

BMJ Open Economic evaluations of clinical pharmacy services in China: a systematic review

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ABSTRACT

Objective This article reviewed research conducted on economic evaluations of clinical pharmacy services (CPS) in China. We aimed to identify the types of CPS and the possible economic effects of these services and to hopefully provide some suggestions for designing future economic evaluations of pharmacy interventions in the region.

Design Systematic review.

Data sources Several English databases (PubMed, Embase, The Cochrane Library, National Health Service Economic Evaluation Database), Chinese databases (China National Knowledge Infrastructure, VIP, Chinese Biomedical Literature Database and WanFang Data) and search engines (Google Scholar and BaiDu Scholar) were searched through December 2017.

Eligibility criteria for selecting studies Studies with an economic assessment of CPSs in China were included.

Data extraction and synthesis Two reviewers independently screened the studies, extracted the data, assessed the quality of the included studies and then qualitatively analysed the results.

Results Forty articles were included in the final analysis. Most studies were performed in hospitals and the intervention populations mainly included adults. The types of pharmaceutical services included antimicrobial management, chronic disease state management and multidimensional clinical pharmaceutical services. A positive economic benefit associated with CPS was noted in 80% (n=32) of these articles, showing that CPS were associated with cost savings and improved patient outcomes. However, only three studies were full economic evaluations, using the method of cost-effectiveness analysis.

Conclusion CPS was associated with cost savings and generated positive economic value. With the expanding role of pharmacists in the healthcare sector, it is suggested that new pharmaceutical services be used in future studies and that high-quality full economic evaluations capturing both expenses and cost savings be conducted.

INTRODUCTION

The concept and practice of clinical pharmacy services (CPS) originated in the USA.¹ The American College of Clinical Pharmacy's (ACCP) definition of clinical pharmacy refers to the contribution that pharmacists make

Strengths and limitations of this study

- This study is the first to review economic evaluation studies on clinical pharmacy services in China by using a formal systematic review approach.
- This study was based on an evidence-based methodology to provide evidence to healthcare decision makers regarding the economic value of clinical pharmacy services, and it provides some suggestions and references for designing future economic evaluations of pharmacy interventions in the region.
- The possible risk of bias in the included studies was assessed using the American College of Clinical Pharmacy checklist that was designed specifically to grade the quality of economic methods, the Cochrane Collaboration Methodology or the Newcastle-Ottawa Scale.
- However, the heterogeneity among the included trials was relatively high, so we analysed the results qualitatively.

in applying their professional knowledge to ensure high-quality rational drug therapy to produce optimal patient outcomes.² The published literature suggests that CPS could improve patient clinical outcomes, as pharmacists use their skills and knowledge to make the best use of medications in order to ensure safe and effective pharmacotherapy.^{3 4} Pharmacist participation in physician rounds and provision of medication guidance can reduce the frequency of adverse drug events (ADEs) and medication errors and improve medication adherence.⁵ In addition to clinical benefits, patients' physical, emotional, functional and social well-being have also been positively affected when measured using health-related quality-of-life assessments.⁶

In 2009, wide-ranging reforms of the healthcare system were announced in China. Hospitals account for approximately three-quarters of pharmaceutical sales in China. To compensate for diminishing state contributions, hospitals were permitted to charge a mark-up of up to 15% on medicines. The

mark-up has had serious consequences. Doctors' salaries and bonuses were linked to drug sales, spurring excessive and inappropriate prescriptions.⁷ In 2009, this system of mark-ups was abolished, and billions of yuan were poured into the public system, which aimed to control China's increasing health expenditure to provide affordable healthcare.⁷ However, healthcare costs have continued to rise in China, which means that healthcare institutions need to identify and adopt efficient ways to control these costs. Although CPS have been developed in China and play an important role in improving patients' clinical outcomes, faced with limited resources and skyrocketing healthcare costs, healthcare policy-makers haven't grown increasingly focused on the economic effectiveness and cost of services.

