Evaluating the National System for Rare Diseases in China from the Point of Drug Access: Progress and Challenges

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Abstract

Background: There are about 7000 rare diseases worldwide, of which only 5% of the diseases can be treated with medicines, showing that it's important to improve patient access to orphan drugs. Recently, China has actively worked to set up a national system for rare diseases to improve the diagnosis and treatment capabilities and ensure the accessibility of drugs. However, the benefits of the system have yet not to be measured. This study aimed to provide an overview of orphan drug access based on the Compendium of China's First List of Rare Diseases and National Network to Collaborate on Diagnosis and Treatment of Rare Diseases, expecting to map a blueprint for orphan drug access in China.

Methods: Framework of China's national system for rare diseases was summarized. We surveyed the availability and affordability of 79 approved orphan drugs based on the Compendium of China's First List of Rare Diseases in 30 leading provincial institutions from 2017 to 2020. The availability was measured annually at 3 levels (market, hospital and drug), and affordability was reflected by comparing costs of daily defined dose with per capita income of urban and rural residents, with the National Basic Medical Insurance considered.

Results: The market availability of orphan drugs in China showed an upward trend. As of 2020, the median hospital-level availability was 41.1% (increased by 1.5 times), highly available drugs increased by 16.5%. There were 64 / 74 orphan drugs that were affordable to rural/urban residents with the National Basic Medical Insurance considered (an increase of 14.1%), and the urban-rural gap of affordability ratio was narrowed (down by 6.0%). Comprehensive analysis showed the proportions of drugs with better availability and affordability in urban and rural areas by 2020 were 26.53% and 21.43%, respectively, which had increased but were still at a low level.

Conclusions: China's national system for rare diseases has made great progress in orphan drug access, indicating that it's been functioning under the joint reformation of medical treatment, medical insurance and medicines supply. The list of rare diseases will be updated and collaboration in networks will be enhanced to further improve the system.

Background

Rare diseases are diseases that affect a small number of the population. Although every single rare disease affects only an extremely limited number of patients, which is defined as affects no more than 1 person in 2000 in Europe and affects less than 200000 people in the United States. There are a total of 7000 rare diseases along with 250 to 280 new additional ones annually(1, 2). Rare diseases impact more people than cancer and AIDs, and approximately 30% of patients with rare diseases die before the age of 5(3). Although rare diseases vary in etiology and clinical manifestations, most of them are associated with significant disease burden(4, 5).

Orphan drugs are intended to treat, prevent or diagnose rare diseases. It was estimated that 95% of rare diseases are lacking drug treatments, demonstrating that the accessibility of orphan drugs is critical(3). In addition, the high price of orphan drugs poses challenges for both patients and governments. For example, the annual cost of eculizumab is over $409,500, which is used to treat Paroxysmal nocturnal haemoglobinuria, and the annual cost of idursulfase is over $375,000, which is used to treat Mucopolysaccharidosis II.(6) Affordability of orphan drugs is a serious public health issue in China, as they are in other countries. A survey made by the Chinese Organization for Rare Disorders (CORD) with 5810 patients registered in 2019 showed that the employment rate for CORD adult patients was only 40%, and 80% of the income is spent on disease management. Poverty caused by the significant disease burden is a common experience for them and their families(7). Orphan drugs, which account for a large proportion of treatment spending, deserves more attention.

The Orphan Drug Act was enacted in 1983 in the US. Only 10 orphan drugs had been approved by the US Food and Drug Administration (FDA) in the decade before 1983, while more than 350 orphan drugs had been approved by 2010. The Orphan Drug Act also inspired similar policies in Singapore, Australia, Japan and Europe(8). China's attention to rare diseases started late. However, in recent years, the importance of orphan drugs has gradually appeared in various policy documents. For example, the Compendium of China's First List of Rare Diseases (2018) (CLRD), which includes 121 rare diseases(9), first clarified the concept and scope of rare diseases in China. Besides, the CLRD has made China the first country to delineate the boundaries of rare diseases in the form of a catalogue. The National Network to Collaborate on Diagnosis and Treatment of Rare Diseases (NCDTRD) was established in China in 2019, consisting of 324 hospitals nationwide, including 1 leading national institution (Peking Union Medical College Hospital), and 32 leading provincial institutions, achieving rare disease resource sharing(10). As the core contents of the national system for rare diseases in China, they played a key role in solving problems of rare diseases.

Improving orphan drugs access is a core priority for China's policies. There have been studies assessing access to orphan drugs in Europe, the U.S., and South Africa(11–14). However, very few studies have assessed the availability and affordability of orphan drugs in China, and most of them were made before release of the CLRD and NCDTRD(15, 16). In comparison, for the first time on the basis of CLRD and NCDTRD, we evaluated the accessibility of orphan drugs that have been approved for CLRD indication in the U.S.(17), EU(18), Japan(19) and China in 30 leading provincial institutions of NCDTRD, exploring the concrete effects of the China's national system from the point of drug access.

Results

The National System for Rare Diseases in China

The national system of rare diseases in China currently carries out from three aspects: information collection and clinical research, diagnosis and treatment, as well as drug policies (Fig. 1). Specifically, the CLRD has made China the first country to define rare diseases in form of a catalogue, and it is an important foundation of the system that guides the development of other policies. The management of rare diseases is a complex and systematic work. It's evident from the China's national system that the rare diseases had received a high national attention and widespread social concern, especially in drug policies.

From policy support to legal protection, China is gradually establishing a multi-party cooperation system for rare diseases and realizing resource integration, although it still needs continuous efforts to improve. The effectiveness of the system is urgently needed to be testified.

Availability

Market availability Among the surveyed drugs with CLRD definitions, the average time lag was 8.9 years (SD, 11.3) after the U.S., 2.1 years (SD, 10.9) after EU, and 5.3 years (SD, 12.9) after Japan until 2020. The number of surveyed orphan drugs approved from 2017 to 2020 is 20, exceeding the total number of orphan drugs approved in the 10-year period from 2007 to 2016 by 15. Among them, 27.8% of them were approved in 2017, 2018 and 2019 respectively and 16.7% were approved in 2020. In addition, according to the International Classification of Diseases 11th Revision (ICD-11),(20) "endocrine, nutritional and metabolic diseases", "diseases of the nervous system" and "diseases of blood or hematopoietic organs" were in the top 3, accounting for 34.7%, 26.5% and 14.3%, respectively. Idiopathic pulmonary hypertension had the most approved drugs (9 drugs), followed by Parkinson's disease (young-onset, early-onset) and Multiple sclerosis, with 8 approved drugs each.

