BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051277
Article Type:	Original research
Date Submitted by the Author:	17-Mar-2021
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Keywords:	EDUCATION & TRAINING (see Medical Education & Training), HEALTH ECONOMICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH, QUALITATIVE RESEARCH

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Title Page

Title

Knowledge, perceptions, and practices of pharmacists regarding generic substitution in China: A cross-sectional study

Author

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Word count

3842 words totally.

Keywords

Generic Substitution; Knowledge; Perceptions; Practices; Pharmacists

Abstract

Objective: To evaluate pharmacists' knowledge, perceptions and practices towards generic substitution in the 11 pilot locations in China.

Design: An online cross-sectional survey using questionnaires was conducted. A convenience sampling technique was implemented to recruit pharmacists.

Setting and participants: The study took place in public and private hospitals of 11 pilot locations in China. 2291 pharmacists participated in the study.

Results: Most of the participants had good knowledge of requirements for evaluating the quality and efficacy of generic drugs (n=2118; 92.4%), and the definition of generic drugs (n=2078; 90.7%). In terms of perceptions, 67.3% of respondents believed generic drugs are equally as effective as the brand-name drugs, and 69.0% of respondents believed that generic drugs are as safe as brand equivalents. A high percentage of participants supported the policy of generic substitution (n=1634; 71.4%). A significant positive correlation was demonstrated between total knowledge score and total perception score (ρ= 0.267; P <0.001). Efficacy, safety, and the direction of national policies and hospital regulations were the main factors affecting pharmacists' willingness to dispense generic drugs.

Conclusions: The study identified gaps in respondents' knowledge and perceptions of generic substitution. Pharmacists who are more knowledgeable in generic drugs tend to hold a more supportive attitude towards generic substitution. Although it appeared that pharmacists in China have largely accepted generic substitution, they still have concerns regarding the reliability and quality of generic drugs.

Strengths and limitations of this study

- This cross-sectional study is one of the few surveys evaluating the knowledge, perceptions, and practices of pharmacists regarding generic drugs after implementing the national centralized procurement in China.
- This survey recruited a large number of respondents (n=2291). The Cronbach's alpha value for perceptions is equal to 0.833, indicating a good level of reliability.
- The web-based sample survey tool could be a limitation because of non-randomized sampling.
- This study was performed in 11 locations in China, which could limit generalizability of the findings.

Introduction

Healthcare expenditures have been constantly increasing worldwide, [1,2] and drug spending is one of the fastest growing components of healthcare spending.[3-5] Generic drugs offer an opportunity for substantial savings to healthcare systems. Currently, generic drug prescribing has become a major cost-minimizing strategy to reduce the fiscal expenditures and financial burden to patients, and to increase accessibility of essential drugs globally. The World Health Organization defined a generic drug as "a pharmaceutical product, usually intended to be interchangeable with an innovator product that is manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusive rights".[6] Generic substitution is defined as the act of substituting a brand-name drug with an equivalent generic drug.[7]

In China, overall medical expenditures accounted for 6.57% of the gross domestic product (GDP) in 2018.[8] Approximately 28% of medical expenditures came from the government [8]. Overall medical expenditures in China steadily increased between 2008 and 2017, at an average annual rate of 12.2%, outpacing the real GDP growth of 8.1%. [9] The per-capita drug consumption in China has risen to the highest in the world.[10]

Controlling drug expenses in public hospitals is vital in controlling overall medical expenditures. According to Alexandra's statistics,[11] due to the large volumes of medications consumed in public hospitals and a substantial price differential between the originator brand and lowest-priced generic products, 370 million U.S. dollars could be saved by switching only four drugs, saving patients an average of 65%. With the March 2019 implementation of the national centralized procurement program, generic substitution in China has become an irresistible trend. [12,13] This program directed by the authorities was a new procurement model for drugs based on volume and bidding, with public institutions forming a procurement alliance.

China has become the second largest producer of pharmaceuticals in the world and is still growing rapidly.[14,15] There are more than 8,135 pharmaceutical companies in China, most of which produce generic drugs. Ensuring that the large amounts of pharmaceutical products in the market are therapeutically equivalent has been challenging for Chinese authorities. Thus in 2013, the National Medical Products Administration (NMPA), formally known as the China Food and Drug Administration (CFDA), established a system to evaluate generic quality.[16] According to the regulations issued by the government in March 2016,[17] assessment of quality and efficacy via "consistency evaluation" is mandatory for generic drugs approved prior to 2007 in the National Essential Medicine List (2012). The NMPA requires that the 90% confidence interval of the geometric mean ratio for main pharmacokinetic parameters, the peak concentration (Cmax) and the area under concentration-time curve (AUC), of the product fall entirely within the range of 80.00%-125.00% in order to be bioequivalent.[18] By November 27, 2019, 323 drug products passed the consistency evaluation for quality and efficacy.[19] In the released NMPA standard reference product list, referenced products were selected from the brand equivalent or the same species acknowledged worldwide if the brand equivalent was not available.

The national centralized procurement program was approved by the State Council in January 2019 to significantly lower drug prices and to improve accessibility of drugs. Four municipalities and seven local cities were selected as the pilot cities, including Beijing, Tianjin, Shanghai, Chongqing, Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu, Xi-an. Twenty-five drug products were selected in the pilot program, of which 22 were generic drugs that had previously passed the consistency evaluation and 3 were brand-name drugs. Drug manufacturers bid to be contracted in this pilot program, and the successful manufacturers established a contract with an agreed upon purchase amount. By setting up this contract, the drug purchase price dropped dramatically. By the end of 2019, the pilot program was extended to more cities and provinces forming a procurement alliance, which covered nearly all the Chinese mainland. The generic substitution policy evolved from this pilot; because more generic drugs cheaper than the originator brand went into the procurement program under the bidding mechanism and made up a large market share.

As essential members of health care system, pharmacists play an important role in spreading awareness about the generic substitution policy. The primary objective of this study was to investigate the knowledge, perceptions, and practices of Chinese pharmacists regarding generic substitution after completion of the pilot year.

Methods

Study design

A self-administered, anonymous, online cross-sectional survey was conducted in the 11 pilot locations in China between April and May 2020.

Questionnaire design

The 29-item questionnaire was developed and distributed in the Chinese language. The preliminary version of the questionnaire was peer-reviewed by 7 researchers, and assessed by 10 experts for appropriateness of clinical terminology, completeness, accuracy and logical sequence of the statements. The final questionnaire was piloted among a sample of 20 pharmacists to test the reliability and validity of the questionnaire. The data of the pilot were not included in the final study's statistical analysis. Surveys questions were created in the Wenjuanxing website and was divided into four sections (demographic information, knowledge about generic drugs, perceptions towards generic substitution and practices on generic substitution).

Demographic information

The first section assessed pharmacists' demographic data including respondents' age, gender, terminal degree, professional title, years in practice, secondary department (e.g., outpatient, inpatient, clinical, laboratory, etc.), and geographical location.

Knowledge about generic drugs

The second section contained five questions evaluating pharmacists' knowledge of the consistency evaluation for generic drugs and national policies related to the national centralized procurement program. For knowledge-based questions, respondents self-assessed their level of knowledge on these 3 questions by indicating either "yes", "no" or "unsure". Response of "yes" were given 1 point, and responses of "no" or "unsure" were scored zero. For true or false questions, correct responses were given 1 point, and a wrong or unsure response was scored zero. The maximum score on this knowledge section was 5 points.

Perceptions towards generic substitution

The third section explored pharmacists' perception of generic substitution with 10 items; a five-point Likert scale was used to measure the level of respondents' agreement with offered statements. Response of strong disagreement was given 1 point and strong agreement was given 5 point. For statistical reasons, the fifth question was reverse scored from 1(strong agreement) to 5 point (strong disagreement).

Practices on generic substitution

In the fourth section, the practices, influencing factors, and difficulties related to generic substitution were examined. This section contained 5 multiple choice questions. For the last four questions, respondents were asked to select the top 3 important items.

Data collection

On April 14th, 2020, the Wenjuanxing hyperlink for this survey was shared with pharmacist groups in the 11 pilot locations in China using WeChat, a multipurpose messaging app. Informed consent from all respondents was gained prior to the commencement of the questionnaire. In order to submit the questionnaire, Respondents had to complete all fields. Respondents were given approximately three weeks to complete the survey. The online survey was closed on May 6, 2020. Data from the survey were synchronously collected using Wenjuanxing website as soon as each respondent had finished the questionnaire.

Patient and public involvement

Patients and/or public were not involved in this research.

Statistical analysis

Data were analyzed with SPSS version 24. Normality of the data was tested using Kolmogorov-Smirnov test. If the data did not comply with the normal distribution, Mann-Whitney-U or Kruskal-Wallis tests were used to compare differences and Spearman's rank correlation was applied to determine associations among variables. *P*-values < 0.05 were considered significant.

Results

Demographics of respondents

We screened data for pharmacists only, and data from other professionals were excluded. A total of 2,291 pharmacists participated in the study. Nearly half of respondents (1,130; 49.3%) were in the age group of 30 to 39 years, and about a quarter of respondents (530; 23.1%) were in the group of 40 to 49 years. The majority of respondents 1,658 (72.4%) were female. The majority of pharmacists worked in a tertiary hospital setting (1,913; 83.5%) and had a bachelor's degree (1,487; 64.9%). 442 (19.3%) of the respondents were senior pharmacists, 928 (40.5%) of the respondents were pharmacists-in-charge, and 867 (37.8%) were primary pharmacists. More details regarding the demographic and professional characteristics are presented in Table 1.

Table 1 Comparison of the total score of knowledge and perceptions across demographic characteristics.

Characteristics	Frequency (%) Total N=2291	Total score of knowledge (Mean ± SD)	P-value*	Total score of perceptions (Mean ± SD)	P-value*
Age(y)					
20-29	377 (16.5)	3.50 ± 0.984		36.85 ± 4.612	
30-39	1130 (49.3)	3.53 ± 0.989		37.10 ± 4.510	
40-49	530 (23.1)	3.71 ± 0.910	**0.000**	37.01 ± 4.527	0.349
50-59	244 (10.7)	3.68 ± 0.819		37.39 ± 4.257	
≥60	10 (0.4)	3.60 ± 0.966		37.30 ± 4.547	
Gender					
Male	633 (27.6)	3.66 ± 0.885	**0.011** [a]	37.61 ± 4.688	**0.000** [a]
Female	1658 (72.4)	3.55 ± 0.980		36.86 ± 4.415	
Terminal degree					
PhD	81 (3.5)	3.75 ± 0.783	**0.002**	35.96 ± 5.009	0.057
Master	460 (20.1)	3.75 ± 0.849		36.77 ± 4.269	

Bachelor	1487 (64.9)	3.54 ± 0.973		37.23 ± 4.567	
Others	263 (11.5)	3.47 ± 1.044		36.98 ± 4.319	
Professional title					
Chief pharmacist	143 (6.2)	3.90 ± 0.799		37.27 ± 4.344	
Associate chief pharmacist	299 (13.1)	3.75 ± 0.806		36.93 ± 4.334	
Pharmacist in charge	928 (40.5)	3.61 ± 0.879		37.07 ± 4.476	
			0.000		0.897
Pharmacist	867 (37.8)	3.44 ± 1.077		37.09 ± 4.607	
No title (e.g. Intern)	50 (2.2)	3.48 ± 0.974		36.92 ± 4.844	
others	4 (0.2)	4.00 ± 0.000		35.00 ± 3.162	
Years in practice					
Less than 5	424 (18.5)	3.56 ± 0.980		36.81 ± 4.436	
6-10	616 (26.9)	3.51 ± 0.971		37.24 ± 4.582	
			0.008		0.417
11-20	632 (27.6)	3.55 ± 0.996		37.02 ± 4.628	
21-30	424 (18.5)	3.70 ± 0.909		37.04 ± 4.304	

More than 30	195 (8.5)	3.68 ± 0.787		37.27 ± 4.422	
Level of medical institution					
Tertiary hospital	1913 (83.5)	3.60 ± 0.953		37.09 ± 4.493	
Secondary hospital	254 (11.1)	3.45 ± 1.011	0.071	36.65 ± 4.425	0.148
Community hospital	27 (1.2)	3.48 ± 1.051		36.67 ± 4.812	
Primary health care institution	97 (4.2)	3.65 ± 0.817		37.89 ± 4.761	
Location					
Beijing	551 (24.1)	3.66 ± 0.903		37.52 ± 4.693	
Tianjin	190 (8.3)	3.70 ± 0.902		37.55 ± 4.554	
Shanghai	178 (7.8)	3.53 ± 1.037		36.02 ± 4.929	
Chongqing	102 (4.5)	3.75 ± 0.875	**0.000**	36.45 ± 4.099	**0.000**
Shenyang	187 (8.2)	3.55 ± 0.911		37.19 ± 4.584	
Dalian	261 (11.4)	3.62 ± 0.952		37.67 ± 4.488	
Xiamen	90 (3.9)	3.69 ± 0.895		37.27 ± 4.292	

Guangzhou	159 (6.9)	3.58 ± 0.957	36.23 ± 4.286
Shenzhen	262 (11.4)	3.51 ± 0.942	36.97 ± 4.754
Chengdu	99 (4.3)	3.62 ± 0.765	36.86 ± 3.623
Xi-an	212 (9.3)	3.26 ± 1.182	36.52 ± 3.683

Bold *P*-values represent statistical significance.

*P-value calculated using Kruskal-Wallis test.

[a] P-value calculated using Mann-Whitney U test.

Knowledge about generic drugs

Knowledge of generic drugs was tested in five questions (for a total of five points), and the median knowledge score was 4.00 (mean ± SD: 3.58 ± 0.956). However, Table 1 shows statistically significant differences in knowledge scores related to variances in demographic and professional characteristics. Pharmacists within the range of 40-49 years had the highest score of knowledge (mean ± SD: 3.71 ± 0.989), followed by those of 50-59 years (mean ± SD: 3.68 ± 0.819) and more than 60 years (mean ± SD: 3.60 ± 0.966). Men scored significantly higher than women (mean: 3.66 versus 3.55; $P<0.05$). Among different levels of terminal degrees and professional titles, pharmacists with doctoral degrees (mean ± SD: 3.75 ± 0.783) higher professional titles (mean ± SD: 3.90 ± 0.799) were more knowledgeable of generic drugs.

