is between 0.77 and 0.99. The China Scale Collaborative Group has applied the Global Assessment Scale (GAS) and Social Introversion Scale (SI) to check parallel validity of SCL-90; a negative correlation was found between the total score of SCL-90 and GAS ($p<0.05–0.01$) and a positive correlation was found between SCL-90 score and SI ($p<0.01$). All these results indicate that SCL-90 has good reliability and validity among the normal population. The reliability and validity meet the requirements of measurement [13].

Eysenck Personality Questionnaire (EPQ)

EPQ was compiled by a British psychologist, H. J. Eysenck, as a self-report scale, and was developed on the basis of the "Eysenck Personality Inventory" (EH) [14]. The number of items in the revised version in China was changed from 107 to 88 [15], including 4 subscales: internal and external propensity scale (E), neuroticism (N), psychoticism (P), and validity scale (L). The reliability of E, N, and L scales is between 0.74 and 0.78. However, the P scale reliability is between 0.54 and

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0.60, suggesting that EP makes RSC not only inherit the advantage of original questionnaire with high reliability of E, N and L scale, but also retain the disadvantage of an unstable P scale.

Data collection method

Healthy volunteers were randomly selected from a phase I clinical trial database of a qualified upper first-class hospital in Beijing. Potential volunteers were first contacted by phone to inform them about the purposes and procedures of study. If they agreed to participate, they came to the drug clinical trial institution personally for a check-up. The personnel responsible for information collection were professionally trained to ensure that used a standard approach, such as using the same tone of voice and attitude to communicate with volunteers. Thus, the effect of subjective factors of researchers on information acquisition was minimized and the subjective bias resulting from human factors was reduced. During the process of questionnaires collection, any missing items were carefully checked to ensure all questions were complete. The survey was conducted by 2 trained researchers with direct inquiry, one asked questions and the other recorded answers from a volunteer. A total of 200 questionnaires were issued, and 200 valid questionnaires were recovered. The recovery rate and the effective rate in this method were both 100%.

Statistical method

All data were input using Epidata 3.0 software and SPSS 18.0 was used for statistical analysis. Continuous variables are expressed as mean ± standard deviation. The comparison between constituent ratios and rates was conducted using the chi-square test. P<0.05 was considered as statistical significance.

Results

General information

Average age of the healthy volunteers was 28.6±7.8 years old. Table 1 lists their data, including age, gender, education, work, and income.

SCL-90 results

The average value of positive factors was 10.32±14.26 by self-assessment of healthy volunteers. Among all factors, somatization factor was 1.13±0.13, compulsive symptom factor was 1.29±0.27, interpersonal sensitivity factor was 1.31±0.21, depression factor was 1.26±0.33, anxiety factor was 1.21±0.21, hostility factor was 1.08±0.26, phobia factor was 1.05±0.18, paranoid factor was 1.12±0.23, and psychotic symptom factor was 1.17±0.26.

Table 1. General information of healthy volunteers.

Items	Healthy volunteers (n=200)
Age	
Less than 30	112
Between 30 and 44	88
Between 45 and 59	N/A
More than 60	N/A
Gender	
Male	146
Female	54
Education	
Primary school	3
Junior school	42
High School	82
College	55
University and above	18
Work	
Employed	142
Unemployed	46
Retired	N/A
Housewife	N/A
Student	12
Annual income	
Less than RMB 30,000	48
Between RMB 30,000 and RMB 50,000	110
Between RMB 50,000 and RMB 70,000	19
Between RMB 70,000 and RMB 90,000	22
More than 90,000	1

Compared to the norm in China, the score of each factor of healthy volunteers was relatively low. The *t* test results show that the difference has statistical significance (P<0.001), and the data are listed in Table 2.

EPQ scores

According to EPQ results, P score was 4.59±2.33, E score was 13.13±4.32, N score was 6.89±5.26, and L score was 13.21±4.25 for the 200 healthy volunteers. Compared to the norm in China, the P and N scores were relatively lower, and the E and L scores were relatively higher. The *t* test results show that the difference has statistical significance (P<0.001), and the data are listed in Table 3.

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Table 2. Comparison of results obtained by self-assessment of healthy volunteers and norm data $\bar{\chi}$±SD).

Item	Healthy volunteers (n=200)	Norm (n=1388)	*P*
Somatization	1.13±0.13	1.37±0.48	0.000
Compulsive symptom	1.29±0.27	1.62±0.52	0.000
Interpersonal sensitivity	1.31±0.21	1.65±0.61	0.000
Depression	1.26±0.33	1.50±0.59	0.000
Anxiety	1.21±0.21	1.39±0.43	0.000
Hostility	1.08±0.26	1.46±0.55	0.000
Phobia	1.05±0.18	1.23±0.41	0.000
Paranoid	1.12±0.23	1.43±0.57	0.000
Psychotic symptom	1.17±0.26	1.29±0.42	0.000
Average positive factors	10.32±14.26	24.92±18.41	0.000

Table 3. Comparison of EPQ results obtained by healthy volunteers and norm data ($\bar{\chi}$±SD).