Hospital-level availability Of the total drugs, seven of them were not found in 30 institutions. The hospital-level availability of the remaining drugs nationwide and in 3 areas showed a significant upward trend from 2017 to 2020 (Table 1). By 2020, it reached 41.1% nationwide and 43.0% in eastern area. The increase of availability at hospital level in 2020 was significantly higher than that in 2018 ($P = 0.01$) and 2019 ($P = 0.006$), which meant that the availability in 2020 is significantly improved. The proportion of imported and domestic drugs was 65.3% and 56.9% as of 2020, among which 22.2% had both imported and domestic drugs, domestic drugs accounted for more than half. In addition, the majority of drugs were available in single dosage forms, seven drugs were available in two dosage forms, while Sirolimus is available in three dosage forms: tablet (imported), oral liquid and capsule (domestic) (Additional file 1: Table S1 shows the brand names and dosage forms of surveyed drugs in China.).

Table 1
Median Availability of Orphan Drugs at Hospital Level in China From 2017 to 2020 (%).

Year (numbers of Marketed Orphan Drugs)	Nationwide		Eastern Area		Middle Area		Western Area		
	Availability (IQR)[a]	Median of Hospital-Specific Change (IQR)[b]	Availability (IQR)	Median of Hospital-Specific Change (IQR)	Availability (IQR)	Median of Hospital-Specific Change (IQR)	Availability (IQR)	Median of Hospital-Specific Change (IQR)	p Value[c]
2017	27.2 (10.4)		31.0 (8.9)		24.7 (27.8)		27.2 (7.9)		
2018	32.9 (10.1)	1.9 (5.1)	34.8(18.7)	1.9 (3.1)	25.3 (32.3)	1.3 (4.7)	32.9 (10.1)	3.2 (6.6)	0.000
2019	34.8 (11.4)	1.9 (3.5)	36.1 (19.3)	2.5 (5.4)	30.4 (29.1)	3.2 (2.8)	34.2 (10.1)	1.3 (4.7)	0.000
2020	41.1 (12.3)	5.1 (7.6)	43.0 (20.3)	3.2 (10.8)	36.7 (27.8)	5.1 (9.2)	36.7 (14.6)	8.9 (9.2)	0.000

[a]: IQR: interquartile range, equals to the difference between 75th and 25th percentiles. [b]: Median of hospital-specific change is defined as the median of orphan drug availability annual change in each hospital. [c]: p value of Wilcoxon rank-sum test for the difference of orphan drugs' average availability at hospital level between eastern, western, and middle areas each year.

Drug-level availability Overall, the availability at drug level nationwide was 43.3% until 2020, with no significant difference among areas. The median availability in nationwide and in 3 areas also showed a growing trend from 2017 to 2020 (Additional file 2: Table S2 shows the median availability of orphan drugs at drug-level in China from 2017 to 2020 (%); Additional file 3: Table S3 shows the availability classification of orphan drugs at drug-level in China from 2017 to 2020 (%)). Cumulative frequency distribution of availability at drug level from 2017 to 2020 was shown in Fig. 2. According to the WHO and Health Action International (HAI) classification criteria, about 77.2% and 62.1% of surveyed drugs were "low" availability, while 0.0% and 16.1% were at "high" level in 2017 and 2020, respectively. There was a huge leap in 2020 compared to 2017. Atorvastatin for Homozygous familial hyperlipidemia, which could be obtained in 29 hospitals, had the highest availability.

Affordability

Cost In order to ensure the accuracy of the survey, taking into account the different indications and dosage forms correspond to different daily defined dose (DDD) values of the same drug, 99 drug-single indication matches were found among 72 drugs available in 30 hospitals. The median unit prices of drugs ranged from $0.00015 /mg (Hydroxyurea) to $8574.8 /mg (Nusinersen). By 2020, the median defined daily dose cost (DDDc) is $7.7, which is equivalent to 0.4 days' income for urban residents and 1.1 days' income for rural residents without the National Basic Medical Insurance (NBMI) considered. National DDDc showed a slight upward trend from 2017 to 2020 (Additional file 4: Table S4 shows the cost of DDD (DDDc) for surveyed orphan drugs from 2017 to 2020 in China (USD).)

Affordability In general, the range of the number of days a resident had to work under average daily income to pay for the DDDc of each drug was from 0.00004-day Tranexamic acid to 1052.9-day Coagulation factor VIIa. The maximum value of days decreased year by year, from 388.6 days in 2017 to 288.5 days in 2020 in urban areas, and from 1052.9 days in 2017 to 738.5 days in 2020 in rural areas. A total of 20 surveyed drugs were included in Part A, 3 of which were imported drugs. Besides, 27 drugs were included in Part B in 2018, 6 of which were imported drugs, while 42 drugs were included Part B in 2020, 18 of which were imported drugs. Among them, 7 drugs (Teriflunomide, etc.) were included into Part B after 2018 through price negotiation. It can be seen that the proportion of orphan drugs increased, and the reimbursement of imported drugs increased. We further analyzed the affordability under NBMI and

price negotiation, the affordability rate of rural residents rose from 50.5% in 2018 to 64.6% in 2020, and that of urban residents rose from 60.6% in 2018 to 74.7% in 2020 (Additional file 5: Table S5 shows the affordability for surveyed orphan drugs from 2018 to 2020 in China (USD); Additional file 6: Table S6 shows the affordability of surveyed orphan drugs in China among eastern areas, middle areas and western areas in 2020). It was found that NBMI significantly increased the affordability of orphan drugs, and reduced the urban-rural gap. By 2020, Alpha-galactosidase A for Fabry disease is the most unaffordable drug for residents, whose cost of one day's treatment is equivalent to 142.7 days' income of urban residents and 365.2 days' income of rural residents. This was followed by Imiglucerase for Gaucher's disease (124.9 days in urban, 319.7 days in rural) and Alglucosidase alfa for Glycogen storage disease (82.9 days in urban, 212.3 days in rural) (Table 2). All 3 drugs were not included in NBMI during the survey.

Table 2
Affordability of surveyed orphan drugs in China in 2020.