Table 2 represents pharmacists' responses to the knowledge items. The vast majority of the respondents understood that the government has carried out the program of consistency evaluation (2,118; 92.4%), and that generic drugs selected in the national centralized procurement program have passed the consistency evaluation (2,067; 90.2%). A high percentage of pharmacists (1,718; 75.0%) reported they were aware of how to identify generics that have passed consistency. However, only 225 (9.8%) pharmacists correctly identified the pharmacokinetic parameters to be assessed in determining bioequivalence per consistency evaluation. 2078 (90.7%) of pharmacists identified the correct definition of a generic drugs have the same active ingredients, dosage forms, routes of administration and therapeutic effects as the brand name drug. Associations between knowledge items and characteristics are displayed in the Supplementary file Table S1.

Table 2 Pharmacists' knowledge about generic drugs.

Statement	Yes or Correct response N (%)	No or Incorrect response N (%)	Unsure N (%)
Were you aware that China carries out the program of quality and efficacy consistency evaluation of generic drugs?	2118 (92.4)	74 (3.2)	99 (4.3)
Were you aware of the logo "Have passed the Consistency Evaluation" on the generic products?	1718 (75.0)	320 (14.0)	253 (11.0)
True/False: In principle, the method of bioequivalence tests in vivo is used for Consistency Evaluation. The standard of bioequivalence is that the 90% confidence interval of the geometric mean experiment/ reference ratios for main pharmacokinetic parameters (Cmax and AUC) falls entirely within the range of 90.00% ~ 120.00%.	225 (9.8)	1666 (72.7)	400 (17.5)
Were you aware that all the generic drugs in national centralized procurement have passed the consistency evaluation of quality and efficacy?	2067 (90.2)	68 (3.0)	156 (6.8)
True/False: The generic drugs in the national centralized procurement have the same active ingredients, dosage forms, routes of administration and therapeutic effects with the brand drugs.	2078 (90.7)	57 (2.5)	156 (6.8)

Perceptions towards generic substitution

Ten items were designed to assess attitudes on generic substitution, the median score was calculated to be 37.00 (mean ± SD: 37.07 ± 4.503). Men had a higher total perception score and thus more positive attitude regarding generic substitution (P<0.001; Table 1). Details on perceptions can be found in Table 3.

Table 3 Pharmacists' perceptions towards generic drugs.

Statement	Strongly Agree N (%)	Agree N (%)	Neutral N (%)	Disagree N (%)	Strongly Disagree N (%)
Generic drugs that have passed the consistency evaluation are as effective as brand-name equivalents.	361 (15.8)	1179 (51.5)	684 (29.9)	58 (2.5)	9 (0.4)
Generic drugs that have passed the consistency evaluation are as safe as brand-name equivalents.	355 (15.5)	1226 (53.5)	657 (28.7)	50 (2.2)	3 (0.1)
Generic drugs that have passed the consistency evaluation are less expensive than brand-name equivalents.	1076 (47.0)	987 (43.1)	218 (9.5)	10 (0.4)	0 (0.0)
Generic drugs that have passed the consistency evaluation are interchangeable with brand-name drugs.	314 (13.7)	1085 (47.4)	784 (34.2)	96 (4.2)	12 (0.5)
Replacing brand-name drugs with generic drugs that passed the consistency evaluation may change the clinical outcomes of medication treatment.	189 (8.2)	615 (26.8)	1047 (45.7)	387 (16.9)	53 (2.3)
Application of generic drugs that passed the consistency evaluation could improve adherence to medication treatment of patients.	228 (10.0)	873 (38.1)	1005 (43.9)	169 (7.4)	16 (0.7)
Health providers need to explain detailed information about generic drugs to patients in order to ensure that they correctly understand and use generic drugs.	640 (27.9)	1369 (59.8)	258 (11.3)	20 (0.9)	4 (0.2)
Generic drugs can be exempted from clinical trials for approval if they passed bioequivalence trials in vivo.	191 (8.3)	510 (22.3)	759 (33.1)	673 (29.4)	158 (6.9)
Relevant organizations should formulate and issue standard guidelines for generic substitution.	661 (28.9)	1312 (57.3)	296 (12.9)	20 (0.9)	2 (0.1)
I support the current policy of substituting brand-name drugs with generic	409 (17.9)	1225 (53.5)	619 (27.0)	32 (1.4)	6 (0.3)

drugs that have passed the consistency evaluation.

About two-thirds of the respondents agreed that generic drugs that passed the consistency evaluation were as efficacious (1,540; 67.3%) or as safe (1,581; 69.0%) as the brand-name equivalent. A total of 2,063 (90.1%) respondents reported that generic drugs have significant cost-minimizing advantages over the brand-name drugs. 1,399 (61.1%) pharmacists believed generic drugs that passed the consistency evaluation were interchangeable with the brand-name drugs; while 784 (34.2%) pharmacists held a neutral attitude towards interchangeability. Furthermore, 804 (35.0%) respondents believed that replacing the brand-name drugs with generic drugs may change clinical outcomes of medication treatment.

With regard to medication adherence, 1,101 (48.1%) respondents stated use of generic drugs could improve adherence to medication, but 1,005 (43.9%) respondents were neutral on this. A large percentage of respondents (2,009; 87.7%) recognized the importance of explaining detailed information about generic drugs to patients. While, a similar percentage of respondents (1,973; 86.2%) highlighted the need for standard guidelines for generic substitution, 701 (30.6%) believed that drugs that pass bioequivalence trials *in vivo* should be exempted from additional clinical trials before marketing. 759 (33.1%) pharmacists were neutral about this, and 831 (36.3%) disagreed. A large number of participant pharmacists (1,634; 71.4%) supported the national policy of generic substitution. A statistically significant association was found between geographic location and supportive attitudes toward generic substitution (P <0.001), see Supplementary file Table S2. The highest percentage of pharmacists in favor of generic substitution were from Xiamen (78.9%), followed by Tianjin (77.4%) and Beijing (76.8%), while the lowest percentage were from Shanghai (53.3%) (see Supplementary file Table S3).

A significant positive correlation was observed between pharmacists' perception on the efficacy and safety (ρ=0.761; P<0.001). The positive attitude towards either efficacy (ρ=0.681; P<0.001) or safety (ρ=0.640; P<0.001) of generic drugs was associated with generic interchangeability. There were also significant associations between generic interchangeability and support for generic substitution (ρ=0.602; P<0.001). In addition, a significant positive correlation was demonstrated between total knowledge score and total perception score (ρ= 0.267; P <0.001).

Practices on generic substitution

A total of 1,850 (80.8%) pharmacists noted increased use of generic drugs in their medical institutions, of whom 1046 (45.7%) reported a dramatically increased trend. Table 4 illustrates possible influencing factors related to dispensing and selection of generic drugs; most pharmacist respondents reported that the three main factors affecting their willingness to dispense generic drugs were efficacy (25.0%), safety (19.2%), and the direction of national policies and hospital regulations (18.7%).

Pharmacists reported that they think the top three factors patients considered when selecting generic drugs were efficacy of generic drugs (23.9%), preferences for brand-name drugs and medication habits (19.9%), and safety of generic drugs (17.4%). The most commonly cited difficulties in implementation of the centralized procurement and use of generic drugs were lack of trust in efficacy and safety (31.0%), challenge to change patients' preference (29.0%), and lack of time to provide patient education (23.6%). Suggestions for promoting generic substitution included encouraging generic substitution by health insurance policies (27.6%), publicizing these policies (25.5%), and educating health providers about generics and guidelines regarding their use (21.1%).

Table 4 Generic substitution practices.

Item	Statement	N (%)
How has the amount of generic drugs used in your medical institution changed after the implementation of national centralized procurement of drugs?	Significantly increased	1046 (45.7)
	Increased somewhat	805 (35.1)
	Basically unchanged	163 (7.1)
	Decreased	23 (1.0)
	Unsure	254 (11.1)
What factors do you think affect the selection of generic drugs? Please select the top 3 important items.	National policies and hospital regulations	1284 (18.7)
	Efficacy of generic drugs	1716 (25.0)
	Safety of generic drugs	1321 (19.2)
	Economy of generic drugs	686 (10.0)
	Accessibility of generic drugs and brand-name drugs	350 (5.1)
	Physicians' clinical expertise in medication treatment	324 (4.7)
	Patient’s financial burden	357 (5.2)
	Patients' willingness and preferences	548 (8.0)
	Promotion of drug representatives	94 (1.4)
	Reputation of generic drugs manufacturers	182 (2.6)
	Others	11 (0.2)
What factors do you think affect patients’ choice of selecting generic drugs in the national centralized procurement? Please select the top 3 important items.	Patients' preference for brand-name drugs and medication habits	1368 (19.9)
	Efficacy of generic drugs	1641 (23.9)
	Safety of generic drugs	1198 (17.4)
	Out-of-pockets cost of drugs	737 (10.7)
	Patient’s financial burden	888 (12.9)
	Physicians' suggestions	625 (9.1)
	National policies	412 (6.0)
	Others	4 (0.1)

What do you think is the largest challenge in implementing the national centralized procurement and use of generic drugs? Please select the top 3 important items.	There is no enough time to explain details to patients.	1621 (23.6)
	It is difficult to change patients' preference.	1992 (29.0)
	Lack of trust in the efficacy and safety of generic drugs.	2134 (31.0)
	There is an increased risk of errors in dispensing drugs.	529 (7.7)
	There is an increased cost in maintenance and manpower.	558 (8.1)
	Others	39 (0.6)
What measures should be taken to promote the national centralized procurement and use of generic drugs? Please select the top 3 important items.	Encourage patients to use generic drugs by use of health insurance policies.	1899 (27.6)
	Increase publicity of centralized procurement policies.	1751 (25.5)
	Educate health providers on centralized procurement policies and information about selected drugs.	1450 (21.1)
	Medical institutions should restrict the use of the brand-name drugs with the same generic name, and retain only the selected generic drugs.	513 (7.5)
	Medical institutions should restrict the use of all brand-name drugs with the same pharmacological action.	271 (3.9)
	Standard guidelines on generic substitution should be issued.	942 (13.7)
	Others	47 (0.7)

Discussion

This cross-sectional study is one of the few surveys evaluating the knowledge, perceptions, and practices of pharmacists regarding generic drugs after implementing the national centralized procurement in China. The Cronbach's alpha value for perception is equal to 0.833, indicating a good level of reliability. This survey recruited a large number of respondents. In general, pharmacists had fair amount of knowledge regarding consistency evaluation and the definition of generic drugs. It appears that Chinese pharmacists are generally supportive of generic substitution; although, they still acknowledge some reservations regarding the quality, efficacy and safety of generic drugs. Measures such as encouraging generic substitution by health insurance programs, publicizing generic drugs policies, educating health providers about generics and guidelines regarding their use should be taken to promote generic substitution.

In this study, more than 90% of the respondents were aware of the definition of generic drugs. This was higher than some published studies, in other countries, like Poland, Pakistan, and Malaysia (63%).[20-22] In our study, few respondents (9.8%) identified the correct criteria for bioequivalence, this lack of knowledge on the regulatory requirements may lead to less confidence in the quality of generic drugs. In a study set in Palestine, 302 community pharmacists were asked to identify the correct Food and Drug Administration (FDA) acceptance criteria for bioequivalence; a similar percentage of community pharmacists (12.6%) provided the correct answer.[23] Nearly 30% of respondents had a neutral attitude towards efficacy (29.9%), safety (28.7%) of generic drugs, and interchangeability with brand-name equivalents (34.2%). The reason may be that the quality of generic drugs may not be clearly evident in pharmacists' clinical practice sites since generic substitution had only been implemented for one year. 71.4% of Chinese pharmacists surveyed supported the national policy of generic substitution. These results were similar to various studies conducted in Iran (71.6%), Poland (67.1%), Saudi Arabia (68.5%), Lebanon (64%).[20, 24-26] It was interesting to find a significant positive correlation between total knowledge score regarding generics and total perception score, indicating that pharmacists who are more knowledgeable in generic drugs may hold a more supportive attitude towards generic substitution. This may suggest the importance of mass educational effort among pharmacists. More information on the issues of generic drugs make pharmacists confident in using and dispensing those products. Besides, significant differences were observed by location in both knowledge and perception, which could lead to locational differences in the implementation of the generic substitution policy.

In more recent years, China has made a significant effort to promote generic substitution. The NMPA requires that generic drugs approved before 2007 must be proved bioequivalent with brand innovators by the end of 2021. Drug products that have not passed the consistency evaluation will no longer be selected for the national centralized drug procurement if more than three other generic drug manufacturers have passed. On average drug prices dramatically decreased by 52% of the selected drugs because of price negotiations and volume-based national centralized drug procurement.[27] In 2017, NMPA published Approved Drug Lists in China, similar to the U.S.'s Orange Book, this list includes 17 varieties of approved generic drugs passed the consistency evaluation. Pharmaceutically equivalent products and therapeutically equivalent products are clearly coded in this list. However, further steps need to be taken to educate pharmacists.

To correct misconceptions on generic drugs, the NMPA should ensure that generic drugs meet quality standards by using the Good Manufacturing Practices. The generic drug approval process should be rigorous and transparent to the public. Negative perceptions and skepticisms can be

reduced through education that will create more awareness about generic drugs and the importance of generic substitution among healthcare providers and patients. As some studies have demonstrated, information with regard to generic substitution should be taught in college curricula to better prepare healthcare providers for future work.[28-30] One proposed measure that could be implemented to promote rational use of generic drugs is the establishment of standard operating procedures for generic substitution and formulary of the medical institutions.[31] Currently, generic drug use has been greatly encouraged in public hospitals in the 11 pilot locations. Although this national centralized procurement brought tremendous use of generic drugs, physicians tend to veer towards using brand-name drugs with the same pharmacological action. A small number of our survey respondents agreed that in order to promote generic substitution medical institutions should restrict the use of brand-name drugs 513 (22.4%) and 271 (11.8%) responded that hospitals should only retain the corresponding generic drugs or drugs in the same pharmacologic drug class.