Economic evaluations play an important role in informing resource allocation decision and lead to the provision of information to public policy-makers and healthcare payers about the good value for the invested money afforded by a healthcare programme.⁸ Published evidence of the economic value of CPS is an important resource, which can be used to justify pharmacist-led programmes and can also improve net revenue by reducing medical expenses. Beyond that, economic evaluations can also help improve the quality of CPS by guiding the choice of the most effective and cost-effective pharmacy programmes.⁹⁻¹¹

China became interested in CPS as early as 1962; however, due to the economic and political climate, CPS were finally developed in the 21st century. While still in the early stages of development, CPS are becoming firmly established with the support of China's Ministry of Health (MoH) of the People's Republic of China.¹² In 2011, the MoH issued a policy that all secondary and tertiary hospitals should have at least three and five full-time clinical pharmacists, respectively. Furthermore, pharmacists needed to be trained in infectious diseases to be able to give guidance and approval for restricted antimicrobial use.¹³ In 2018, the MoH indicated that pharmacists have the ultimate responsibility for prescription review.¹⁴ The role of the pharmacist is becoming increasingly important, but whether and how to 'pay pharmacists for patient care' is still an area of debate.

In China, many significant original studies have been published about the measurement of the economic impact of CPS. To date, no study has reviewed economic evaluation studies on CPS in China using a formal systematic review approach. The objective of this study was to review these studies, to identify the types of CPS and the possible economic effects of these services in China, and to provide evidence of the economic value of CPS to healthcare decision makers. Additionally, this study provides some suggestions and references for designing future economic evaluations of pharmacy interventions in the region.

METHOD

This study was largely based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews.¹⁵ The PRISMA checklist is shown in the online supplementary file.

Inclusion criteria

Participants

Any patient group and the associated prescriptions were included.

Intervention

All CPS performed by a pharmacist or team of pharmacists were considered interventions. In this review, the term intervention conforms to the unabridged ACCP definition of a clinical pharmaceutical intervention, in which pharmacists provide patient care that optimises medication therapy and disease prevention and promotes health.²

Outcomes

The primary outcome was a full or partial economic assessment of the cost to provide a service. A full economic evaluation was conducted using four techniques: cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis. Partial economic evaluations were considered in terms of costs and consequences.¹⁶

Study design

Randomised controlled trials, semirandomised controlled trials, non-randomised controlled trials, cohort studies and before-and-after studies were included.

Setting

The research sites were in China.

Language

The articles were published in English or Chinese.

Exclusion criteria

Studies were excluded that evaluated only humanistic or clinical outcomes without an economic assessment; studies published in abstract form only or unoriginal work (letters or reviews) were also excluded. When full texts of the studies were unavailable, they were also excluded, and repeated publications were excluded.

Search strategy

Relevant studies were identified by electronically searching the following databases: English databases (PubMed, Embase, the Cochrane Library, National Health Service Economic Evaluation Database), Chinese databases (China National Knowledge Infrastructure, WanFang Database, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals) and search engines (Google Scholar and Bai Du Scholar). Articles were retrieved from the date of the inception of the database to 24 December 2017. In addition, the bibliographies of relevant identified articles were manually searched. The search terms combined the Medical Subject Headings (MeSH) headings

with free-text words, including ‘clinical pharmacy’, ‘pharmaceutical services’, ‘pharmaceutical care’, ‘pharmacy service’, ‘pharmacist’, ‘economic evaluation’, ‘cost-utility analysis’, ‘cost-benefit analysis’ and ‘cost-effectiveness analysis’. More details about the search strategy can be found in the attachment (shown in online supplementary file).

Study selection and data extraction

Two study investigators independently screened and cross-checked all articles and extracted the data. In instances of disagreement, two reviewers resolved their differences of opinion by discussion to reach a consensus or consulted a third independent investigator to reach a consensus. Study selection was based on titles and abstracts, and the full texts were read after excluding obviously unrelated studies to make the ultimate decision regarding whether the study would be included. The extracted data included: the study design, setting, population, sample size, type of intervention, type of economic evaluation and economic outcomes.