NO	Generic name	Indication	Dosage form	Median Unit Price (USD)[1]	Defined Daily Dose[2]	Coverage of NBMI (Y/N)	2020 Affordability		Affordability (if 5% OOP)	
							U	R	U	R
1	Edaravone	Amyotrophic lateral sclerosis	Injection	0.11/mg	60mg	N	Y	Y	Y	Y
2	Riluzole	Amyotrophic lateral sclerosis	Tablets	0.07/mg	100mg	Y, Part B	Y	N	Y	Y
3	Amantadine Hydrochloride	Parkinson Disease (Young-onset, Early-onset)	Tablets	0.0002/mg	200mg	Y, Part A	Y	Y	Y	Y
4	Apomorphine Hcl	Parkinson Disease (Young-onset, Early-onset)	Tablets	_#	75mg	Y, Part A	_#	_#	_#	_#
5	Droxidopa	Multiple System Atrophy	Capsules	0.01/mg	900mg	Y, Part B	Y	N	Y	Y
6	Droxidopa	Parkinson Disease (Young-onset, Early-onset)	Capsules	0.01/mg	900mg	Y, Part B	Y	N	Y	Y
7	Levodopa And Carbidopa (Sinemet)	Parkinson Disease (Young-onset, Early-onset)	Tablets	0.001/mg	250mg	Y, Part B	Y	Y	Y	Y
8	Levodopa And Carbidopa (Stalevo)	Parkinson Disease (Young-onset, Early-onset)	Tablets	0.004/mg	325mg	Y, Part B	Y	Y	Y	Y
9	Selegiline Hcl	Parkinson Disease (Young-onset, Early-onset)	Tablets	0.10/mg	10mg	Y, Part B	Y	Y	Y	Y
10	Ropinirole	Parkinson Disease (Young-onset, Early-onset)	Tablets	2.40/mg	0.75mg	Y, Part B	Y	Y	Y	Y
11	Pramipexole	Parkinson Disease (Young-onset, Early-onset)	Tablets	3.32/mg	2.44mg	Y, Part B	Y	N	Y	Y
12	Rasagiline	Parkinson Disease (Young-onset, Early-onset)	Tablets	6.20/mg	1mg	Y, Part B	Y	Y	Y	Y
13	Siponimod	Multiple Sclerosis	Tablets	17.79/mg	2mg	N	N	N	N	N
14	Idebenone	Progressive muscular dystrophy	Tablets	0.02/mg	675mg	N	Y	N	Y	N
15	Idebenone	Leber's hereditary optic neuropathy	Tablets	0.02/mg	900mg	N	Y	N	Y	N
16	Pyridostigmine Bromide	Generalized Myasthenia Gravis	Tablets	0.002/mg	270mg	Y, Part A	Y	Y	Y	Y
17	Neostigmine	Generalized Myasthenia Gravis	Injection	2.01/mg	1.25mg	Y, Part A	Y	Y	Y	Y
18	Baclofen	Hereditary spastic paraplegia	Tablets	0.02/mg	60mg	Y, Part B	Y	Y	Y	Y
19	Baclofen	Multiple Sclerosis	Tablets	0.02/mg	60mg	Y, Part B	Y	Y	Y	Y
20	Teriflunomide	Multiple Sclerosis	Tablets	2.96/mg	7mg	Y, Part B	N	N	Y	Y
21	Fingolimod Hydrochloride	Multiple Sclerosis	Capsules	88.68/mg	0.5mg	N	N	N	N	N
22	Nusinersen	Spinal Muscular Atrophy	Injection	8574.75/mg	0.1mg	N	N	N	N	N
23	Tizanidine	Multiple Sclerosis	Tablets	0.20/mg	18mg	Y, Part B	Y	Y	Y	Y
24	Tizanidine	Amyotrophic Lateral Sclerosis	Tablets	0.20/mg	18mg	Y, Part B	Y	Y	Y	Y
25	Antihemophilic Factor Ⅷ ª	Hemophilia	Injection	0.59/IU	1750IU	Y, Part B	N	N	N	N

[1]: Use the minimum specifications as the standards about the investigated drugs. Translated the price and took the median values as analysis objects; [2]: In the calculations, we used the following average values: adult weight at 70 kg, children 15 kg, baby 1.5 kg; the body surface area at 1.7 m^2. "U": for urban residents. "R": for rural residents. "NBMI": National Basic Medical Insurance. "Part A" or "Part B" means a drug is covered by the Part A or Part B drug list of National Basic Medical Insurance. "OOP": out-of-pocket expenses. Y = Yes N = No. Y: The affordability of drugs changed from "N" to "Y" after NMBI.

#: Apomorphine HCl was absent in 2020.