In this survey, only a few pharmacists reported other factors influencing patients' acceptance of generic substitution, such as patients' financial burden (12.9%), out-of-pockets cost of drugs (10.7%) and physicians' suggestions (9.1%). Currently, generic substitution has been supported by several Chinese health insurers, providing greater reimbursement for generic drugs (versus brand-name drugs). Because the survey respondents were from well-developed cities in China, the difference in drug cost may not have been a barrier for these patients. However, cost-saving factor may be pivotal for patients in lower-income areas; therefore, cost may not be the only incentive that should be offered to encourage generic substitution. Many of the respondents proposed that supply issues for generic drugs resulted in frequent medication changes and poor medication adherence. Therefore, supply guarantee of selected drugs and sustainability of formulary in the national procurement should be strengthened. The government should formulate regulations or acts for consistency evaluation of generic drugs and rigid quality supervision.

Pharmacists play a key role in managing rational use of medications, balancing between efficacy, safety and economic use of drugs. Pharmacotherapy monitoring and adverse drug reaction reporting should be emphasized to identify safety concerns regarding generic drugs. It is important for pharmacists to provide proper education to prevent patient confusion related to generic substitution and thus improve patient adherence. Pharmacists should also provide education and guidance to physicians and consumers on proper use of generic drugs. Therefore, attitudes of pharmacists may be a crucial factor affecting the acceptance of generics by both physicians and patients. In some states in the U.S., pharmacists must substitute a generically equivalent drug if available. Other states allow the pharmacists to decide to provide substitution – if not otherwise indicated by the physician. And still other states impose an additional restriction that require pharmacists to obtain patients' consent before substituting with a generic product.[32] Several studies from Lebanon, Palestine and Qatar concluded pharmacists should have authority to perform generic substitution without consulting the prescribing physician.[23,26,33] However, pharmacists do not have authority to modify medication orders to allow for substitution in China, thus further progress needs to be made to improve this situation. We believe pharmacists may be authorized in implementing generic substitution for any medication in future.

There are some limitations for this research. This study was performed in 11 locations in China, and most respondents were from large public hospitals; therefore, findings cannot be generalized to pharmacists practicing in other cities in China. The survey had a limited access to pharmacists in community settings or rural areas. This also limits generalizability of the findings. The data were

not collected from a random sample, which may weaken the representativeness and reduce the accuracy. Moreover, because of the web-based sample survey tool, we cannot compute a response rate to the questionnaire and adjust for possible non-response bias. In addition, due to the self-administered format of questionnaires, we cannot rule out the possibility of social desirability bias because the content of questionnaires about generic substitution correlates to the national policies and politics as well as the knowledge scores represent the respondents' perception.

Future research is needed to explore physicians' and patients' perceptions and practices regarding implementation of the national centralized procurement and generic substitution program in China. Generic drugs on the market are required to be bioequivalent to the reference product; however, their therapeutic equivalence may not necessarily be identical, especially for narrow therapeutic index drugs. Therefore, evidence of the efficacy and safety of generic drugs should be obtained from real-world studies to prove therapeutic equivalence.

Conclusion

In conclusion, Chinese pharmacists have a fairly good knowledge of generic drugs used in the national centralized procurement program and generally have positive attitudes towards generic substitution. The main obstacle for further utilization of generic drugs is lack of trust in efficacy and safety. Education and awareness of generic substitution should be promoted and clear standard guidelines need to be created.

Acknowledgments

The authors would like to thank all the pharmacists who participated in the study. The authors would also like to express their gratitude to all the experts and researchers for providing feedback on this questionnaire.

Funding

This study was partially funded by Peking Pharmacological Society. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Author contributions

J.Q. led the overall study design, conducted the statistical analyses, interpreted the data, and wrote the first draft of the manuscript. W.Z. and B.Z. made the study design, collected the data, contributed to interpretation of findings and edited the manuscript. S.W., L.D., X.L., Y.G., J.L., X.D., and D.M. were involved in the design of the questionnaire. H.P., L.D., X.D., and D.M. participated in distributing the questionnaire. R.L.T., K.W.S., and S.L. contributed to editing the manuscript and interpretation of findings. All the authors read, made comments on manuscripts, approved the final manuscript and agreed on its submission.

Conflicts of Interest

The authors declare that they have no competing interest.

Ethical approval

The study was approved by the Institutional Review Board (IRB) of Peking Union Medical College Hospital in China (IRB#: S-K1136) and St. Louis College of Pharmacy in the USA (IRB#: 2020-18). Anonymity was ensured by gathering and analyzing data in aggregate and only allowing members of the research team access to the password-protected data.

Data availability statement

Data are available on reasonable request. The data generated and/or analyzed during the present study are not publicly available, but they are available from the corresponding author on reasonable request.

Supplementary file

Table S1. Pharmacists' knowledge about generic drugs. Table S2. Association between pharmacists' perception and demographic characteristics. Table S3. Crosstabs between support for generic substitution and locations.

References

1. Squires D, Anderson C. U.S. health care from a global perspective: spending, use of services, prices, and health in 13 countries. *Issue Brief (Commonw Fund)*. 2015;15:1-15.
2. Hassali MA, Alrasheedy AA, McLachlan A, et al. The experiences of implementing generic medicine policy in eight countries: A review and recommendations for a successful promotion of generic medicine use. *Saudi Pharm J*. 2014;22(6):491-503.
3. Wouters OJ, Kanavos PG, McKEE M. Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. *Milbank Q*. 2017;95(3):554-601.
4. Wouters OJ, Kanavos PG. A comparison of generic drug prices in seven European countries: a methodological analysis. *BMC Health Serv Res*. 2017;17(1):242. Published 2017 Mar 31. doi:10.1186/s12913-017-2184-5.
5. Vogler S, Paris V, Ferrario A, et al. How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries. *Appl Health Econ Health Policy*. 2017;15(3):307-321.
6. World Health Organization. Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability. Available online: 2005http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_093Rev4_final.pdf, (accessed on 9th April 2020).
7. Posner J, Griffin JP. Generic substitution. British Journal of Clinical Pharmacology, 2011;72(5):731-2.
8. National Health Commission. Chinese Health Statistics Yearbook 2019. National Bureau of Statistics: Beijing, China, 2020.
9. Yip W, Fu H, Chen A T, et al. 10 years of health-care reform in China: progress and gaps in Universal Health Coverage. *The Lancet*, 2019, 394(10204):1192-1204.
10. Manning N. The Reform of Health Policy in China – Left Behind in the Race to Industrialize?. *Social Policy & Administration*, 2011, 45(6):649-661.
11. Cameron A, Mantel-Teeuwisse AK, Leufkens HG, et al. Switching from originator brand medicines to generic equivalents in selected developing countries: how much could be saved?. *Value Health*. 2012;15(5):664-673.
12. Hu L, Yu Z, Yuan Q, Hu Y, Ung COL. Opportunities and Challenges of Multinational Pharmaceutical Enterprises in Transforming Pharmaceutical Market in China. *Ther Innov Regul Sci*. 2019;53(2):207-214.
13. Huang B, Barber SL, Xu M, Cheng S. Make up a missed lesson-New policy to ensure the interchangeability of generic drugs in China. *Pharmacol Res Perspect*. 2017;5(3):e00318.
14. Lulin Z, Antwi HA, Wang W, et al. The effect of herd formation among healthcare investors on health sector growth in China. *Int J Equity Health*. 2016;15:113.
15. Zuo J, Gao Y, Bou-Chacra N, et al. Challenges and Opportunities to Use Biowaivers to Compare Generics in China. *AAPS PharmSciTech*, 2014, 15(5):1070-1075.
16. China Food and Drug Administration. Evaluation scheme of generic quality consistency. China Food and Drug Administration.2013. Available online: http://www.nmpa.gov.cn/WS04/CL2196/323980.html. (accessed on 31st May 2020).
17. State Council of the People's Republic of China. Notification on the carrying out consistency evaluation of the quality and efficacy of generic drugs. Available online: http://www.gov.cn/zhengce/content/2016-03/05/content_5049364.htm. (accessed on 31st May 2020).
18. National Medical Products Administration. Guidelines on statistical analysis in bioequivalence studies and technology in bioequivalence studies of high-variation drugs. Available online: http://www.nmpa.gov.cn/WS04/CL2138/331454.html. (accessed on 31st May 2020).
19. State Council Information Office. Regular meeting on the State Council policy on 27th, November,2019. Available online: http://www.nhc.gov.cn/xcs/s7847/201911/dad7e0b2a26a4

f56bd68836d33ab2fe2.shtml. (accessed on 8th August 2020).
20. Drozdowska A, Hermanowski T. Exploring factors underlying the attitude of community pharmacists to generic substitution: a nationwide study from Poland. *International Journal of Clinical Pharmacy*, 2016, 38(1):162-170.
21. Jamshed S, Hassali M, Ibrahim M, et al. Knowledge, perception and attitude of community pharmacists towards generic medicines in Karachi, Pakistan: a qualitative insight. *Trop J Pharm Res*. 2010;9(4).
22. Chua GN, Hassali MA, Shafie AA, et al. A survey exploring knowledge and perceptions of general practitioners towards the use of generic medicines in the northern state of Malaysia. *Health policy*.2010;95(2–3):229–35.
23. Shraim NY, Al Taha TA, Qawasmeh RF, et al. Knowledge, attitudes and practices of community pharmacists on generic medicines in Palestine: a cross-sectional study. *BMC Health Serv Res.* 2017;17(1):847.
24. Nazila Y, Gholamhossein M, Farzad P, et al. Generic substitution policy implementation: A pharmacists' perspective survey. *Journal of generic medicines*, 2015.
25. Alkhuzaee FS, Almalki HM, Attar AY, et al. Evaluating community pharmacists' perspectives and practices concerning generic medicines substitution in Saudi Arabia: A cross-sectional study. *Health Policy*. 2016;120(12):1412-1419.
26. El-Jardali F, Fadlallah R, Morsi RZ, et al. Pharmacists' views and reported practices in relation to a new generic drug substitution policy in Lebanon: a mixed methods study. *Implement Sci*. 2017;12(1):23.
27. China Daily. China to further pilot medicine procurement program. Available online: https://www.chinadaily.com.cn/a/201904/04/WS5ca5fe88a3104842260b4844.html. (accessed on 8th August 2020).
28. Shrank WH, Liberman JN, Fischer MA, et al. Physician perceptions about generic drugs. *Ann Pharmacother* 2011;45:31-8.
29. Al-Tamimi SK, et al. The need to incorporate generic medicines topic in the curriculum of Yemeni pharmacy colleges. *Int J Pharm Pract*. 2016;24(1):72-3.
30. Alrasheedy AA, Hassali MA, Aljadhey H, Al-Tamimi SK. The need to cover generic medications and generic substitution practice in the curricula of pharmacy colleges in Saudi Arabia. *Am J Pharm Educ*. 2014;78(5):108.
31. Chuaa GN, Hassali MA, Shafie AA, et al. A survey exploring knowledge and perceptions of general practitioners towards the use of generic medicines in the northern state of Malaysia. *Health Policy*,2010; 95:229-35.
32. Assistant Secretary for Planning and Evaluation (ASPE) U.S. Department of Health and Human Services. Expanding the use of generic drugs. Available online: https://aspe.hhs.gov/basic-report/expanding-use-generic-drugs#Legislative. (accessed on 21st June 2020).
33. Awaisu A, Kheir N, Ibrahim MI, et al. Knowledge, attitudes, and practices of community pharmacists on generic medicines in Qatar. *Int J Clin Pharm*, 2014;36(2):394–404.

Table S1. Pharmacists' knowledge about generic drugs.

Statement	Yes or Correct response N (%)	No or Incorrect response N (%)	Unsure N (%)	Age (P-value)[a]	Terminal Degree (P-value) [a]	Years in practice (P-value) [a]	Professional title (P-value) [a]	Gender (P-value)*	Location (P-value)*	Medical Institution (P-value)*
Were you aware that China carries out the program of quality and efficacy consistency evaluation of generic drugs?	2118 (92.4)	74 (3.2)	99 (4.3)	0.142	**0.000**	0.447	**0.000**	0.155	**0.026**	0.794
Were you aware of the logo "Have passed the Consistency Evaluation" on the generic products?	1718 (75.0)	320 (14.0)	253 (11.0)	**0.010**	0.129	0.070	0.068	**0.020**	**0.000**	0.450
True/False: In principle, the method of bioequivalence tests in vivo is used for Consistency Evaluation. The standard of bioequivalence is that the 90% confidence interval of the geometric mean experiment/ reference ratios for main pharmacokinetic parameters (Cmax and AUC) falls entirely within the range of	225 (9.8)	1666 (72.7)	400 (17.5)	0.052	0.164	0.734	0.096	0.251	**0.000**	0.254

90.00% ~ 120.00%.										
Were you aware that all the generic drugs in national centralized procurement have passed the consistency evaluation of quality and efficacy?	2067 (90.2)	68 (3.0)	156 (6.8)	0.094	0.153	0.076	**0.001**	0.097	**0.003**	0.449
True/False: The generic drugs in the national centralized procurement have the same active ingredients, dosage forms, routes of administration and therapeutic effects with the brand drugs.	2078 (90.7)	57 (2.5)	156 (6.8)	0.338	0.104	0.467	**0.046**	0.213	**0.047**	0.108

Bold *P*-values represent statistical significance.

*P-value calculated using Chi-square.

[a] P-value calculated using Kruskal-Wallis test.

Table S2. Association between pharmacists' perception and demographic characteristics.