Study appraisal and analysis

The assessment of study quality was performed with the checklist from the ACCP that was designed specifically to grade the quality of the economic methods used, which included three assessment items: (1) the description of the comparator group used; (2) the evaluation and description of the programme costs; and (3) the evaluation and description of the outcomes.⁹ Studies were considered ‘good quality’ when they met all three criteria. Studies that lacked a comparator or had multiple or fatal flaws were determined to be ‘poor quality’. All other studies were labelled ‘fair quality’ if they only contained an evaluation and description of the economic outcomes. In addition, we assessed the risk of bias in the included studies. The included randomised controlled trials (RCTs) were assessed using the Cochrane risk-of-bias criteria.¹⁷ The cohort and before-and-after studies were assessed using the Newcastle-Ottawa Scale (NOS), which uses the semi-quantisation star system with a full score of 9 stars, and the content evaluated includes the study selection, comparability and outcome. On the NOS, ≥ 7 stars indicates good quality, 5–7 stars indicates intermediate quality and ≤ 4 stars indicates poor quality.¹⁸

The heterogeneity of the results prevented a combined statistical analysis, so a qualitative analysis was carried out in this review to classify these articles by the type of CPS, setting and different perspectives, and to analyse the economic impact, existing research status and problems.

Patients and public involvement statement

Patients and the public were not involved in this study.

RESULTS

A total of 2438 relevant papers were obtained from the search, of which 608 were excluded because they were duplicates. Based on the abstracts, 1764 were excluded because they were irrelevant ($n=792$), did not include

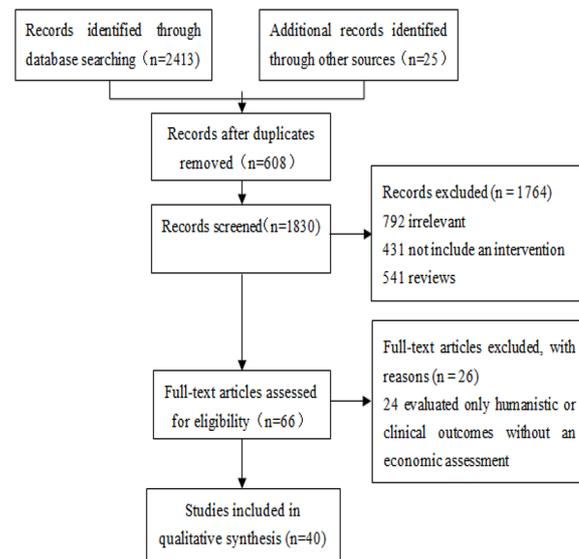


Figure 1 Literature search method and screening results.

an intervention ($n=431$) or were reviews ($n=541$). Of the remaining 66 articles, 26 articles were excluded from the review because they evaluated only humanistic or clinical outcomes without an economic assessment. A total of 40 studies met the inclusion criteria for the review. The screening process and results are shown in figure 1.

Basic characteristics and risk of bias in included studies

The number of studies on this topic has gradually increased since 2010. The study designs were divided into RCTs ($n=13$), cohort studies ($n=16$) and before-and-after intervention studies ($n=11$). Among the included studies, 38 (95%) were conducted in hospitals, while the others were performed in clinics or community pharmacies. The research population mainly focused on adults, and only one study focused entirely on a paediatric population. All of these studies had a concurrent or historical control and were conducted from the perspective of the hospital. Four studies (10%) were deemed to be ‘good quality’, while the others were described as being ‘fair quality’ as they only evaluated and described the economic outcomes, such as the drug or hospitalisation cost savings. The characteristics of the 40 included studies are summarised in table 1.

The results of the assessment of the risk of bias in the RCTs are shown in table 2. The bias of risk with regard to the ‘blinding of participants and personnel (performance bias)’ and the ‘blinding of outcome assessment (detection bias)’ were high in the included RCTs (because the pharmacist must interact with the patient face to face to provide drug-use guidance according to each patient’s condition). In addition, ‘random sequence generation (selection bias)’ and ‘allocation concealment (selection bias)’ had high levels of the risk of bias in almost all the included RCTs; they reported that a randomisation method was employed but do not clearly describe it. The risk-of-bias assessments in the cohort and before-and-after studies showed that 18.5% ($n=5$) of the studies were ‘good quality’, while the others ($n=22$, 81.5%) were ‘intermediate quality’. The results of