NO	Generic name	Indication	Dosage form	Median Unit Price (USD)[1]	Defined Daily Dose[2]	Coverage of NBMI (Y/N)	2020 Affordability		Affordability (if 5% OOP)	
							U	R	U	R
26	Coagulation Factor IX a	Hemophilia	Injection	1.21/IU	1750IU	Y, Part B	N	N	N	N
27	Coagulation Factor Viia	Hemophilia	Injection	808.82/mg	6.3mg	Y, Part B	N	N	N	N
28	Human Prothrombin Complex a	Hemophilia	Injection	0.14/IU	1750IU	Y, Part B	N	N	Y	N
29	Tranexamic Acid (Tranexamic Acid and Sodium Chloride Injection)	Hemophilia	Injection	0.008/mg	1.375mg	Y, Part B	Y	Y	Y	Y
30	Tranexamic Acid (Tranexamic Acid Injection)	Hemophilia	Injection	0.002/mg	1.375mg	Y, Part A	Y	Y	Y	Y
31	Tranexamic Acid (Tranexamic Acid Tablets)	Hemophilia	Tablets	0.0006/mg	4000mg	Y, Part B	Y	Y	Y	Y
32	Danazol	Hereditary Angioedema (HAE)	Capsules	0.001/mg	400mg	Y, Part B	Y	Y	Y	Y
33	Treprostinil	Idiopathic pulmonary arterial hypertension	Injection	72.24/mg	0.04mg	N	Y	Y	Y	Y
34	Selexipag	Idiopathic pulmonary arterial hypertension	Tablets	40.44/mg	3.2mg	Y, Part B	N	N	Y	Y
35	Tadalafil	Idiopathic pulmonary arterial hypertension	Tablets	0.66/mg	40mg	N	N	N	N	N
36	Ambrisentan	Idiopathic pulmonary arterial hypertension	Tablets	0.67/mg	10mg	Y, Part B	Y	Y	Y	Y
37	Iloprost Inhalation Solution	Idiopathic pulmonary arterial hypertension	Inhalation	3516.62/mg	0.03 mg	N	N	N	N	N
38	Sildenafil Citrate	Idiopathic pulmonary arterial hypertension	Tablets	0.12/mg	60mg	N	Y	N	Y	N
39	Riociguat	Idiopathic pulmonary arterial hypertension	Tablets	3.62/mg	7.5mg	Y, Part B	N	N	N	Y
40	Macitentan	Idiopathic pulmonary arterial hypertension	Tablets	2.03/mg	10mg	Y, Part B	N	N	Y	Y
41	Bosentan Hydrate	Idiopathic pulmonary arterial hypertension	Tablets	0.06/mg	250mg	Y, Part B	Y	N	Y	Y
42	Evolocumab	Homozygous familial hypercholesterolaemia	Injection	1.36/mg	14 mg	N	N	N	N	N
43	Rosuvastatin	Homozygous familial hypercholesterolaemia	Tablets	0.08/mg	20mg	Y, Part B	Y	Y	Y	Y
44	Simvastatin	Homozygous familial hypercholesterolaemia	Tablets	0.006/mg	40mg	Y, Part A	Y	Y	Y	Y
45	Atorvastatin	Homozygous familial hypercholesterolaemia	Tablets	0.045/mg	45mg	Y, Part B	Y	Y	Y	Y
46	Atorvastatin	Homozygous familial hypercholesterolaemia	Capsules	0.002/mg	45mg	Y, Part B	Y	Y	Y	Y
47	Ezetimibe	Homozygous familial hypercholesterolaemia	Tablets	0.10/mg	10mg	Y, Part B	Y	Y	Y	Y
48	Ezetimibe	Sitosterolemia	Tablets	0.10/mg	10mg	N	Y	Y	Y	Y

[1]: Use the minimum specifications as the standards about the investigated drugs. Translated the price and took the median values as analysis objects; [2]: In the calculations, we used the following average values: adult weight at 70 kg, children 15 kg, baby 1.5 kg; the body surface area at 1.7 m^2. "U": for urban residents. "R": for rural residents. "NBMI": National Basic Medical Insurance. "Part A" or "Part B" means a drug is covered by the Part A or Part B drug list of National Basic Medical Insurance. "OOP": out-of-pocket expenses. Y = Yes N = No. Y: The affordability of drugs changed from "N" to "Y" after NMBI.

[#]: Apomorphine HCl was absent in 2020.

NO	Generic name	Indication	Dosage form	Median Unit Price (USD)[1]	Defined Daily Dose[2]	Coverage of NBMI (Y/N)	2020 Affordability		Affordability (if 5% OOP)	
							U	R	U	R
49	Alirocumab	Homozygous familial hypercholesterolaemia	Injection	3.70/mg	10.7mg	N	N	N	N	N
50	Ivabradine	Idiopathic Cardiomyopathy	Tablets	0.25/mg	5mg	Y, Part B	Y	Y	Y	Y
51	Mexiletine Hydrochloride	Congenital Myotonia Syndrome (Non-Dystrophic Myotonia, NDM)	Tablets	0.0004/mg	333mg	Y, Part A	Y	Y	Y	Y
52	Immune Globulin Infusion (Human)	Multifocal motor neuropathy	Injection	0.04/mg	3.38mg	Y, Part B	Y	Y	Y	Y
53	Nintedanib	Idiopathic Pulmonary Fibrosis	Capsules	0.23/mg	300mg	N	N	N	N	N
54	Nintedanib	Systemic Sclerosis	Capsules	0.23/mg	300mg	N	N	N	N	N
55	Pirfenidone	Idiopathic Pulmonary Fibrosis	Capsules	0.02/mg	1800mg	Y, Part B	N	N	Y	Y
56	Pirfenidone	Idiopathic Pulmonary Fibrosis	Tablets	0.02/mg	1800mg	Y, Part B	N	N	Y	Y
57	Everolimus	Lymphangioleiomyomatosis(LAM)	Tablets	3.82/mg	10mg	Y, Part B	N	N	Y	Y
58	Everolimus	Tuberous sclerosis complex	Tablets	3.82/mg	8.5mg	Y, Part B	N	N	Y	Y
59	Sirolimus	Lymphangioleiomyomatosis	Tablets	5.98/mg	2mg	N	Y	N	Y	N
60	Sirolimus	Lymphangioleiomyomatosis	Oral Solution	3.05/mg	2mg	N	Y	Y	Y	Y
61	Sirolimus	Lymphangioleiomyomatosis	Capsules	5.51/mg	2mg	N	Y	N	Y	N
62	Tocilizumab	Systemic Sclerosis	Injection	1.53/mg	23.14mg	N	N	N	N	N
63	Tocilizumab	Castleman disease	Injection	1.53/mg	40mg	N	N	N	N	N
64	Cyclophosphamide Hydrate	Fanconi anemia	Injection	0.02/mg	150mg	Y, Part A	Y	Y	Y	Y
65	Cyclophosphamide Hydrate	Generalized Myasthenia Gravis	Injection	0.02/mg	600mg	Y, Part A	Y	N	Y	Y
66	Tacrolimus Hydrate	Generalized myasthenia gravis	Capsules	3.39/mg	3mg	Y, Part B	Y	N	Y	Y
67	Interferon Beta-1b (Recombinant)	Multiple Sclerosis	Injection	181.74/mg	0.125mg	N	N	N	N	N
68	Mitoxantrone	Multiple Sclerosis	Injection	0.85/mg	0.23mg	Y, Part B	Y	Y	Y	Y
69	Vemurafenib	Erdheim-Chester	Tablets	0.07/mg	1920 mg	Y, Part B	N	N	Y	Y
70	Filgrastim	Severe Congenital Neutropenia	Injection	75.49/mg	0.84mg	Y, Part B	N	R	Y	Y
71	Hydroxycarbamide	Sickle-cell disease	Tablets	0.00015/mg	1575mg	Y, Part A	Y	Y	Y	Y
72	Colchicine	Familial Mediterranean fever (FMF)	Tablets	0.06/mg	1.8mg	Y, Part A	Y	Y	Y	Y
73	L-Glutamine (Marzulene-S)	Sickle cell disease	granule	0.0004/mg	21000mg	N	Y	N	Y	N
74	L-Glutamine (Glutamine And Guaiazulene Sulfonate Sodium Grannules)	Sickle cell disease	granule	0.0002/mg	21000mg	N	Y	Y	Y	Y
75	Levocarnitine (Levocarnitine For Injection)	Primary carnitine deficiency	Injection	0.005/mg	3500mg	N	Y	N	Y	N