Statement	Strongly Agree N (%)	Agree N (%)	Neutral N (%)	Disagree N (%)	Strongly Disagree N (%)	Age (P-value) *	Gender (P-value) [a]	Terminal Degree (P-value) *	Years in practice (P-value) *	Location (P-value) *	Professional title (P-value) *	Medical institution (P-value) *
Generic drugs that have passed the consistency evaluation are as effective as brand-name equivalents.	361 (15.8)	1179 (51.5)	684 (29.9)	58 (2.5)	9 (0.4)	0.752	**0.000**	**0.000**	0.400	**0.001**	**0.004**	0.582
Generic drugs that have passed the consistency evaluation are as safe as brand-name equivalents.	355 (15.5)	1226 (53.5)	657 (28.7)	50 (2.2)	3 (0.1)	0.572	**0.001**	**0.000**	0.441	0.269	**0.016**	0.554
Generic drugs that have passed the consistency evaluation are less expensive than brand-name equivalents.	1076 (47.0)	987 (43.1)	218 (9.5)	10 (0.4)	0 (0.0)	0.312	**0.030**	**0.000**	0.464	0.108	0.131	0.099
Generic drugs that have passed the consistency evaluation are interchangeable with brand-name drugs.	314 (13.7)	1085 (47.4)	784 (34.2)	96 (4.2)	12 (0.5)	0.074	**0.000**	**0.000**	0.050	**0.000**	0.188	0.131
Replacing brand-name drugs with generic drugs that passed the consistency evaluation may change the clinical outcomes of	189 (8.2)	615 (26.8)	1047 (45.7)	387 (16.9)	53 (2.3)	**0.000**	**0.002**	0.062	**0.001**	**0.004**	**0.000**	0.190

medication treatment.*												
Application of generic drugs that passed the consistency evaluation could improve adherence to medication treatment of patients.	228 (10.0)	873 (38.1)	1005 (43.9)	169 (7.4)	16 (0.7)	0.029	**0.022**	**0.002**	**0.037**	**0.042**	**0.003**	0.204
Health providers need to explain detailed information about generic drugs to patients in order to ensure that they correctly understand and use generic drugs.	640 (27.9)	1369 (59.8)	258 (11.3)	20 (0.9)	4 (0.2)	0.415	**0.033**	**0.028**	0.167	0.143	0.119	0.151
Generic drugs can be exempted from clinical trials for approval if they passed bioequivalence trials in vivo.	191 (8.3)	510 (22.3)	759 (33.1)	673 (29.4)	158 (6.9)	0.075	**0.024**	**0.001**	0.128	**0.002**	0.593	**0.034**
Relevant organizations should formulate and issue standard guidelines for generic substitution.	661 (28.9)	1312 (57.3)	296 (12.9)	20 (0.9)	2 (0.1)	0.503	0.051	**0.000**	0.415	**0.033**	**0.005**	0.217
I support the current policy of substituting brand-name drugs with generic drugs that have passed the consistency evaluation.	409 (17.9)	1225 (53.5)	619 (27.0)	32 (1.4)	6 (0.3)	0.135	**0.000**	0.051	0.410	**0.000**	0.662	**0.026**

Bold *P*-values represent statistical significance.

*P-value calculated using Kruskal-Wallis test.

[a] P-value calculated using Mann-Whitney U test.

Table S3. Crosstabs between support for generic substitution and locations.

N (%)	Beijing	Tianjin	Shanghai	Chongqing	Shenyang	Dalian	Xiamen	Guangzhou	Shenzhen	Chengdu	Xi-an	Total
Agreed	423 (76.8%)	147 (77.4%)	95 (53.3%)	66 (64.7%)	127 (67.9%)	189 (72.4%)	71 (78.9%)	104 (65.4%)	191 (72.9%)	71 (71.7%)	150 (70.7%)	1634 (71.3%)
Neutral	118 (21.4%)	43 (22.6%)	76 (42.7%)	34 (33.3%)	55 (29.4%)	70 (26.8%)	18 (20.0%)	52 (32.7%)	66 (25.2%)	26 (26.3%)	61 (28.8%)	619 (27.0%)
Disagreed	10 (1.8%)	0 (0.0%)	7 (4.0%)	2 (2.0%)	5 (2.7%)	2 (0.8%)	1 (1.1%)	3 (1.9%)	5 (1.9%)	2 (2.0%)	1 (0.5%)	38 (1.7%)
Total	551 (100.0%)	190 (100.0%)	178 (100.0%)	102 (100.0%)	187 (100.0%)	261 (100.0%)	90 (100.0%)	159 (100.0%)	262 (100.0%)	99 (100.0%)	212 (100.0%)	2291 (100.0%)

BMJ Open

Knowledge, perceptions, and practices of pharmacists regarding generic substitution in China: A cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051277.R1
Article Type:	Original research
Date Submitted by the Author:	29-Aug-2021
Complete List of Authors:	Qu, Jinghan; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Zuo, Wei; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Wang, Shaohong; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Du, Liping; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Liu, Xin; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Gao, Yang; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Li, Jiantao; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Pan, Hui; Peking Union Medical College Hospital, Department of Medical Administration Du, Xiaoli; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Mei, Dan; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Department of Pharmacy Took, Roxane; St. Louis College of Pharmacy, Department of Pharmacy

	Practice Schafermeyer, Kenneth; St. Louis College of Pharmacy, Department of Pharmaceutical and Administrative Sciences Lukas, Stephanie; St. Louis College of Pharmacy, Department of Pharmaceutical and Administrative Sciences Zhang, Bo; Chinese Academy of Medical Sciences and Peking Union Medical College, Department of Pharmacy
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health economics, Health services research, Medical education and training, Pharmacology and therapeutics, Public health
Keywords:	EDUCATION & TRAINING (see Medical Education & Training), Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Title Page

Title

Knowledge, perceptions, and practices of pharmacists regarding generic substitution in China: A cross-sectional study

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Word count

4293 words totally.

Keywords

Generic Substitution; Knowledge; Perceptions; Practices; Pharmacists

Abstract

Objective: To evaluate pharmacists' knowledge, perceptions and practices towards generic substitution in the 11 pilot locations in China.

Design: An online cross-sectional survey using questionnaires was conducted. A convenience sampling technique was implemented to recruit pharmacists.

Setting and participants: The study took place in medical institutions of 11 pilot locations that participated in the pilot national centralized procurement program in 2019. Two thousand, two hundred and ninety-one (2291) pharmacists including hospital pharmacists or community pharmacists based on health-systems or clinics participated in the study.

Results: Most of the participants had the good knowledge of requirements for evaluating the quality and efficacy of generic drugs (n=2118; 92.4%), and the definition of generic drugs (n=2078; 90.7%). In terms of perceptions, 67.3% of respondents were of the opinion that generic drugs are equally as effective as the brand-name drugs, and 69.0% of respondents were of the opinion that generic drugs are as safe as brand equivalents. A high percentage of participants supported the policy of generic substitution (n=1634; 71.4%). A significant positive correlation was demonstrated between total knowledge score and total perception score ($\rho = 0.267$; $P < 0.001$). Efficacy, safety, and the direction of national policies and hospital regulations were the main factors affecting pharmacists' willingness to dispense generic drugs.

Conclusions: The study identified gaps in respondents' knowledge and perceptions of generic substitution. Pharmacists who are more knowledgeable in generic drugs tend to hold a more supportive attitude towards generic substitution. Although it appeared that pharmacists in China have largely accepted generic substitution, they still have concerns regarding the reliability and quality of generic drugs. The current issues need to be addressed for the realization of the true value of generic drugs as part of the country's healthcare cost-containment strategy as well as the implementation of generic substitution policy in China.

Strengths and limitations of this study

- This cross-sectional study is one of the few surveys evaluating the knowledge, perceptions, and practices of pharmacists regarding generic drugs after implementing the national centralized procurement in China.
- The current findings have important implications in improvement of generic drugs policy and its implementation.
- This survey recruited a large number of respondents (n=2291). The Cronbach's alpha value for perceptions is equal to 0.833, indicating a good level of reliability.
- The web-based sample survey tool could be a limitation because of non-randomized sampling.
- This study was performed in only 11 locations in China, which could limit generalizability of the findings.

Introduction

Healthcare expenditures have been constantly increasing worldwide, [1, 2] and expenditure on drugs is one of the fastest growing components of healthcare spending.[3-5] Generic drugs offer an opportunity for substantial savings to healthcare systems. Currently, generic drug prescribing has become a major cost-minimizing strategy to reduce the fiscal expenditures and financial burden to patients, and to increase accessibility to essential drugs globally. The World Health Organization defined a generic drug as "a pharmaceutical product, usually intended to be interchangeable with an innovator product that is manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusive rights".[6] Generic substitution is defined as the act of substituting a brand-name drug with an equivalent generic drug.[7]

In China, overall medical expenditures accounted for 6.57% of the gross domestic product (GDP) in 2018.[8] Approximately 28% of medical expenditures came from the government [8]. Overall medical expenditures in China steadily increased between 2008 and 2017, at an average annual rate of 12.2%, outpacing the real GDP growth of 8.1%. [9] The per-capita drug consumption in China has risen to the highest in the world.[10]

Controlling drug expenses in public hospitals is vital in controlling overall medical expenditures. According to Alexandra's statistics,[11] due to the large volumes of medications consumed in public hospitals and a substantial price differential between the originator brand and lowest-priced generic products, 370 million U.S. dollars could be saved by switching only four drugs, saving patients an average of 65%. With the March 2019 implementation of the national centralized procurement program, generic substitution in China has become an irresistible trend. [12, 13] This program directed by the authorities was a new procurement model for drugs based on volume and bidding, with public institutions forming a procurement alliance.

China has become the second largest producer of pharmaceuticals in the world and is still growing rapidly.[14, 15] There are more than 8,135 pharmaceutical companies in China, most of which produce generic drugs. Ensuring that the large amounts of pharmaceutical products in the market are therapeutically equivalent has been challenging for Chinese authorities. Thus in 2013, the National Medical Products Administration (NMPA), formally known as the China Food and Drug Administration (CFDA), established a system to evaluate generic quality.[16] According to the regulations issued by the government in March 2016,[17] assessment of quality and efficacy via "consistency evaluation" is mandatory for generic drugs approved prior to 2007 in the National Essential Medicine List (2012). The NMPA requires that the 90% confidence interval of the geometric mean ratio for main pharmacokinetic parameters, the peak concentration (Cmax) and the area under concentration-time curve (AUC), of the product fall entirely within the range of 80.00%-125.00% in order to be bioequivalent.[18] By November 27, 2019, 323 drug products passed the consistency evaluation for quality and efficacy.[19] In the released NMPA standard reference product list, referenced products were selected from the brand equivalent or the same species acknowledged worldwide if the brand equivalent was not available.

The national centralized procurement program was approved by the State Council in January 2019 to significantly lower drug prices and to improve accessibility of drugs. Four municipalities and seven local cities were selected as the pilot cities, including Beijing, Tianjin, Shanghai, Chongqing, Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu, Xi-an. Twenty-five drug products were selected in the pilot program, of which 22 were generic drugs that had previously passed the consistency evaluation and 3 were brand-name drugs. Drug manufacturers bid to be

contracted in this pilot program, and the successful manufacturers established a contract with an agreed upon purchase amount. By setting up this contract, the drug purchase price dropped dramatically. Generic drugs accounted for 63% in the Chinese market in 2018.[20] Due to the drug price gap between brand drugs and generic drugs, the brand drugs are highly accessible in large cities, while generic drugs are more accessible in small cities or rural areas. After the implementation of the national centralized procurement policy, the price of selected generic varieties decreased, subsequently the brand drugs price significantly declined, which promote the access to the brand and generic drugs. The selected generic varieties almost accounted for all market shares among non-brand drugs in the pilot locations.[21] By the end of 2019, the pilot program was extended to more cities and provinces forming a procurement alliance, which covered nearly all the Chinese mainland. The generic substitution policy evolved from this pilot; because more generic drugs cheaper than the originator brand went into the procurement program under the bidding mechanism and made up a large market share.

As essential members of health care system, pharmacists play an important role in spreading awareness about the generic substitution policy. Pharmacists advise physicians on the selection, dosages, interactions, and side effects of generic drugs in collaboration practice, and provide education and counseling about generic drugs for patients when dispensing drugs according to medical prescription. The primary objective of this study was to investigate the knowledge, perceptions, and practices of Chinese pharmacists regarding generic substitution after completion of the pilot year.

Methods

Study design

A self-administered, anonymous, online cross-sectional survey was conducted among hospital pharmacists or community pharmacists based on health-systems or clinics in the 11 pilot locations in China between April and May 2020. The 11 pilot locations were those participated in the national centralized procurement program in 2019.

Questionnaire design

The questionnaire was developed in the Chinese language after extensive literature search and review. [22-28] The first draft of the questionnaire consisted of 32 items. The preliminary version of the questionnaire was peer-reviewed by 7 researchers, and assessed by 10 experts for appropriateness of clinical terminology, completeness, accuracy and logical sequence of the statements. Based on the suggestions, we refined it and deleted four items--the type of medical institutions, the familiarity with generic drugs, the knowledge of policy on generic drugs, and perceptions on access to generic drugs. Then the questionnaire was piloted among a sample of 20 hospital pharmacists in Beijing to test the reliability and validity of the questionnaire. The data of the pilot study (Supplemental file 1 Table S1 and Table S2) were not included in the final study's statistical analysis. Minor changes were made according to feedbacks on ambiguities. The final questionnaire consisted of 29 items (Supplemental file 2). Survey questions were created in the Wenjuanxing website and was divided into four sections (demographic information, knowledge about generic drugs, perceptions towards generic substitution and practices on generic substitution).

Section I. Demographic information

The first section assessed pharmacists' demographic data including respondents' age, gender, terminal degree, professional title, years in practice, secondary department (e.g., outpatient, inpatient, clinical, laboratory, etc.), and geographical location.