Item	Healthy volunteers (n=200)	Norm (n=458)	*P*
P score	4.59±2.33	7.86±3.05	0.000
E score	13.13±4.32	9.85±4.36	0.000
N score	6.89±5.26	10.81±4.45	0.000
L score	13.21±4.25	11.75±3.55	0.000

Discussion

Adverse events data collection uses tools such as SCL-90, which is one of most widely used test scales for psychological health worldwide. In this method, 10 factors are selected to reflect the psychological symptoms of a person, including somatization, compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobia, and paranoid and psychotic symptoms. It is commonly used by psychiatric and psychological counseling clinics to understand the psychological status of counselors, and to examine the mental problems among people having different occupations. Previous studies have shown that the questionnaire has good reliability and validity [16]. SCL-90 has been widely used domestically and internationally in high school students [17], college students [18,19], soldiers [20], tumor patients [21], and other groups of people.

Relevant studies have shown that psychological status of volunteers in phase I clinical trial mainly includes phobia, anxiety, and unstable emotion [22]. Due to the lack of correct understanding of experimental drugs and programs, phase I volunteers might exhibit suspicion and phobia regarding drugs and adverse events, as well as a resistance to blood sampling [23]. These observations are consistent with the results of the present study. Jiang et al. [24] applied the self-rating anxiety scale and self-rating depression scale to assess psychological status of 35 healthy volunteers before and after clinical trials. They found that healthy volunteers had anxiety before and after clinical trials. The study demonstrated that the score of each factor in SCL-90 was lower than the norm data of Chinese adults in 1986 [25], suggesting that the overall level of psychological health of Chinese healthy volunteers is significantly lower than in general population adults. This result is closely related to low income, unstable employment, and high life stress. The present study found no symptoms of anxiety, phobia, somatization, or paranoia in healthy volunteers, which might be related to 2 aspects. First, these volunteers have participated in phase I clinical trials before. Second, they are not currently participating in a clinical trial.

During a phase I clinical trial, the drugs are used in humans for the first time. Therefore, it is inevitably for the healthy volunteers to have fluctuation in their psychological conditions. This fluctuation will affect final result [26] and result in psychological unease [27]. In our study, the items such as somatization, compulsive symptom, anxiety, paranoia, and psychotic symptoms in SCL-90 can reflect a subjective sense of physical discomfort and trigger physical characterizations related to adverse events. Other factors such as interpersonal sensitivity, depression, hostility, and phobia mainly reflect individual

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thinking, which is related to the compliance during the clinical trial. Therefore, understanding the emotional characteristics of volunteers before phase I clinical trials is critical for the management of volunteers and adverse events, which further affect the quality and outcome of the overall clinical trial.

The EPQ describes the personality of volunteers from 3 mutually orthogonal dimensions: introversion and extroversion (E), neuroticism (N), and psychoticism (P). Researchers can understand different personal characteristics from these 3 aspects. In our study, the adult questionnaire by Gong containing 88 questions [15] was applied to investigate personality characteristics of healthy volunteers. The results from this study will be helpful for research on the effects of emotion on clinical results of volunteers in phase I clinical trials.

The present study demonstrated that the score of E factor of healthy volunteers is higher than the norm data, suggesting that the volunteers in this experimental group are more extroverted, with a more outgoing personality, better social skills, and are more eager to experience excitement and adventure. They belong to the type of spontaneous emotion with higher social immaturity level. The scores of P and N dimensional factors are lower than the norm data, suggesting that the volunteers in this group are more stable, sympathetic, and concerned about others. This is consistent with results reported by Ouyang et al., who studied 119 healthy volunteers [28], but is slightly different from the study by Jiang et al. on 35 healthy volunteers in a phase I clinical trial [24]. This might due to the difference in the representativeness of the samples. In the study of Jiang et al., the age of healthy volunteers was mainly between 18 and 22 years old, with greater emotional fluctuation. The score of L factor in this study indicates that present study has better stability.

Relevant studies [29] have demonstrated that personal characteristics of volunteers can influence pharmacokinetics or pharmacodynamics of a drug. According to Meyer et al. [30], a single dose of 0.3 mg/kg diazepam given to an extroverted individual can significantly damage the reaction ability, while the reaction ability of an introvert was not affected by the same dose. Nakano et al. showed that the oral intake of caffeine and diazepam has a significantly faster effect in individuals with higher scores of N dimensional factor [31]. The present study suggests that assessment of personality characteristics of healthy volunteers is highly relevant to the outcome of clinical trials.

This study has shown that the personality characteristics and emotional qualities of healthy volunteers are both different from the Chinese norm data, and both factors significantly affect the management and results of clinical trials. Our results suggest that valid assessment methods should be used to predict the emotional qualities and personality characteristics of volunteers before they are involved the experimental groups of clinical trials, which can provide theoretical foundations for the management of volunteers and test results. During clinical trials, the different emotions and personality characteristics of volunteers can be effectively managed to improve compliance of volunteers and to minimize the occurrence of false or adverse events, thus improving the quality and efficiency of clinical trials.

Conclusions

This study selected a single clinical unit to conduct the research; therefore, the results contain bias and deviation. In the future, this type of clinical trial should be carried out in multiple clinical centers to minimize the selection bias and to produce results that are more representative and useful. It should be noted that the survey methods used in this study are not suitable for quantitative analysis and multi-factor analysis of relevant factors. A specific method for measurement should be formulated and evaluated to access the cognition and willingness to participate in clinical trials, which will significantly facilitate the comparison between different studies.

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