[1]: Use the minimum specifications as the standards about the investigated drugs. Translated the price and took the median values as analysis objects; [2]: In the calculations, we used the following average values: adult weight at 70 kg, children 15 kg, baby 1.5 kg; the body surface area at 1.7 m^2. "U": for urban residents. "R": for rural residents. "NBMI": National Basic Medical Insurance. "Part A" or "Part B" means a drug is covered by the Part A or Part B drug list of National Basic Medical Insurance. "OOP": out-of-pocket expenses. Y = Yes N = No. Y: The affordability of drugs changed from "N" to "Y" after NMBI.

[#]: Apomorphine HCl was absent in 2020.

NO	Generic name	Indication	Dosage form	Median Unit Price (USD)[1]	Defined Daily Dose[2]	Coverage of NBMI (Y/N)	2020 Affordability		Affordability (if 5% OOP)	
							U	R	U	R
76	Levocarnitine (Levocarnitine Oral Solution)	Primary carnitine deficiency	Oral solution	0.001/mg	4000mg	Y, Part B	Y	Y	Y	Y
77	Miglustat	Gaucher's Disease	Capsules	0.19/mg	300mg	N	N	N	N	N
78	Miglustat	Niemann-Pick Disease	Capsules	0.19/mg	600mg	Y, Part B	N	N	Y	Y
79	Miglustat	Fabry Disease	Capsules	0.19/mg	200mg	N	N	N	N	N
80	Alglucosidase Alfa	Glycogen Storage Disease	Injection	14.65/mg	100mg	N	N	N	N	N
81	Imiglucerase [a]	Gaucher's Disease	Injection	7.35U	300U	N	N	N	N	N
82	Follitropin Alfa, Recombinant [a]	Idiopathic hypogonadotropic hypogonadism	Injection	0.49IU	112.5IU	N	N	N	N	N
83	Sapropterin Hydrochloride	Hyperphenylalaninemia	Tablets	0.43/mg	700mg	N	N	N	N	N
84	Sapropterin Hydrochloride	Phenylketonuria	Tablets	0.43/mg	700mg	N	N	N	N	N
85	Sapropterin Hydrochloride	Tetrahydrobiopterin Deficiency	Tablets	0.43/mg	700mg	N	N	N	N	N
86	Ceramide Trihexosidase/Alpha-Galactosidase A	Fabry Disease	Injection	251.97/mg	10mg	N	N	N	N	N
87	Desmopressin Acetate	Hemophilia	Injection	506.17/mg	0.042mg	Y, Part A	N	N	Y	Y
88	Desmopressin Acetate	Hemophilia	Tablets	8.49/mg	0.1mg	Y, Part A	Y	Y	Y	Y
89	Hydrocortisone	Congenital Adrenal Hypoplasia	Tablets	0.007/mg	20mg	Y, Part A	Y	Y	Y	Y
90	Hydrocortisone	21-Hydroxyulase Deficiency	Tablets	0.007/mg	21.25mg	Y, Part A	Y	Y	Y	Y
91	Hydrocortisone	21-Hydroxyulase Deficiency	Injection	0.004/mg	21.25mg	Y, Part A	Y	Y	Y	Y
92	Hydrocortisone	Generalized Myasthenia Gravis	Injection	0.004/mg	17.5mg	Y, Part A	Y	Y	Y	Y
93	Somatropin	Noonan Syndrome	Injection	7.01/mg	0.99mg	N	Y	N	Y	N
94	Somatropin	Prader-Willi Syndrome	Injection	7.01	0.525mg	N	Y	Y	Y	Y
95	Penicillamine	Hepatolenticular Degeneration (Wilson Disease)	Tablets	0.0009/mg	875mg	Y, Part A	Y	Y	Y	Y
96	Dimercaptosuccininic Acid	Hepatolenticular Degeneration (Wilson Disease)	Capsules	0.003/mg	875mg	Y, Part A	Y	Y	Y	Y
97	Zinc Suisate	Hepatolenticular Degeneration (Wilson Disease)	Oral solution	0.02/mg	661.8mg	N	Y	N	Y	N
98	Cholic Acid	Inborn errors of bile acid synthesis	Capsules	0.005/mg	1050mg	Y, Part A	Y	Y	Y	Y
99	Sodium Cholate	Inborn Errors of Bile Acid Synthesis	Tablets	0.0003/mg	250mg	N	Y	Y	Y	Y

[1]: Use the minimum specifications as the standards about the investigated drugs. Translated the price and took the median values as analysis objects; [2]: In the calculations, we used the following average values: adult weight at 70 kg, children 15 kg, baby 1.5 kg; the body surface area at 1.7 m^2. "U": for urban residents. "R": for rural residents. "NBMI": National Basic Medical Insurance. "Part A" or "Part B" means a drug is covered by the Part A or Part B drug list of National Basic Medical Insurance. "OOP": out-of-pocket expenses. Y = Yes N = No. Y: The affordability of drugs changed from "N" to "Y" after NMBI.

[#]: Apomorphine HCl was absent in 2020.

Comprehensive analysis We presented four quadrant diagrams by the drug-level availability and affordability in 2018 and 2020 with NBMI considered (Fig. 3). From 2018 to 2020, the number of drugs with better availability and affordability in quadrant IV increased among urban and rural residents. The proportion of drugs with better availability and affordability was 26.53% in urban areas and 21.43% in rural areas by 2020, respectively, which was still at a low level although rising.

Discussion

In this study, we conducted an annual and regional comparative analysis of access to orphan drugs in China, hoping to provide a reference for the development of countries with a late start in rare diseases in the world by taking the national system in China as an example.