Section II. Knowledge about generic drugs

The second section contained five questions evaluating pharmacists' knowledge of the consistency evaluation for generic drugs and national policies related to the national centralized procurement program. For knowledge-based questions, respondents self-assessed their level of knowledge on these 3 questions by indicating either "yes", "no" or "unsure". Response of "yes" were given 1 point, and responses of "no" or "unsure" were scored zero. For true or false questions, correct responses were given 1 point, and a wrong or unsure response was scored zero. The maximum score on this knowledge section was 5 points.

Section III. Perceptions towards generic substitution

The third section explored pharmacists' perception of generic substitution with 10 items; a five-point Likert scale was used to measure the level of respondents' agreement with offered statements. Response of strong disagreement was given 1 point and strong agreement was given 5 point. For statistical reasons, the fifth question was reverse scored from 1(strong agreement) to 5 point (strong disagreement). The maximum score on this perception section was 50 points.

Section IV. Practices on generic substitution

In the fourth section, the practices, influencing factors, and difficulties related to generic substitution were examined. This section contained 5 multiple choice questions. For the last four questions, respondents were asked to select the top 3 important items.

Data collection

On April 14th, 2020, the Wenjuanxing hyperlink for this survey was shared with pharmacist groups in the 11 pilot locations in China using WeChat, a multipurpose messaging app. Informed consent from all respondents was gained prior to the commencement of the questionnaire. In order to submit the questionnaire, Respondents had to complete all fields. Respondents were given approximately three weeks to complete the survey. The online survey was closed on May 6, 2020. Data from the survey were synchronously collected using Wenjuanxing website as soon as each respondent had finished the questionnaire.

Inclusion and exclusion criteria

Pharmacists including hospital pharmacists or community pharmacists based on health-systems or clinics in the 11 locations were included in the survey. Data from other professionals in the medical institutions were excluded. Participation was voluntary; no incentive was provided for enrollment of participants.

Patient and public involvement

Patients and/or public were not involved in this research.

Statistical analysis

Data were analyzed with SPSS version 24. Reliability analysis (Cronbach alpha coefficient) of items focused on the perceptions towards generic substitution was applied. Normality of the data was tested using Kolmogorov-Smirnov test. If the data did not comply with the normal distribution, Mann-Whitney-U or Kruskal-Wallis tests were used to compare differences and Spearman's rank correlation was applied to determine associations among variables. P-values < 0.05 were considered significant.

Results

Demographics of respondents

A total of 2,291 pharmacists participated in the study. Nearly half of respondents (1,130; 49.3%) were in the age group of 30 to 39 years, and about a quarter of respondents (530; 23.1%) were in the group of 40 to 49 years. The majority of respondents 1,658 (72.4%) were female. The majority of pharmacists worked in a tertiary hospital setting (1,913; 83.5%) and had a bachelor's degree (1,487; 64.9%). Four hundred and forty-two (19.3%) of the respondents were senior pharmacists, 928 (40.5%) of the respondents were pharmacists-in-charge, and 867 (37.8%) were primary pharmacists. More details regarding the demographic and professional characteristics are presented in Table 1.

Table 1 Comparison of the total score of knowledge and perceptions across demographic characteristics.

Characteristics	Frequency (%) N=2291	Total score of knowledge (Mean ± SD)	*P*-value*	Total score of perceptions (Mean ± SD)	*P*-value*
Age(y)					
20-29	377 (16.5)	3.50 ± 0.984		36.85 ± 4.612	
30-39	1130 (49.3)	3.53 ± 0.989		37.10 ± 4.510	
40-49	530 (23.1)	3.71 ± 0.910	**0.000**	37.01 ± 4.527	0.349
50-59	244 (10.7)	3.68 ± 0.819		37.39 ± 4.257	
≥60	10 (0.4)	3.60 ± 0.966		37.30 ± 4.547	
Gender					
Male	633 (27.6)	3.66 ± 0.885	**0.011** †	37.61 ± 4.688	**0.000** †
Female	1658 (72.4)	3.55 ± 0.980		36.86 ± 4.415	
Terminal degree					
PhD	81 (3.5)	3.75 ± 0.783	**0.002**	35.96 ± 5.009	0.057
Years in practice					
Less than 5	424 (18.5)	3.56 ± 0.980		36.81 ± 4.436	
6-10	616 (26.9)	3.51 ± 0.971		37.24 ± 4.582	
11-20	632 (27.6)	3.55 ± 0.996	**0.008**	37.02 ± 4.628	0.417
21-30	424 (18.5)	3.70 ± 0.909		37.04 ± 4.304	
More than 30	195 (8.5)	3.68 ± 0.787		37.27 ± 4.422	
Level of medical institution					
Tertiary hospital	1913 (83.5)	3.60 ± 0.953		37.09 ± 4.493	
Secondary hospital	254 (11.1)	3.45 ± 1.011	0.071	36.65 ± 4.425	0.148
Community hospital	27 (1.2)	3.48 ± 1.051		36.67 ± 4.812	
Primary health care institution	97 (4.2)	3.65 ± 0.817		37.89 ± 4.761	

Master	460 (20.1)	3.75 ± 0.849		36.77 ± 4.269		**Location**					
Bachelor	1487 (64.9)	3.54 ± 0.973		37.23 ± 4.567		Beijing	551 (24.1)	3.66 ± 0.903		37.52 ± 4.693	
Others	263 (11.5)	3.47 ± 1.044		36.98 ± 4.319		Tianjin	190 (8.3)	3.70 ± 0.902		37.55 ± 4.554	
Professional title						Shanghai	178 (7.8)	3.53 ± 1.037		36.02 ± 4.929	
Chief pharmacist	143 (6.2)	3.90 ± 0.799		37.27 ± 4.344		Chongqing	102 (4.5)	3.75 ± 0.875		36.45 ± 4.099	
Associate chief pharmacist	299 (13.1)	3.75 ± 0.806		36.93 ± 4.334		Shenyang	187 (8.2)	3.55 ± 0.911		37.19 ± 4.584	
Pharmacist in charge	928 (40.5)	3.61 ± 0.879	**0.000**	37.07 ± 4.476	0.897	Dalian	261 (11.4)	3.62 ± 0.952	**0.000**	37.67 ± 4.488	**0.000**
Pharmacist	867 (37.8)	3.44 ± 1.077		37.09 ± 4.607		Xiamen	90 (3.9)	3.69 ± 0.895		37.27 ± 4.292	
No title (e.g. Intern)	50 (2.2)	3.48 ± 0.974		36.92 ± 4.844		Guangzhou	159 (6.9)	3.58 ± 0.957		36.23 ± 4.286	
others	4 (0.2)	4.00 ± 0.000		35.00 ± 3.162		Shenzhen	262 (11.4)	3.51 ± 0.942		36.97 ± 4.754	
						Chengdu	99 (4.3)	3.62 ± 0.765		36.86 ± 3.623	
						Xi-an	212 (9.3)	3.26 ± 1.182		36.52 ± 3.683	

Bold *P*-values represent statistical significance. **P*-value calculated using Kruskal-Wallis test. † *P*-value calculated using Mann-Whitney U test.

Knowledge about generic drugs

Knowledge of generic drugs was tested in five questions (for a total of five points), and the median knowledge score was 4.00 (mean ± SD: 3.58 ± 0.956). However, Table 1 shows statistically significant differences in knowledge scores related to variances in demographic and professional characteristics. Pharmacists within the range of 40-49 years had the highest score of knowledge (mean ± SD: 3.71 ± 0.989), followed by those of 50-59 years (mean ± SD: 3.68 ± 0.819) and more than 60 years (mean ± SD: 3.60 ± 0.966). Men scored significantly higher than women (mean: 3.66 versus 3.55; $P<0.05$). Among different levels of terminal degrees and professional titles, pharmacists with doctoral degrees (mean ± SD: 3.75 ± 0.783) higher professional titles (mean ± SD: 3.90 ± 0.799) were more knowledgeable of generic drugs.

Table 2 represents pharmacists' responses to the knowledge items. The vast majority of the respondents understood that the government has carried out the program of consistency evaluation (2,118; 92.4%), and that generic drugs selected in the national centralized procurement program have passed the consistency evaluation (2,067; 90.2%). A high percentage of pharmacists (1,718; 75.0%) reported they were aware of how to identify generics that have passed consistency. However, only 225 (9.8%) pharmacists correctly identified the pharmacokinetic parameters to be assessed in determining bioequivalence per consistency evaluation. Two thousand and seventy-eight (90.7%) of pharmacists identified the correct definition of a generic drugs have the same active ingredients, dosage forms, routes of administration and therapeutic effects as the brand name drug. Associations between knowledge items and characteristics are displayed in the Supplemental file 3 Table S3.

Table 2 Pharmacists' knowledge about generic drugs.

Statement	Yes or Correct response N (%)	No or Incorrect response N (%)	Unsure N (%)
Were you aware that China carries out the program of quality and efficacy consistency evaluation of generic drugs?	2118 (92.4)	74 (3.2)	99 (4.3)
Were you aware of the logo "Have passed the Consistency Evaluation" on the generic products?	1718 (75.0)	320 (14.0)	253 (11.0)
True/False: In principle, the method of bioequivalence tests in vivo is used for Consistency Evaluation. The standard of bioequivalence is that the 90% confidence interval of the geometric mean experiment/ reference ratios for main pharmacokinetic parameters (Cmax and AUC) falls entirely within the range of 90.00% ~ 120.00%.	225 (9.8)	1666 (72.7)	400 (17.5)
Were you aware that all the generic drugs in national centralized procurement have passed the consistency evaluation of quality and efficacy?	2067 (90.2)	68 (3.0)	156 (6.8)
True/False: The generic drugs in the national centralized procurement have the same active ingredients, dosage forms, routes of administration and therapeutic effects with the brand drugs.	2078 (90.7)	57 (2.5)	156 (6.8)

Perceptions towards generic substitution

Ten items were designed to assess attitudes on generic substitution. The Cronbach's alpha value for perception is equal to 0.833. The total median score was calculated to be 37.00 (mean ± SD: 37.07 ± 4.503). Men had a higher total perception score and thus more positive attitude regarding generic substitution (P<0.001; Table 1). Details on perceptions can be found in Table 3.

Table 3 Pharmacists' perceptions towards generic drugs.

Statement	Strongly Agree N (%)	Agree N (%)	Neutral N (%)	Disagree N (%)	Strongly Disagree N (%)
Generic drugs that have passed the consistency evaluation are as effective as brand-name equivalents.	361 (15.8)	1179 (51.5)	684 (29.9)	58 (2.5)	9 (0.4)
Generic drugs that have passed the consistency evaluation are as safe as brand-name equivalents.	355 (15.5)	1226 (53.5)	657 (28.7)	50 (2.2)	3 (0.1)
Generic drugs that have passed the consistency evaluation are less expensive than brand-name equivalents.	1076 (47.0)	987 (43.1)	218 (9.5)	10 (0.4)	0 (0.0)
Generic drugs that have passed the consistency evaluation are interchangeable with brand-name drugs.	314 (13.7)	1085 (47.4)	784 (34.2)	96 (4.2)	12 (0.5)
Replacing brand-name drugs with generic drugs that passed the consistency evaluation may change the clinical outcomes of medication treatment.	189 (8.2)	615 (26.8)	1047 (45.7)	387 (16.9)	53 (2.3)
Application of generic drugs that passed the consistency evaluation could improve adherence to medication treatment of patients.	228 (10.0)	873 (38.1)	1005 (43.9)	169 (7.4)	16 (0.7)
Health providers need to explain detailed information about generic drugs to patients in order to ensure that they correctly understand and use generic drugs.	640 (27.9)	1369 (59.8)	258 (11.3)	20 (0.9)	4 (0.2)
Generic drugs can be exempted from clinical trials for approval if they passed bioequivalence trials in vivo.	191 (8.3)	510 (22.3)	759 (33.1)	673 (29.4)	158 (6.9)
Relevant organizations should formulate and issue standard guidelines for generic substitution.	661 (28.9)	1312 (57.3)	296 (12.9)	20 (0.9)	2 (0.1)
I support the current policy of substituting brand-name drugs with generic drugs that have passed the consistency evaluation.	409 (17.9)	1225 (53.5)	619 (27.0)	32 (1.4)	6 (0.3)

About two-thirds of the respondents agreed that generic drugs that passed the consistency evaluation were as efficacious (1,540; 67.3%) or as safe (1,581; 69.0%) as the brand-name equivalent. A total of 2,063 (90.1%) respondents reported that generic drugs have significant cost-minimizing advantages over the brand-name drugs. One thousand and three hundred ninety-nine (61.1%) pharmacists were of the opinion that generic drugs that passed the consistency evaluation were interchangeable with the brand-name drugs; while 784 (34.2%) pharmacists held a neutral attitude towards interchangeability. Furthermore, 804 (35.0%) respondents believed that replacing the brand-name drugs with generic drugs may change clinical outcomes of medication treatment.

With regard to medication adherence, 1,101 (48.1%) respondents stated that the use of generic drugs could improve adherence to medication, but 1,005 (43.9%) respondents were neutral on this. A large percentage of respondents (2,009; 87.7%) recognized the importance of explaining detailed information about generic drugs to patients. While, a similar percentage of respondents (1,973; 86.2%) highlighted the need for standard guidelines for generic substitution, 701 (30.6%) thought that drugs that pass bioequivalence trials *in vivo* should be exempted from additional clinical trials before marketing. Seven hundred and fifty-nine (33.1%) pharmacists were neutral about this, and 831 (36.3%) disagreed. A large number of participant pharmacists (1,634; 71.4%) supported the national policy of generic substitution. A statistically significant association was found between geographic location and supportive attitudes toward generic substitution (P <0.001), see Supplemental file 3 Table S4. The highest percentage of pharmacists in favor of generic substitution were from Xiamen (78.9%), followed by Tianjin (77.4%) and Beijing (76.8%), while the lowest percentage were from Shanghai (53.3%) (see Supplemental file 3 Table S5).

A significant positive correlation was observed between pharmacists' perception on the efficacy and safety (ρ=0.761; P<0.001). The positive attitude towards either efficacy (ρ=0.681; P<0.001) or safety (ρ=0.640; P<0.001) of generic drugs was associated with generic interchangeability. There were also significant associations between generic interchangeability and support for generic substitution (ρ=0.602; P<0.001). In addition, a significant positive correlation was demonstrated between total knowledge score and total perception score (ρ= 0.267; P <0.001).