Table 1 Characteristic of studies eligible for inclusion in this review

Author/year	Study design	Setting/ patients	Simple size (I/C)	Study period	Pharmacist's intervention(s)	Type of economic evaluation	Outcomes measure	Results	Quality of economic method
Antimicrobial management (type of pharmaceutical services)									
Shen <i>et al</i> 2011 ¹⁹	Randomised controlled trial	Hospital/ adults	354 (176/178)	July 2009–April 2010	Pharmacist making recommendations to clinical team of nurses and physicians. Control was absence of pharmacist involvement	Partial economic evaluations	Total costs of hospitalisation and cost of antibiotics	The total costs of hospitalisation in the intervention group were significantly lower compared with the control group (US\$1442.3±684.9 vs US\$1729.6±773.7). Cost of antibiotics (US\$832.0±373.0 vs US\$943.9±412.0). P<0.05.	Fair
Yang 2016 ²⁰	Randomised controlled trial	Hospital/ adults	500 (250/250)	September 2013–September 2015	Provided DI, pharmaceutical monitoring; advised changes in therapy;	Partial economic evaluations	Cost of antibiotics	The cost of antibiotics in the intervention group was lower compared with the control group (¥177.59±18.11 vs ¥315.33±25.46. P<0.05.	Fair
Xu 2017 ²¹	Randomised controlled trial	Hospital/ adults	380 (190/190)	August 2014–August 2016	Attended rounds; guided the use of antibiotics and advised changes in therapy	Partial economic evaluations	Cost of antibiotics and the proportion of antibiotics in total medical expenses	Antibiotics: intervention group ¥156.82±11.35 versus control group ¥304.27±19.92; the proportion of antibiotics in total medical expenses: intervention group 10.26%±0.21% versus control group 15.26%±0.64%. P<0.05.	Fair
He <i>et al</i> 2017 ²²	Randomised controlled trial	Hospital/ adults	200	July 2015–July 2016	Attended rounds; reviewed sterile operation monitoring to advise antibiotic therapy; provided DI	Partial economic evaluations	Total costs of hospitalisation and cost of antibiotics	Antibiotics: intervention group ¥30.53±4.22 versus control group ¥312.43±13.25; total hospitalisation: intervention group ¥5200±43 versus control group ¥7500±102. P<0.05.	Fair
Wang 2017 ²³	Randomised controlled trial	Hospital/ adults	200 (100/100)	August 2014–August 2015	Attended rounds; reviewed prescriptions to advise antibiotic therapy; provided pharmaceutical care	Partial economic evaluations	Cost of antibiotics	The cost of antibiotics in the intervention group was lower compared with the control group (¥1962.2±261.8 vs ¥2671.8±316.7). P<0.05.	Fair
Kadler and Tan 2016 ²⁴	Randomised controlled trial	Hospital/ adults	160 (80/80)	June 2014–June 2015	Established guidelines for using antibiotics; provided DI, pharmaceutical consultation; attended rounds	Partial economic evaluations	Cost of antibiotics	The cost of antibiotics in the intervention group was lower compared with the control group (¥134.8±2.89 vs ¥365±23.89). P<0.05.	Fair
Peng 2017 ²⁵	Retrospective cohort study	Hospital/ adults	800 (400/400)	January 2014–January 2016	Provided antibiotic information; reviewed prescriptions; investigated satisfaction of patient	Partial economic evaluations	Total costs of treatment and cost of antibiotics	Total costs of treatment: preintervention ¥2578.16±511.83 versus ¥1919.65±575.14. Cost of antibiotics: preintervention ¥534.25±151.37 versus ¥233.94±149.32. P<0.05.	Fair
Cai <i>et al</i> 2015 ²⁶	Retrospective cohort study	Hospital/ adults	244 (122/122)	July 2012–September 2012, July 2013–September 2013	Advised antibiotic therapy	Partial economic evaluations	Cost of antibiotics	Antibiotics: preintervention ¥295.34 versus ¥46.41. P<0.05.	Fair