There are four main findings in this study. First, the market availability of orphan drugs in China is still relatively low in 2020. However, the number of drugs approved between 2017 and 2020 exceeds the number approved in the decade 2007 to 2016, indicating that the implementation of the China's national system for rare diseases played an important role in the increasement of market availability. Meanwhile, there are thirteen orphan drugs for ten rare diseases of the CLRD were approved in China in 2021, making a huge leap in access to orphan drugs. In addition, it should also be noted that compared with other 3 countries, and the marketing time of surveyed drugs still lagged behind, indicating that the R&D of orphan drugs were still the top priority of rare disease management in China. The high market accessibility rare diseases (endocrine, nutritional and metabolic diseases, etc.) reflects the morbidity and treatment needs of rare diseases in China (oncology and infectious diseases are not included in the CLRD). Second, the availability of surveyed drugs increased year by year in 3 areas and in nationwide. In 2020, the hospital-level availability increased to more than 1.5 times that of 2017, with domestic drugs accounting for more than half, indicating that the China's national system has achieved significant results. Seven drugs were absent in the surveyed institutions, five of them were approved 5 years before 2020. The reasons for the delay of hospital orphan drugs access may be related to the low ability of diagnosis and treatment, the immature procurement and management system of orphan drugs. In addition, the availability at drug level also showed an increasing trend by year and by region, which also confirmed the remarkable effect of the system. However, it should also be noted that the proportion of "high" availability drugs remained low (16.5%), and the availability of high-price drugs was low. By 2020, Alpha-galactosidase A, Imiglucerase and Alglucosidase alfa, the top three most unaffordable orphan drugs for residents under NBMI, were all in the "very low" grade of availability (3.3%). Thirdly, the median DDDc increased by year during 2017–2020, which may be related to the newly approved high-price orphan drugs encouraged by rare disease policies in recent years. Our results show that the average DDDc of newly approved drugs in the four years is $54.0, $56.4, $865.3 and $35.6, respectively. Moreover, these are beyond the affordable range of urban residents in 2020 (equivalent to 2.0–49.0 days of urban residents' income from work) and rural residents' affordable range (equivalent to 5.2-125.4 days of rural residents' income from work), which also confirms our conclusions above. Finally, the economic burden of patients with rare diseases is decreasing, but the overall affordability is still not optimistic. By 2020, the affordability rate was 64.6% in rural areas and 74.7% in urban areas, respectively, but the proportion of better availability and affordability drugs was still not unfavorable (26.53% in urban areas after NBMI). The list of Part A and Part B includes 62.6% of the surveyed drugs. The proportion of surveyed orphan drugs included in Part B increased from 27.3–42.4% during our survey, and the proportion of imported drugs also increased significantly, further explaining that the NBMI has attached more importance to rare disease drugs. Teriflunomide and other 7 drugs have been included in Part B reimbursement through price negotiation after 2018. After being reimbursed, all 7 drugs have changed from unaffordable to affordable. It further indicates that the price negotiation system and NBMI play an important role in the affordability of orphan drugs, and significantly narrow the affordability gap between urban and rural areas. In addition, although the availability and affordability of orphan drugs has increased, it is still at a low level, deep reasons behind that deserve further discussion.

Definitions of rare diseases and orphan drugs Compared with the US, the EU and Japan, the definition of rare diseases in China has not been fundamentally resolved for a long time (21). Considering national conditions, the definition will coexist with the updated list for a period of time to come. It should become the main reference for the definition of orphan drugs in China, and the change of the two corresponds.

Orphan drug incentive polices There are two barriers to R&D of orphan drugs: first, the number of patients with rare diseases is fairly small, and many diseases have not yet developed accurate diagnosis and treatment level; second, return on investment is an issue that drug institutions must consider, while orphan drugs rely on more advanced instruments, which means greater investment and risks.(22) In the US, orphan drug clinical research costs can be tax-deductible by 50%, with extended tax-deductible periods and tax relief for orphan drugs. Exempting applicants for orphan drugs from FDA review fees, and a 7-year market monopoly period. In China, it's better to direct the incentives toward orphan drugs with low availability, and more specific incentives are needed to establish targeted subsidies for orphan drugs. In addition, further promote the use of real-world research in orphan drugs, an orphan drug import tariff reduction system and a free public platform for all stakeholders to share information on orphan drugs also need to be developed. International cooperation will play a crucial role in the response to rare diseases (23).

Orphan drug payment China has a breakthrough in the guarantee of high-price orphan drugs as of 2020. Nusinersen for spinal muscular atrophy and Alglucosidase alfa for Fabre disease have been included in the National Catalogue of Medical Insurance (24) .However, there's still a lot of room for the improvement in China's payment system for orphan drugs. The current payment system in China includes four parts: first, the NBMI which covers most of the population; followed by Critical Illness Insurance, charity programs and commercial insurance. There are many factors influence the medical insurance payment, so it's necessary to evaluate the risks, ethics, fairness and sustainability. Multi-criteria decision analysis (MCDA) has recently been considered as a proper tool for orphan drug payment research(25–28). International experience shows that multi-party healthcare payment is the ideal model for orphan drugs, and China should consider developing matching payment schemes, such as installment payment and efficacy insurance.(29) In addition, there have been a number of donated drug projects in China, including hemophilia, pulmonary hypertension, multiple sclerosis drugs and so on.

Hospital orphan drug management It's challenging for the diagnoses and treatment of rare diseases. The establishment of the collaboration network is a good demonstration, but the specific resource scheduling of the huge collaboration network still needs to be considered. Doctors' professionalism of rare diseases also needs to be enhanced, especially in primary institutions (30, 31). At present, online multi- disciplinary team (MDT) for rare diseases with primary institutions is a referable approach, but it's not a fundamental solution (10). In addition, there is no clear orphan drugs procurement policies and use of norms, and no special management measures in the hospital pharmacy in China. A study to assess the accessibility of explicit diagnosis of rare diseases in Chinese adults showed that about 72.97% of patients were misdiagnosed, and patients waited an average of 4.30 times and visited 2.97 hospitals before being diagnosed (32). In the future, more attention should be paid to the uneven distribution of medical networks for rare diseases and quality medical services.

Talent training of rare diseases In terms of early drug development, the lack of domestic talent remains a key problem. Talent introduction and internal training are two ways, and talent development also needs a process. There may be a shortage of early talent in the field of rare diseases in China, and it is urgent to cultivate talents compared to more popular fields such as oncology, immunity and metabolic diseases.