Practices on generic substitution

A total of 1,850 (80.8%) pharmacists noted increased use of generic drugs in their medical institutions, of whom 1046 (45.7%) reported a dramatically increased trend. Table 4 illustrates possible influencing factors related to dispensing and selection of generic drugs; most pharmacist respondents reported that the three main factors affecting their willingness to dispense generic drugs were efficacy (25.0%), safety (19.2%), and the direction of national policies and hospital regulations (18.7%).

Pharmacists reported that they think the top three factors patients considered when selecting generic drugs were efficacy of generic drugs (23.9%), preferences for brand-name drugs and medication habits (19.9%), and safety of generic drugs (17.4%). The most commonly cited difficulties in implementation of the centralized procurement and use of generic drugs were lack of trust in efficacy and safety (31.0%), challenge to change patients' preference (29.0%), and lack of time to provide patient education (23.6%). Suggestions for promoting generic substitution included encouraging generic substitution by health insurance policies (27.6%), publicizing these policies (25.5%), and educating health providers about generics and guidelines regarding their use (21.1%).

Table 4 Generic substitution practices.

Item	Statement	N (%)
How has the amount of generic drugs used in your medical institution changed after the implementation of national centralized procurement of drugs?	Significantly increased	1046 (45.7)
	Increased somewhat	805 (35.1)
	Basically unchanged	163 (7.1)
	Decreased	23 (1.0)
	Unsure	254 (11.1)
What factors do you think affect the selection of generic drugs? Please select the top 3 important items.	National policies and hospital regulations	1284 (18.7)
	Efficacy of generic drugs	1716 (25.0)
	Safety of generic drugs	1321 (19.2)
	Economy of generic drugs	686 (10.0)
	Accessibility of generic drugs and brand-name drugs	350 (5.1)
	Physicians' clinical expertise in medication treatment	324 (4.7)
	Patient’s financial burden	357 (5.2)
	Patients' willingness and preferences	548 (8.0)
	Promotion of drug representatives	94 (1.4)
	Reputation of generic drugs manufacturers	182 (2.6)
	Others	11 (0.2)
What factors do you think affect patients’ choice of selecting generic drugs in the national centralized procurement? Please select the top 3 important items.	Patients' preference for brand-name drugs and medication habits	1368 (19.9)
	Efficacy of generic drugs	1641 (23.9)
	Safety of generic drugs	1198 (17.4)
	Out-of-pockets cost of drugs	737 (10.7)
	Patient’s financial burden	888 (12.9)
	Physicians' suggestions	625 (9.1)
	National policies	412 (6.0)
	Others	4 (0.1)

What do you think is the largest challenge in implementing the national centralized procurement and use of generic drugs? Please select the top 3 important items.	There is no enough time to explain details to patients.	1621 (23.6)
	It is difficult to change patients' preference.	1992 (29.0)
	Lack of trust in the efficacy and safety of generic drugs.	2134 (31.0)
	There is an increased risk of errors in dispensing drugs.	529 (7.7)
	There is an increased cost in maintenance and manpower.	558 (8.1)
	Others	39 (0.6)
What measures should be taken to promote the national centralized procurement and use of generic drugs? Please select the top 3 important items.	Encourage patients to use generic drugs by use of health insurance policies.	1899 (27.6)
	Increase publicity of centralized procurement policies.	1751 (25.5)
	Educate health providers on centralized procurement policies and information about selected drugs.	1450 (21.1)
	Medical institutions should restrict the use of the brand-name drugs with the same generic name, and retain only the selected generic drugs.	513 (7.5)
	Medical institutions should restrict the use of all brand-name drugs with the same pharmacological action.	271 (3.9)
	Standard guidelines on generic substitution should be issued.	942 (13.7)
	Others	47 (0.7)

Discussion

This cross-sectional study is one of the few surveys evaluating the knowledge, perceptions, and practices of pharmacists regarding generic drugs after implementing the national centralized procurement in China. The Cronbach's alpha value for perception is equal to 0.833, indicating a good level of reliability. The total knowledge score (P<0.05) and the total perception score (P<0.05) were proven non-normally distributed using Kolmogorov-Smirnov test. Mann-Whitney-U or Kruskal-Wallis tests were used to compare differences.

This survey recruited a large number of respondents. In general, pharmacists had fair amount of knowledge regarding consistency evaluation and the definition of generic drugs. It appears that Chinese pharmacists are generally supportive of generic substitution; although, they still acknowledge some reservations regarding the quality, efficacy and safety of generic drugs. Measures such as encouraging generic substitution by health insurance programs, publicizing generic drugs policies, educating health providers about generics and guidelines regarding their use should be taken to promote generic substitution.

In this study, more than 90% of the respondents were aware of the definition of generic drugs. This was higher than some published studies, in other countries, like Poland,[29] Pakistan,[30] Malaysia,[31] and New Zealand. [32] In our study, few respondents (9.8%) identified the correct criteria for bioequivalence. This lack of knowledge on the robustness of regulatory requirements may lead to less confidence in the quality of generic drugs. In studies set in Palestine and US, community pharmacists were asked to identify the correct Food and Drug Administration (FDA) acceptance criteria for bioequivalence; a similar percentage of community pharmacists (12.6% vs 7.3%) provided the correct answer.[23, 33] Nearly 30% of respondents had a neutral attitude towards efficacy (29.9%), safety (28.7%) of generic drugs, and interchangeability with brand-name equivalents (34.2%). The reason may be that the quality of generic drugs may not be clearly evident in pharmacists' clinical practice sites since generic substitution had only been implemented for one year. Seventy one percent of Chinese pharmacists surveyed supported the national policy of generic substitution. These results were similar to various studies conducted in Iran (71.6%),[34] Poland (67.1%),[29] Saudi Arabia (68.5%),[22] Lebanon (64%),[35] while lower than that in Australia (93.7%), [36]Nigeria (92.9%),[37] French (90%), [38] Ireland (80%).[39]

It was interesting to find a significant positive correlation between total knowledge score regarding generics and total perception score, indicating that pharmacists who are more knowledgeable in generic drugs may hold a more supportive attitude towards generic substitution. This may suggest the importance of mass educational effort among pharmacists. More information on the issues of generic drugs makes pharmacists confident in using and dispensing those products. Besides, significant differences were observed by location in both knowledge and perception, which could lead to locational differences in the implementation of the generic substitution policy.

In more recent years, China has made a significant effort to promote generic substitution. The NMPA requires that generic drugs approved before 2007 must be proved bioequivalent with brand innovators by the end of 2021. Drug products that have not passed the consistency evaluation will no longer be selected for the national centralized drug procurement if more than three other generic drug manufacturers have passed. On average drug prices dramatically decreased by 52% of the selected drugs because of price negotiations and volume-based national centralized drug procurement.[40] In 2017, NMPA published Approved Drug Lists in China, similar to the U.S.'s

Orange Book, this list includes 17 varieties of approved generic drugs passed the consistency evaluation. Pharmaceutically equivalent products and therapeutically equivalent products are clearly coded in this list. However, further steps need to be taken to educate pharmacists.

To correct misconceptions on generic drugs, the NMPA should ensure that generic drugs meet quality standards by using the Good Manufacturing Practices. The generic drug approval process should be rigorous and transparent to the public. Negative perceptions and skepticisms can be reduced through education that will create more awareness about generic drugs and the importance of generic substitution among healthcare providers and patients. As some studies have demonstrated, information with regard to generic substitution should be taught in college curricula to better prepare healthcare providers for future work.[22, 31, 41-47]

One proposed measure that could be implemented to promote rational use of generic drugs is the establishment of standard operating procedures for generic substitution and formulary of the medical institutions.[31] Currently, generic drug use has been greatly encouraged in public hospitals in the 11 pilot locations. Although this national centralized procurement brought tremendous use of generic drugs, physicians tend to veer towards using brand-name drugs with the same pharmacological action when one brand-name drug was not accessible. A small number of our survey respondents agreed that in order to promote generic substitution medical institutions should restrict the use of brand-name drugs 513 (22.4%) and 271 (11.8%) responded that hospitals should only retain the corresponding generic drugs or drugs in the same pharmacologic drug class.

In this survey, only a few pharmacists reported other factors influencing patients' acceptance of generic substitution, such as patients' financial burden (12.9%), out-of-pockets cost of drugs (10.7%) and physicians' suggestions (9.1%). Currently, generic substitution has been supported by several Chinese health insurers, providing greater reimbursement for generic drugs (versus brand-name drugs). Many countries enacted generic drugs prices and reimbursement policy to promote generic substitution.[3, 4, 48-51] The survey respondents were from well-developed cities in China, so the difference in drug cost may not have been a barrier for these patients. However, cost-saving factor may be pivotal for patients in lower-income areas. A nationwide study conducted in Australian pharmacies demonstrated that the pharmacists' generic substitution recommendation rate in urban and rural areas was significantly higher than remote areas, while the patients' acceptance rate in remote areas was significantly higher than rural and urban areas.[52] Therefore, cost may not be the only incentive that should be offered to encourage generic substitution in high incomes aeras. In our study some of the respondents proposed that supply issues for generic drugs resulted in frequent medication changes and poor medication adherence. Therefore, supply guarantee of selected drugs and sustainability of formulary in the national procurement should be strengthened. The government should formulate regulations or acts for consistency evaluation of generic drugs and rigid quality supervision.

Pharmacists play a key role in managing rational use of medications, balancing between efficacy, safety and economic use of drugs. Pharmacotherapy monitoring and adverse drug reaction reporting should be emphasized to identify safety concerns regarding generic drugs. It is important for pharmacists to provide proper education to prevent patient confusion related to generic substitution and thus improve patient adherence. Pharmacists should also provide education and guidance to physicians and consumers on proper use of generic drugs. Only by understanding and appreciating the quality of generic drugs can patients and physicians have full confidence in generic substitution. Therefore, attitudes of pharmacists may be a crucial factor affecting the acceptance of

generics by both physicians and patients. Three systematic reviews identified that a significant proportion of physicians, pharmacists and patients hold negative perceptions of generic drugs, perceiving generics as less effective, less safe, and inferior in quality.[25-27] Physicians and patients expressed more negative opinions than pharmacists. All these publications indicated that negative attitudes present barriers to the generic substitution, and education of stakeholders was a requirement for increased usage of generics.

In some states in the U.S., pharmacists must substitute a generically equivalent drug if available. Other states allow the pharmacists to decide to provide substitution – if not otherwise indicated by the physician. And still other states impose an additional restriction that require pharmacists to obtain patients' consent before substituting with a generic product.[53-55] A study investigated the effects of state-level pharmacist regulations on generic substitution of prescription drugs and conclude that mandates generic substitution by pharmacists was found to have an insignificant effect.[55] A review on pharmaceutical regulation in 15 European countries demonstrated that pharmacists are entitled to substitution in Denmark, Germany, Ireland, Poland, and United Kingdom. Generic substitution are even mandatory for pharmacists in Belgium, Finland, Greece, Italy, Netherlands, Portugal, Spain, and Sweden, and incentivized in France.[51] Several studies from Lebanon, Palestine and Qatar concluded pharmacists should have authority to perform generic substitution without consulting the prescribing physician.[23, 35, 56] However, pharmacists do not have authority to modify medication orders to allow for substitution in China, they usually dispense drugs according to medical prescription, thus further progress needs to be made to improve this situation. We believe pharmacists may be authorized in implementing generic substitution for any medication in future.

There are some limitations for this research. This study was performed in 11 locations in China, and most respondents were from large public hospitals; therefore, findings cannot be generalized to pharmacists practicing in other cities in China. The survey had a limited access to pharmacists in community settings or rural areas. This also limits generalizability of the findings. The data were not collected from a random sample, which may weaken the representativeness and the results on the statistical significance of the differences and correlations presented about the data. Moreover, because of the web-based sample survey tool, we cannot compute a response rate to the questionnaire and adjust for possible non-response bias. In addition, due to the self-administered format of questionnaires, we cannot rule out the possibility of social desirability bias because the content of questionnaires about generic substitution correlates to the national policies and politics as well as the knowledge scores represent the respondents' perception.

This survey can serve as a preliminary study and is helpful in understanding the knowledge and perceptions of pharmacists on issues pertaining to generic drugs, and exploring the factors hindering and favoring generic substitution in China. The current findings have important implications in continuous improvement of generic drugs policy and its implementation. Future research is needed to explore physicians' and patients' perceptions and practices regarding the establishment of national centralized procurement and generic substitution program in China. Generic drugs on the market are required to be bioequivalent to the reference product; however, their therapeutic equivalence may not necessarily be identical, especially for narrow therapeutic index drugs.[47, 57-60] Therefore, evidence of the efficacy and safety of generic drugs should be obtained from real-world studies to prove therapeutic equivalence.

Conclusion

The study concluded that Chinese pharmacists have a fairly good knowledge of generic drugs used in the national centralized procurement program and generally have positive attitudes towards generic substitution. The main obstacle for further utilization of generic drugs is lack of trust in efficacy and safety. Education and awareness of generic substitution should be promoted and clear standard guidelines need to be created. All these issues need to be addressed for the realization of the true value of generic drugs as part of the country's healthcare cost-containment strategy as well as the implementation of generic substitution policy in China.

Acknowledgments

The authors would like to thank all the pharmacists who participated in the study. The authors would also like to express their gratitude to all the experts and researchers for providing feedback on this questionnaire.

Funding

This study was partially funded by Peking Pharmacological Society. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Author contributions

J.Q. led the overall study design, conducted the statistical analyses, interpreted the data, and wrote the first draft of the manuscript. W.Z. and B.Z. made the study design, collected the data, contributed to interpretation of findings and edited the manuscript. S.W., L.D., X.L., Y.G., J.L., X.D., and D.M. were involved in the design of the questionnaire. H.P., L.D., X.D., and D.M. participated in distributing the questionnaire. R.L.T., K.W.S., and S.L. contributed to editing the manuscript and interpretation of findings. All the authors read, made comments on manuscripts, approved the final manuscript and agreed on its submission.