Continued

Table 1 Continued

Author/year	Study design	Setting/ patients	Simple size (I/C)	Study period	Pharmacist's intervention(s)	Type of economic evaluation	Outcomes measure	Results	Quality of economic method
Ren and Pu 2016 ²⁷	Retrospective cohort study	Hospital/ adults	80 (40/40)	March 2015–June 2015, March 2016–June 2016	Attended rounds; reviewed prescriptions to manage antibiotic therapy	Partial economic evaluations	Total costs of drugs and cost of antibiotics	Drugs: preintervention ¥7423±101 versus ¥3674±102. Antibiotics: preintervention ¥2476±245 versus ¥487±243. P<0.05.	Fair
Zhang <i>et al</i> 2013 ²⁸	Retrospective cohort study	Hospital/ adults	968 (420/548)	January 2009– December 2009, June 2010–May 2011	Reviewed medical records to advise therapy;	Partial economic evaluations	Total costs of hospitalisation and cost of antibiotics	Hospitalisation: preintervention ¥11 265.50 versus ¥8724.70. Antibiotics: preintervention ¥622.60 versus ¥176.19. P<0.05.	Fair
Du 2016 ²⁹	Retrospective cohort study	Hospital/ adults	2400 (1200/1200)	2013 and 2014	Attended rounds; reviewed prescriptions to provide DI, and suggestions for alternative therapies	Partial economic evaluations	Total costs of drugs and cost of antibiotics	Drugs: preintervention ¥3742±657 versus ¥2124±465. Antibiotics: preintervention ¥1051±243 versus ¥529±87. P<0.05.	Fair
Xu 2016 ³⁰	Retrospective cohort study	Hospital/ adults	2300 (1148/1152)	January 2013– December 2015	Attended rounds; guided the use of antibiotics and provided DI; reviewed medical records to advise therapy	Partial economic evaluations	Cost of antibiotics, total costs of treatment and the ratio	The cost of antibiotics in the intervention group was significantly lower compared with the control group (¥2037 vs ¥3955). The total costs of treatment (¥5081 vs ¥6379). The ratio (40.7% vs 62.0%). P<0.05.	Fair
Lv <i>et al</i> 2011 ³¹	Retrospective cohort study	Hospital/ adults	200 (100/100)	2009 and 2010	Advised changes in therapy	Partial economic evaluations	Cost of antibiotics, medicine and hospitalisation	Antibiotics: preintervention ¥423 versus ¥320. Medicine: preintervention ¥1304 versus ¥1018. P<0.05. Hospitalisation: no obvious difference.	Fair
Huang <i>et al</i> 2014 ³²	Retrospective cohort study	Hospital/ adults	160 (80/80)	2011 and 2012	Provided pharmaceutical monitoring, discharge education, and suggestions for alternative therapies; reported ADR	Partial economic evaluations	Total costs of hospitalisation, drugs, antibiotics and the ratio	The cost of antibiotics in the intervention group was significantly lower compared with the control group (¥2756.25±653.21 vs ¥4156.25±811.28). Total costs of drugs (¥3105.75±1123.54 vs ¥5489.75±1203.47). Total costs of hospitalisation (¥8213.72±1479.33 vs ¥10 812.65±1756.28). The cost of antibiotics/drugs (33.55%±5.01% vs 38.43±5.16%). The cost of drugs/ hospitalisation (37.8%±6.75% vs 50.77±8.78%). P<0.05.	Fair
Liu <i>et al</i> 2011 ³³	Retrospective cohort study	Hospital/ adults	148 (71/77)	September 2009– July 2010	Attended rounds, advised antibiotic therapy	Partial economic evaluations	Total costs of hospitalisation and drugs	Drugs: preintervention ¥1650 versus ¥1162.5, ¥487.5 saved. Hospitalisation: preintervention ¥4893.5 versus ¥4059.9, ¥833.6 saved. P<0.05.	Fair
Hao 2016 ³⁴	Retrospective cohort study	Hospital/ adults	360 (180/180)	January 2013– January 2014, February 2014– February 2015	Provided DI, analysis of drug use	Partial economic evaluations	Cost of antibiotics	Antibiotics: preintervention ¥2504.61±314.49 versus ¥1859.09±259.68. P<0.05.	Fair