Patient organizations of rare diseases There is a certain information block between patients with rare diseases and drug development institutions, and patient organizations can play an important role in this process. The National Organization for Rare Disorders in the US, EURODIS in Europe and Canadian Organization for Rare Disorders have played an important role in leading the development of orphan drug legislation, supporting patients, raising awareness and sponsoring academic research (1, 33–35). The number of patient organizations in China has grown rapidly in recent years. However, these organizations are lack of training, play no role of promoting legislative agenda, and generally not active in the academic research. It's hoped that with the implementation of government policies, the awareness of rare diseases can be better deepened in China.

Limitation In addition, this study has certain limitations. First of all, this study evaluates orphan drugs based on the CLRD, but this list is not very comprehensive, which makes the scope of rare disease drugs relatively narrow. It covers limited types of rare diseases, mainly genetic diseases, and lacks rare tumors and rare infectious diseases, which makes the evaluation data of orphan drugs not comprehensive enough. Second, we measured affordability based on the average income of urban and rural residents, which may not reflect affordability for low- and high-income groups. Finally, our measure of affordability does not take into account other diagnostic or treatment costs, which may make our results an overestimated of actual affordability. It is one-sided to measure the effectiveness of China's rare disease policies only from the perspective of orphan drug access, and more factors should be considered.

Conclusions

Although there is still a gap compared to countries with early development of rare diseases, the accessibility of orphan drug in China improved by year from 2017 to 2020, which preliminary verified that the national system for rare diseases in China has made significant achievements in terms of orphan drug access. This study maps the accessibility of orphan drugs in China. In the future, China will continue to update the CLRD and strengthen the cooperation among the institutions of the national network, thus gradually improving national system for rare diseases in China.

Methods
Data sources

We developed a questionnaire to collect the price and availability information of 79 orphan drugs in 30 leading provincial institutions based on the WHO/HAI methodology.

Selection of diseases and medications

There are 121 rare diseases included in the CLDR (9). Strictly exclude symptomatic drugs, we selected 79 drugs with the CLRD indications and been approved in the U.S. (17), EU (18), Japan (19)(36) and China. Further, the Anatomical Therapeutic Chemical (ATC) classification system was used to identify the ATC code for each drug (Additional file 7: Table S7 shows the lists of 79 orphan drugs surveyed in 30 public tertiary hospitals in China (99 drug-indication matches) .) (37)

Survey and selection of medical facilities

We surveyed the availability and prices of 79 orphan drugs in 30 leading provincial institutions of NCDTRD. The leading provincial institutions are selected based on the evaluation of the diagnosis and treatment capacity of rare diseases in each province. Therefore, we believe that our data can reflect the status of orphan drug access in China. Considering the economic disparities China, 30 institutions from 29 provinces were classified into 3 areas: eastern, middle and western. (Additional file 8: Table S8 shows the list of the surveyed 30 leading provincial institutions of the National Network to Collaborate on Diagnosis and Treatment of Rare Diseases in China.)

Measures and analysis

Based on the analytical framework of WHO/HAI methodology, we measured accessibility of orphan drugs from availability and affordability with economic disparities considered.

Availability Orphan drug availability in China was measured annually at market level, hospital level and drug level from 2017 to 2020 by nonproprietary name. In this study, market availability refers to the time lag in the approval of orphan drugs in China compare to international (the U.S., EU and Japan). Hospital-level availability is the percentage of orphan drugs that can be found in a particular institution, while drug-level availability is the percentage of hospitals in which a particular orphan drug can be found in all surveyed hospitals. Using Wilcoxon rank-sum test to compare the differences of availability between years and areas. Differences in availability across years and regions were compared using the Wilcoxon rank-sum test.

- Absent (0%): none of these orphan drugs were found in the surveyed institutions;
- Very low (< 30%): these orphan drugs were difficult to find in the surveyed institutions;
- Low (30–49%): these orphan drugs were not easy to find;
- Fairly high (50–80%): these orphan drugs were available at many of the surveyed institutions;
- High (80%): these orphan drugs were available in most institutions with good availability.

Costs

According to the WHO Collaborative Center for Drug Statistics Methodology, we calculate the DDDc for each orphan drug by its DDD. We estimated the DDD of each orphan drug based on the official drug label. Differences in availability across years and regions were compared using the Wilcoxon rank-sum test.

DDDc = Median unit price of drug reported by institutions × DDD

The median price of unit dose was calculated based on the price per unit dose we collected from each institution (Additional file 9: Table S9 shows the median unit prices of generic orphan drugs surveyed in 30 leading provincial institutions in China from 2017–2020 (USD)).

Affordability

Affordability was measured as the number of days a lowest paid unskilled government worker worked to pay for a treatment course for a particular drug based on the WHO/HAI methodology. We searched disposable daily income per capita of urban residents and net daily income per capita of rural residents published in the China Statistical Yearbook from 2017 to 2020 (Additional file 10: Table S10 shows the daily disposable income per capita of urban or rural residents from 2017 to 2020 in China) (38). Because most rare diseases required lifelong medication, we measured affordability to compare the DDDc with residents' average daily income in this study. The NBMI is the most comprehensive social medical insurance provided by the Chinese government, covering Part A and Part B drugs. Drugs included in Part A are free for people covered by NBMI, while 5%-20% out-of-pocket expenses (OOPs) for Part B drugs. In addition, the price negotiation system in China was considered (Additional file 11: Table S11 shows the coverage of NBMI of surveyed orphan drugs in China from 2017–2020) (39).

Abbreviations

CORD
Organization for Rare Disorders
FDA
Food and Drug Administration
CLRD
Compendium of China's First List of Rare Diseases (2018)
NCDTRD
National Network to Collaborate on Diagnosis and Treatment of Rare Diseases
ICD-11
International Classification of Diseases 11th Revision
HAI
Health Action International
DDD
Daily Defined Dose
DDDc
Defined Daily Dose cost
NBMI
National Basic Medical Insurance
MCDA
Multi-criteria Decision Analysis
MDT
Multi- disciplinary Team
ATC
Anatomical Therapeutic Chemical
OOPs
Out-of-pocket Expenses.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
 Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the detailed data involving non-public drug information of surveyed institutions but are available from the corresponding author on reasonable request.