Conflicts of Interest

The authors declare that they have no competing interest.

Ethical approval

The study was approved by the Institutional Review Board (IRB) of Peking Union Medical College Hospital in China (IRB#: S-K1136) and St. Louis College of Pharmacy in the USA (IRB#: 2020-18). Anonymity was ensured by gathering and analyzing data in aggregate and only allowing members of the research team access to the password-protected data.

Data availability statement

Data are available on reasonable request. The data generated and/or analyzed during the present study are not publicly available, but they are available from the corresponding author on reasonable request.

Supplemental files

Supplemental file 1. Table S1. Demographic characteristics of pharmacists in the pilot study. Table S2. Data of the pilot study.

Supplemental file 2. The final version of questionnaire.

Supplemental file 3. Table S3. Association between pharmacists' knowledge and demographic characteristics. Table S4. Association between pharmacists' perception and demographic characteristics. Table S5. Crosstabs between support for generic substitution and locations.

References

1. Squires D, Anderson C. U.S. health care from a global perspective: spending, use of services, prices, and health in 13 countries. *Issue Brief (Commonw Fund)*. 2015;15:1-15.
2. Hassali MA, Alrasheedy AA, McLachlan A, *et al*. The experiences of implementing generic medicine policy in eight countries: A review and recommendations for a successful promotion of generic medicine use. *Saudi Pharm J*. 2014;22(6):491-503.
3. Wouters OJ, Kanavos PG, McKEE M. Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. *Milbank Q*. 2017;95(3):554-601.
4. Wouters OJ, Kanavos PG. A comparison of generic drug prices in seven European countries: a methodological analysis. *BMC Health Serv Res*. 2017;17(1):242. Published 2017 Mar 31. doi:10.1186/s12913-017-2184-5.
5. Vogler S, Paris V, Ferrario A, *et al*. How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries. *Appl Health Econ Health Policy*. 2017;15(3):307-321.
6. World Health Organization. Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability. Available online: 2005http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_093Rev4_final.pdf, (accessed on 9th April 2020).
7. Posner J, Griffin JP. Generic substitution. *British Journal of Clinical Pharmacology*, 2011;72(5):731-2.
8. National Health Commission. Chinese Health Statistics Yearbook 2019. *National Bureau of Statistics: Beijing*, China, 2020.
9. Yip W, Fu H, Chen A T, *et al*. 10 years of health-care reform in China: progress and gaps in Universal Health Coverage. *The Lancet*, 2019, 394(10204):1192-1204.
10. Manning N. The Reform of Health Policy in China – Left Behind in the Race to Industrialize?. *Social Policy & Administration*, 2011, 45(6):649-661.
11. Cameron A, Mantel-Teeuwisse AK, Leufkens HG, *et al*. Switching from originator brand medicines to generic equivalents in selected developing countries: how much could be saved?. *Value Health*. 2012;15(5):664-673.
12. Hu L, Yu Z, Yuan Q, *et al*. Opportunities and Challenges of Multinational Pharmaceutical Enterprises in Transforming Pharmaceutical Market in China. *Ther Innov Regul Sci*. 2019;53(2):207-214.
13. Huang B, Barber SL, Xu M, *et al*. Make up a missed lesson-New policy to ensure the interchangeability of generic drugs in China. *Pharmacol Res Perspect*. 2017;5(3):e00318.
14. Lulin Z, Antwi HA, Wang W, *et al*. The effect of herd formation among healthcare investors on health sector growth in China. *Int J Equity Health*. 2016;15:113.
15. Zuo J, Gao Y, Bou-Chacra N, *et al*. Challenges and Opportunities to Use Biowaivers to Compare Generics in China. *AAPS PharmSciTech*, 2014, 15(5):1070-1075.
16. China Food and Drug Administration. Evaluation scheme of generic quality consistency. China Food and Drug Administration.2013. Available online: http://www.nmpa.gov.cn/WS04/CL2196/323980.html. (accessed on 31st May 2020).
17. State Council of the People's Republic of China. Notification on the carrying out consistency evaluation of the quality and efficacy of generic drugs. Available online:

http://www.gov.cn/zhengce/content/2016-03/05/content_5049364.htm. (accessed on 31st May 2020).

18. National Medical Products Administration. Guidelines on statistical analysis in bioequivalence studies and technology in bioequivalence studies of high-variation drugs. Available online: http://www.nmpa.gov.cn/WS04/CL2138/331454.html. (accessed on 31st May 2020).
19. State Council Information Office. Regular meeting on the State Council policy on 27th, November,2019. Available online: http://www.nhc.gov.cn/xcs/s7847/201911/dad7e0b2a26a4f56bd68836d33ab2fe2.shtml. (accessed on 8th August 2020).
20. Analysis and prediction of China's generic drug industry development status and scale in 2020. https://www.chyxx.com/industry/202005/860003.html. (accessed on 26th August 2021)
21. WANG Y，XU W，LU N, *et al*. Analysis of the effect of "4 + 7" centralized procurement policy implementation: Based on the drug sales data of 9 pilot regions. *Chinese Journal of Health Policy*,2021,14(2).
22. lkhuzaee FS, Almalki HM, Attar AY, *et al*. Evaluating community pharmacists' perspectives and practices concerning generic medicines substitution in Saudi Arabia: A cross-sectional study. *Health Policy*. 2016;120(12):1412-1419.
23. Shraim NY, Al Taha TA, Qawasmeh RF, *et al*. Knowledge, attitudes and practices of community pharmacists on generic medicines in Palestine: a cross-sectional study. *BMC Health Serv Res*. 2017;17(1):847.
24. Tsaprantzi AV, Kostagiolas P, Platis C, *et al*. The Impact of Information on Doctors' Attitudes Toward Generic Drugs. *Inquiry*. 2016 Mar 31;53:0046958016637791.
25. Colgan S, Faasse K, Martin LR, *et al*. Perceptions of generic medication in the general population, doctors and pharmacists: a systematic review. *BMJ Open*. 2015;5:e008915.
26. Toverud E-L, Hartmann K, Hakonsen H. A systematic review of physicians' and pharmacists' perspectives on generic drug use: What are the global challenges? *Appl Health Econ Health Policy*. 2015;13(Suppl 1):S35-S45.
27. Dunne SS, Dunne CP. What do people really think of generic medicines? A systematic review and critical appraisal of literature on stakeholder perceptions of generic drugs. *BMC Med*. 2015 Jul 29;13:173.
28. Dunne SS. What Do Users of Generic Medicines Think of Them? A Systematic Review of Consumers' and Patients' Perceptions of, and Experiences with, Generic Medicines. *Patient*. 2016 Dec;9(6):499-510.
29. Drozdowska A, Hermanowski T. Exploring factors underlying the attitude of community pharmacists to generic substitution: a nationwide study from Poland. *International Journal of Clinical Pharmacy*, 2016, 38(1):162-170.
30. Jamshed S, Hassali M, Ibrahim M, *et al*. Knowledge, perception and attitude of community pharmacists towards generic medicines in Karachi, Pakistan: a qualitative insight. *Trop J Pharm Res*. 2010;9(4).
31. Chua GN, Hassali MA, Shafie AA, *et al*. A survey exploring knowledge and perceptions of general practitioners towards the use of generic medicines in the northern state of Malaysia. *Health policy*.2010;95(2–3):229–35.
32. Babar ZU, Grover P, Stewart J, *et al*. Evaluating pharmacists' views, knowledge, and perception regarding generic medicines in New Zealand. *Res Social Adm Pharm*. 2011 Sep;7(3):294-305.

33. Euen BJ, Fadda HM. Community pharmacists' understanding and perceptions of FDA therapeutic equivalence standards. *Res Social Adm Pharm*. 2019 Jan;15(1):77-83.
34. Nazila Y, Gholamhossein M, Farzad P, *et al*. Generic substitution policy implementation: A pharmacists' perspective survey. *Journal of generic medicines*. 2015.
35. El-Jardali F, Fadlallah R, Morsi RZ, *et al*. Pharmacists' views and reported practices in relation to a new generic drug substitution policy in Lebanon: a mixed methods study. *Implement Sci*. 2017;12(1):23.
36. Ping CC, March G, Clark A, *et al*. A Web-Based Survey on Australian Community Pharmacists' Perceptions and Practices of Generic Substitution. *Journal of Generic Medicines*. 2010;7(4):342-353.
37. Auta A, Bala ET, Shalkur D. Generic medicine substitution: a cross-sectional survey of the perception of pharmacists in North-Central, Nigeria. *Med Princ Pract*. 2014;23(1):53-8.
38. Allenet B, Barry H. Opinion and behaviour of pharmacists towards the substitution of branded drugs by generic drugs: survey of 1,000 French community pharmacists. *Pharm World Sci*. 2003 Oct;25(5):197-202.
39. Dunne SS, Shannon B, Cullen W, *et al*. Perceptions and attitudes of community pharmacists towards generic medicines. *J Manag Care Spec Pharm*. 2014 Nov;20(11):1138-46.
40. China Daily. China to further pilot medicine procurement program. Available online: https://www.chinadaily.com.cn/a/201904/04/WS5ca5fe88a3104842260b4844.html. (accessed on 8th August 2020).
41. Shrank WH, Liberman JN, Fischer MA, *et al*. Physician perceptions about generic drugs. *Ann Pharmacother* 2011;45:31-8.
42. Al-Tamimi SK, *et al*. The need to incorporate generic medicines topic in the curriculum of Yemeni pharmacy colleges. *Int J Pharm Pract*. 2016;24(1):72-3.
43. Alrasheedy AA, Hassali MA, Aljadhey H, *et al*. The need to cover generic medications and generic substitution practice in the curricula of pharmacy colleges in Saudi Arabia. *Am J Pharm Educ*. 2014;78(5):108.
44. Domeyer PJ, Aletras V, Anagnostopoulos F, *et al*. Development and validation of a tool to assess knowledge and attitudes towards generic medicines among students in Greece: The ATtitude TOwards GENerics (ATTOGEN) questionnaire. *PLoS One*. 2017 Nov 29;12(11):e0188484.
45. Domeyer PJ, Katsari V, Sarafis P, *et al*. Greek students' attitudes, perception and knowledge regarding generic medicines in times of economic crisis: a cross-sectional study. *BMC Med Educ*. 2018 Nov 15;18(1):262.
46. James PB, Bah AJ, Margao EK, *et al*. Exploring the Knowledge and Perception of Generic Medicines among Final Year Undergraduate Medical, Pharmacy, and Nursing Students in Sierra Leone: A Comparative Cross-Sectional Approach. *Pharmacy (Basel)*. 2018 Jan 4;6(1):3.
47. Chong CP, Hassali MA, Bahari MB, *et al*. Exploring community pharmacists' views on generic medicines: a nationwide study from Malaysia. *Int J Clin Pharm*. 2011 Feb;33(1):124-31.
48. Mansfield SJ. Generic drug prices and policy in Australia: room for improvement? a comparative analysis with England. *Aust Health Rev*. 2014 Feb;38(1):6-15.
49. Ferrario A, Dedet G, Humbert T, *et al*. Strategies to achieve fairer prices for generic and biosimilar medicines. *BMJ*. 2020 Jan 13;368:l5444.

50. Rodwin MA. How the United Kingdom Controls Pharmaceutical Prices and Spending: Learning From Its Experience. *Int J Health Serv*. 2021 Apr;51(2):229-237.
51. Panteli D, Arickx F, Cleemput I, *et al*. Pharmaceutical regulation in 15 European countries review. *Health Syst Transit*. 2016 Oct;18(5):1-122.
52. Chong CP, March G, Clark A, *et al*. A nationwide study on generic medicines substitution practices of Australian community pharmacists and patient acceptance. *Health Policy*. 2011 Feb;99(2):139-48.
53. Assistant Secretary for Planning and Evaluation (ASPE) U.S. Department of Health and Human Services. Expanding the use of generic drugs. Available online: https://aspe.hhs.gov/basic-report/expanding-use-generic-drugs#Legislative. (accessed on 21st June 2020).
54. Darrow JJ, Chong JE, Kesselheim AS. Reconsidering the scope of US state laws allowing pharmacist substitution of generic drugs. *BMJ*. 2020 Jun 23;369:m2236.
55. Song Y, Barthold D. The effects of state-level pharmacist regulations on generic substitution of prescription drugs. *Health Econ*. 2018 Nov;27(11):1717-1737.
56. Awaisu A, Kheir N, Ibrahim MI, *et al*. Knowledge, attitudes, and practices of community pharmacists on generic medicines in Qatar. *Int J Clin Pharm*, 2014;36(2):394–404.
57. Sarpatwari A, Lee MP, Gagne JJ, *et al*. Generic Versions of Narrow Therapeutic Index Drugs: A National Survey of Pharmacists' Substitution Beliefs and Practices. *Clin Pharmacol Ther*. 2018 Jun;103(6):1093-1099.
58. Atif M, Azeem M, Sarwar MR. Potential problems and recommendations regarding substitution of generic antiepileptic drugs: a systematic review of literature. *Springer plus*. 2016 Feb 25;5:182.
59. Dunne S, Shannon B, Hannigan A, *et al*. Physician and pharmacist perceptions of generic medicines: What they think and how they differ. *Health Policy*. 2014.
60. Yamada M, Welty TE. Generic substitution of antiepileptic drugs: a systematic review of prospective and retrospective studies. *Ann Pharmacother*. 2011 Nov;45(11):1406-15.

Supplemental file 1

Table S1. Demographic characteristics of pharmacists in the pilot study.

Characteristics	Pharmacists N=20
Age(y)	
20-29	3
30-39	5
40-49	5
50-59	4
≥60	3
Gender	
Male	7
Female	13
Terminal degree	
PhD	3
Master	9
Bachelor	6
Others	2
Professional title	
Chief pharmacist	3
Associate chief pharmacist	4
Pharmacist in charge	6
Pharmacist	5
No title (e.g. Intern)	1
others	1
Years of experience	
Less than 5	5
6-10	5
11-20	6
21-30	3
More than 30	1

Table S2. Data of the pilot study.

Total score of knowledge (Mean ± SD)	3.85 ± 1.04
Total score of perceptions (Mean ± SD)	40.2 ± 5.16
Cronbach's alpha value for perceptions	0.732

Supplemental file 2

Knowledge, Perceptions and Practices of Pharmacists Regarding Generic Drugs in China

Part I: Demographic characteristics

1. What is your occupation?

A. Pharmacist

B. Other: _____

2. Which of the following range does your age fall in?

A. 20-29 years old

B. 30-39 years old

C. 40-49 years old

D. 50-59 years old

E. Over 60 years old

3. What is your gender?

A. Male

B. Female

4. What is your terminal education degree?

A. PhD

B. Master degree

C. Bachelor degree

D. Others

5. What is your secondary department?

A. Outpatient pharmacy

B. Inpatient pharmacy

C. Emergency Pharmacy

C. Pharmacy storage

D. Clinical pharmacy

E. Compounding room

F. Drug clinical trial institution / laboratory

G. Other:_____

6. What is your professional title?

A. Chief pharmacist

B. Associate chief pharmacist

C. Pharmacist in charge

D. Pharmacist

E. No title (e.g. Intern)

F. Other: _____

7. By the end of March 2020, how many years have you worked as a pharmacist?

A. Less than 5 years

B. 6-10 years

C. 11-20 years

D. 21-30 years

E. Over 30 years

8. Where are you from?

City _____, Province _____

9. What is the level of your medical institution?

A. Tertiary hospital

B. Secondary hospital

C. Community hospital

D. Primary healthcare institutions (including community health service center, township health center, village health office, clinics)

Part II: Knowledge of generic drugs

10. Were you aware that China carries out the program of quality and efficacy consistency evaluation of generic drugs? (hereinafter referred to as "Consistency Evaluation")?

A. Yes

B. No

C. Unsure

11. Were you aware of the logo "Have passed the Consistency Evaluation" on the generic products?

A. Yes

B. No

C. Unsure

12. For the standard criteria of bioequivalence, please judge whether the following statements are correct or not.

In principle, the method of bioequivalence tests in vivo is used for Consistency Evaluation. The standard of bioequivalence is that the 90% confidence interval of the geometric mean experiment/ reference ratios for main pharmacokinetic parameters

(Cmax and AUC) falls entirely within the range of 90.00% ~ 120.00%.

A. True

B. False

C. Unsure

13. Were you aware that all the generic drugs in national centralized procurement have passed the consistency evaluation of quality and efficacy?

A. Yes

B. No

C. Unsure

14. Please judge whether the following statement is correct or not.

The generic drugs in the national centralized procurement have the same active ingredients, dosage forms, routes of administration and therapeutic effects with the brand drugs.

A. True

B. False

C. Unsure

Part III: Perceptions of generic substitution

15. Generic drugs that have passed the consistency evaluation are as effective as brand-name equivalents.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

16. Generic drugs that have passed the consistency evaluation are as safe as brand-name equivalents.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

17. Generic drugs that have passed the consistency evaluation are less expensive than brand-name equivalents.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

18. Generic drugs that have passed the consistency evaluation are interchangeable with brand-name drugs.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

19. Replacing brand-name drugs with generic drugs that passed the consistency evaluation may change the clinical outcomes of medication treatment.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

20. Application of generic drugs that passed the consistency evaluation could improve

adherence to medication treatment of patients.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

21. Health providers need to explain detailed information about generic drugs to patients in order to ensure that they correctly understand and use generic drugs.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

22. Generic drugs can be exempted from clinical trials for approval if they passed bioequivalence trials in vivo.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

23. Relevant organizations should formulate and issue standard guidelines for generic substitution.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

24. I support the current policy of substituting brand-name drugs with generic drugs that have passed the consistency evaluation.

☐Strongly agree ☐Agree ☐Neutral ☐Disagree ☐Strongly disagree

Part IV: Practices of generic substitution

25. How has the amount of generic drugs used in your medical institution changed after the implementation of national centralized procurement of drugs?

A. Significantly increased

B. Increased somewhat

C. Basically unchanged

D. Decreased

E. Unsure

26. What factors do you think affect the selection of generic drugs? Please select the top 3 important items.

☐ National policies and hospital regulations

☐ Efficacy of generic drugs

☐ Safety of generic drugs

☐ Economy of generic drugs

☐ Accessibility of generic drugs and brand-name drugs

☐ Physicians clinical expertise in medication treatment

☐ Patients financial burden

☐ Patients willingness and preferences

☐ Promotion of drug representatives

☐ Reputation of generic drugs manufacturers

☐ Other:_____

27. What factors do you think affect patients' choice of selecting generic drugs in the national centralized procurement? Please select the top 3 important items.

☐ Patients preference for brand-name drugs and medication habits

☐ Efficacy of generic drugs

☐ Safety of generic drugs

☐ Out-of-pockets cost of drugs

☐ Patients financial burden

☐ Physicians suggestion s

☐ National policies

☐ Other:_____

28. What do you think is the largest challenge in implementing the national centralized procurement and use of generic drugs? Please select the top 3 important items.

☐ There is no enough time to explain details to patients.

☐ It is difficult to change patients preference.

☐ Lack of trust in the efficacy and safety of generic drugs.

☐ There is an increased risk of errors in dispensing drugs.

☐ There is an increased cost in maintenance and manpower.

☐ Other:_____

29. What measures should be taken to promote the national centralized procurement and use of generic drugs? Please select the top 3 important items.

☐ Encourage patients to use generic drugs by use of health insurance policies.

☐ Increase publicity of centralized procurement policies.

☐ Educate health providers on centralized procurement policies and information about selected drugs.

☐ Medical institutions should restrict the use of the brand-name drugs with the same generic name, and retain only the selected generic drugs.

☐ Medical institutions should restrict the use of all brand-name drugs with the same pharmacological action.

☐ Standard guidelines on generic substitution should be issued.

☐ Other:_____

That's all. Thank you very much for the participation!

Supplemental file 3.

Table S3 Association between pharmacists' knowledge and demographic characteristics.

Statement	Yes or Correct response N (%)	No or Incorrect response N (%)	Unsure N (%)	Age (P-value) *	Terminal Degree (P-value) *	Years of experience (P-value) *	Professional title (P-value) *	Gender (P-value) †	Location (P-value) †	Medical Institution (P-value) †
Were you aware that China carries out the program of quality and efficacy consistency evaluation of generic drugs?	2118 (92.4)	74 (3.2)	99 (4.3)	0.142	**0.000**	0.447	**0.000**	0.155	**0.026**	0.794
Were you aware of the logo "Have passed the Consistency Evaluation" on the generic products?	1718 (75.0)	320 (14.0)	253 (11.0)	**0.010**	0.129	0.070	0.068	**0.020**	**0.000**	0.450
True/False: In principle, the method of bioequivalence tests in vivo is used for Consistency Evaluation. The standard of bioequivalence is that the 90% confidence interval of the geometric mean experiment/	225 (9.8)	1666 (72.7)	400 (17.5)	0.052	0.164	0.734	0.096	0.251	**0.000**	0.254

reference ratios for main pharmacokinetic parameters (Cmax and AUC) falls entirely within the range of 90.00% ~ 120.00%.										
Were you aware that all the generic drugs in national centralized procurement have passed the consistency evaluation of quality and efficacy?	2067 (90.2)	68 (3.0)	156 (6.8)	0.094	0.153	0.076	**0.001**	0.097	**0.003**	0.449
True/False: The generic drugs in the national centralized procurement have the same active ingredients, dosage forms, routes of administration and therapeutic effects with the brand drugs.	2078 (90.7)	57 (2.5)	156 (6.8)	0.338	0.104	0.467	**0.046**	0.213	**0.047**	0.108

Bold *P*-values represent statistical significance.

* P-value calculated using Kruskal-Wallis test.

† P-value calculated using Chi-square.

Table S4 Association between pharmacists' perceptions and demographic characteristics.

Statement	Strongly Agree N (%)	Agree N (%)	Neutral N (%)	Disagree N (%)	Strongly Disagree N (%)	Agree (P-value) *	Gender (P-value) †	Terminal Degree (P-value) *	Years of experience (P-value) *	Location (P-value) *	Professional title (P-value) *	Medical institution (P-value) *
Generic drugs that have passed the consistency evaluation are as effective as brand-name equivalents.	361 (15.8)	1179 (51.5)	684 (29.9)	58 (2.5)	9 (0.4)	0.752	**0.000**	**0.000**	0.400	**0.001**	**0.004**	0.582
Generic drugs that have passed the consistency evaluation are as safe as brand-name equivalents.	355 (15.5)	1226 (53.5)	657 (28.7)	50 (2.2)	3 (0.1)	0.572	**0.001**	**0.000**	0.441	0.269	**0.016**	0.554
Generic drugs that have passed the consistency evaluation are less expensive than brand-name equivalents.	1076 (47.0)	987 (43.1)	218 (9.5)	10 (0.4)	0 (0.0)	0.312	**0.030**	**0.000**	0.464	0.108	0.131	0.099
Generic drugs that have passed the consistency evaluation are interchangeable with brand-name drugs.	314 (13.7)	1085 (47.4)	784 (34.2)	96 (4.2)	12 (0.5)	0.074	**0.000**	**0.000**	0.050	**0.000**	0.188	0.131
Replacing brand-name drugs with generic drugs that passed the consistency evaluation may change the clinical outcomes of	53 (2.3)	387 (16.9)	1047 (45.7)	615 (26.8)	189 (8.2)	**0.000**	**0.002**	0.062	**0.001**	**0.000**	**0.000**	0.190

medication treatment.*												
Application of generic drugs that passed the consistency evaluation could improve adherence to medication treatment of patients.	228 (10.0)	873 (38.1)	1005 (43.9)	169 (7.4)	16 (0.7)	0.029	**0.022**	**0.002**	**0.037**	**0.042**	**0.003**	0.204
Health providers need to explain detailed information about generic drugs to patients in order to ensure that they correctly understand and use generic drugs.	640 (27.9)	1369 (59.8)	258 (11.3)	20 (0.9)	4 (0.2)	0.415	**0.033**	**0.028**	0.167	0.143	0.119	0.151
Generic drugs can be exempted from clinical trials for approval if they passed bioequivalence trials in vivo.	191 (8.3)	510 (22.3)	759 (33.1)	673 (29.4)	158 (6.9)	0.075	**0.024**	**0.001**	0.128	**0.002**	0.593	**0.034**
Relevant organizations should formulate and issue standard guidelines for generic substitution.	661 (28.9)	1312 (57.3)	296 (12.9)	20 (0.9)	2 (0.1)	0.503	0.051	**0.000**	0.415	**0.033**	**0.005**	0.217
I support the current policy of substituting brand-name drugs with generic drugs that have passed the consistency evaluation.	409 (17.9)	1225 (53.5)	619 (27.0)	32 (1.4)	6 (0.3)	0.135	**0.000**	0.051	0.410	**0.000**	0.662	**0.026**

Bold *P*-values represent statistical significance.

*P-value calculated using Kruskal-Wallis test.

† P-value calculated using Mann-Whitney U test.

Table S5 Crosstabs between support for generic substitution and locations.

N (%)	Beijing	Tianjin	Shanghai	Chongqing	Shenyang	Dalian	Xiamen	Guangzhou	Shenzhen	Chengdu	Xi-an	Total
Agreed	423 (76.8%)	147 (77.4%)	95 (53.3%)	66 (64.7%)	127 (67.9%)	189 (72.4%)	71 (78.9%)	104 (65.4%)	191 (72.9%)	71 (71.7%)	150 (70.7%)	1634 (71.3%)
Neutral	118 (21.4%)	43 (22.6%)	76 (42.7%)	34 (33.3%)	55 (29.4%)	70 (26.8%)	18 (20.0%)	52 (32.7%)	66 (25.2%)	26 (26.3%)	61 (28.8%)	619 (27.0%)
Disagreed	10 (1.8%)	0 (0.0%)	7 (4.0%)	2 (2.0%)	5 (2.7%)	2 (0.8%)	1 (1.1%)	3 (1.9%)	5 (1.9%)	2 (2.0%)	1 (0.5%)	38 (1.7%)
Total	551 (100.0%)	190 (100.0%)	178 (100.0%)	102 (100.0%)	187 (100.0%)	261 (100.0%)	90 (100.0%)	159 (100.0%)	262 (100.0%)	99 (100.0%)	212 (100.0%)	2291 (100.0%)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page, Line Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page1, line3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page2, line2-25
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page3 to Page4, line20
Objectives	3	State specific objectives, including any prespecified hypotheses	Page4, line 18-20
Methods			
Study design	4	Present key elements of study design early in the paper	Page4, line 22-26
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page4, line 22 to Page5, line26
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page5, line30-34
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page5, line1-21
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page5, line1-21, Table1
Bias	9	Describe any efforts to address potential sources of bias	Page4, line28-40 and Page5, line25-29
Study size	10	Explain how the study size was arrived at	Page5, line25-29
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page5, line38-43
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page5, line38-43
		(*b*) Describe any methods used to examine subgroups and interactions	Table1, TableS5
		(*c*) Explain how missing data were addressed	Page5, line25-26
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page5, line38-43
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page5, line30-34
		(b) Give reasons for non-participation at each stage	Page5, line30-34
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic,	Page6, line1-9 and

		clinical, social) and information on exposures and potential confounders	Table1
		(b) Indicate number of participants with missing data for each variable of interest	Page5, line25-26
Outcome data	15*	Report numbers of outcome events or summary measures	Page9-15 (Table2,3,4)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table1
		(*b*) Report category boundaries when continuous variables were categorized	Table1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table1, Table S5
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page16, line8-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page18, line22-32
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page16, line15 to Page18, line21
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page18, line22-42
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page19, line 12-14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.