Authors' contributions

BZ and SZ conceived and designed the study, and BZ contacted the pharmacists of surveyed institutions to fill in the questionnaires. LQ collected questionnaires, analyzed and interpreted the data, then wrote the manuscript. XL helped to analyze data and revise the first draft. XL, JS and JJ contributed to the study design, JS also responsible for data check. WZ, TX, and JQ assisted to conduct data analysis. All authors read and approved the final manuscript.

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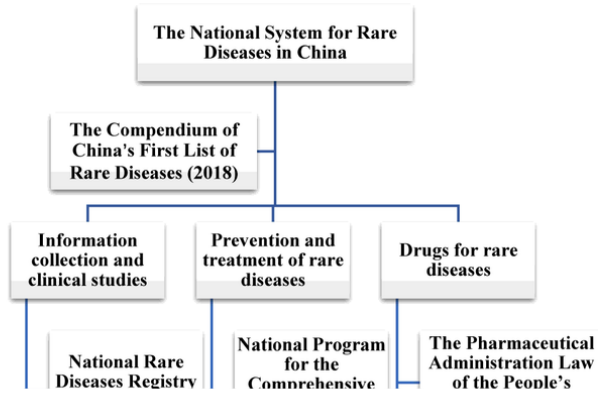
Figures

Figure 1

The national system for rare diseases in China.

Based on the definition of rare diseases, the national system for rare diseases in China. currently carries out from three aspects: information collection and clinical research, diagnosis and treatment, with each part has some crucial policies. Specifically, the Compendium of China's First List of Rare Diseases (2018) (CLRD) has made China the first country to delineate the boundaries of rare diseases in the form of a catalogue, which is the core innovation of the system. Representative work in each aspect is listed in the figure.
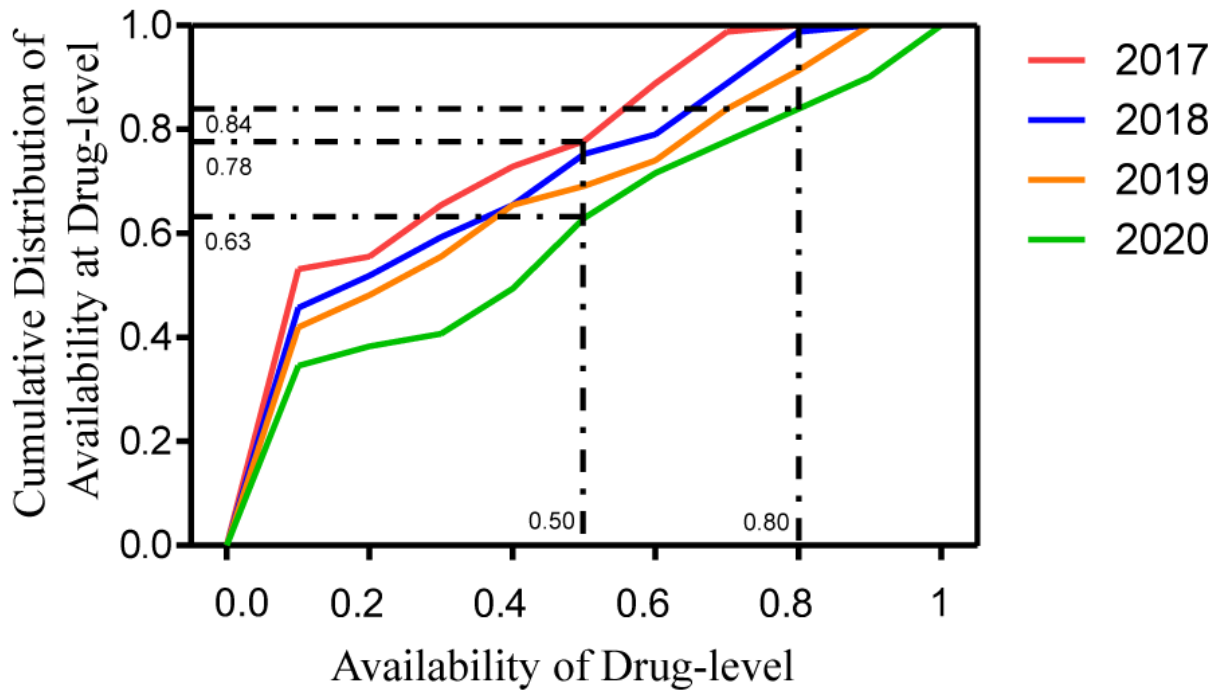
Figure 2

Cumulative frequency distribution of orphan drug availability at drug level from 2017 to 2020.

The red, blue, orange, and green lines represent the cumulative frequency trend of orphan drug availability at drug level for 2017, 2018, 2019, and 2020, respectively.
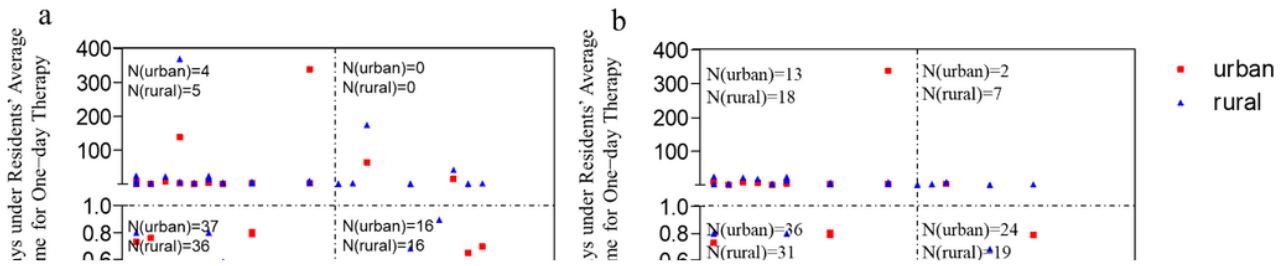
Figure 3

Four quadrant diagram of drug-level availability rate and affordability for urban and rural residents.

a) Drug-level availability and affordability without NBMI for urban and rural residents in 2018. b) Drug-level availability and affordability with NBMI for urban and rural residents in 2018. c) Drug-level availability and affordability without NBMI for urban and rural residents in 2020. d) Drug-level availability and affordability with NBMI for urban and rural residents in 2020.

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