Continued

Table 1 Continued

Author/year	Study design	Setting/ patients	Simple size (I/C)	Study period	Pharmacist's intervention(s)	Type of economic evaluation	Outcomes measure	Results	Quality of economic method
Li and Yang 2014 ³⁵	Retrospective cohort study	Hospital/ adults	2400 (1200/1200)	2009 and 2010	Attended rounds; provided DI, pharmaceutical consultation; reviewed medical records	Partial economic evaluations	Total costs of treatment and cost of antibiotics	Total costs of treatment: preintervention ¥2576.25±512.47 versus ¥1920.42±576.30. Cost of antibiotics: preintervention ¥533.10±260.55 versus ¥234.50±150.20. P<0.05.	Fair
Feng 2014 ³⁶	Retrospective cohort study	Hospital/ adults	4800 (2400/2400)	2011 and 2013	Established guidelines for using antibiotics; provided pharmaceutical consultation; reviewed prescriptions	Partial economic evaluations	Cost of antibiotics, and the average course of use of antibiotics	Antibiotics: preintervention ¥542.2±168.3 versus ¥267.4±154.5. Average course: preintervention 4.5±1.1 d versus 3.4±0.9 d. P<0.05.	Fair
Chu 2016 ³⁷	Retrospective cohort study	Hospital/ adults	336 (168/168)	January 2014– June 2014, July 2014–December 2014	Attended rounds; reviewed medical records to optimise antibiotic therapy; provided pharmaceutical care	Partial economic evaluations	Total costs of hospitalisation	Hospitalisation: preintervention ¥3105.60±285.20 versus ¥2560.70±229.40. P<0.05.	Fair
Gan 2016 ³⁸	Before-and- after study	Hospital/ adults	200 (100/100)	2014 and 2015	Attended rounds; reviewed and advised antibiotic therapy	Partial economic evaluations	Cost of antibiotics	Antibiotics: preintervention ¥6950.50±981.58 versus ¥4208.19±650.04. P<0.05.	Fair
Tao and Hu 2014 ³⁹	Before-and- after study	Hospital/ adults	600 (300/300)	2011 and 2012	Attended rounds; provided DI	Partial economic evaluations	Cost of antibiotics	Antibiotics: preintervention ¥1591.4±300.2 versus ¥1102.4±298.5. P<0.05.	Fair
Guo 2015 ⁴⁰	Before-and- after study	Hospital/ adults	2000 (1000/1000)	March 2012– March 2013, June 2013–June 2014	Established guidelines for using antibiotics; provided DI, pharmaceutical consultation; reviewed medical records	Partial economic evaluations	Total costs of quinolones	Total costs of quinolones: preintervention ¥36.2 thousands versus ¥24.4 thousands.	Fair
Zhou et al 2015 ⁴¹	Before-and- after study	Hospital/ adults	/	2010 to 2013	Attended rounds; provided DI; analysed and guided the use of antibiotics	Partial economic evaluations	Total drug cost, antibiotic cost and antibiotic cost percentage	Comparison of the 2013 data with those of 2010 showed that average antibiotic cost decreased by 246.94 dollars; the cost of antibiotics as a percentage of total drug cost decreased by 27.7%	Fair
Chronic disease state management									
Li et al/ 2011 ⁴²	Randomised controlled trial	Clinical/adults	150 (79/71)	Not report	Pharmaceutical care (eg, lectures on pharmaceutical, establishment of connection...)	Partial economic evaluations	Cost-effectiveness analysis	Intervention group: 684.82±805.97 was better than control group 1376.01±2063.37. P<0.05.	Good
Chen 2016 ⁴³	Randomised controlled trial	Hospital/ adults	504 (254/250)	July 2015– December 2015	Provided DI and suggestions for alternative therapies; prevented ADR	Full economic evaluations	Cost-effectiveness analysis	The observation group cost- effectiveness ratio was significantly lower than the control group (C/ E=1627.9 vs 2654.6; p<0.05); sensitivity analysis (C/E=1557.5 vs 2570.0)	Good

Continued

Table 1 Continued

Author/year	Study design	Setting/ patients	Simple size (I/C)	Study period	Pharmacist's intervention(s)	Type of economic evaluation	Outcomes measure	Results	Quality of economic method
Huang and Hu 2013 ⁴⁴	Randomised controlled trial	Hospital/ adults	300 (150/150)	January 2012– December 2012	Established guidelines for using antibiotics; attended rounds; provided DI; advised changes in therapy	Partial economic evaluations	Cost of treatment	The cost of treatment in the observation group was significantly decreased (¥33.27±9.36 to ¥25.68±7.24; p<0.05); control group (¥33.29±9.55 to ¥32.74±9.03; p>0.05)	Fair
Chen and Su 2016 ⁴⁵	Retrospective cohort study	Hospital/ adults	80 (40/40)	July 2012–July 2014	Provided DI, pharmaceutical monitoring and psychological counselling; guided the use of drugs	Partial economic evaluations	Cost of treatment	Cost of treatment: intervention ¥11 274.26±5930.28 versus ¥14173.49±6293.39; P<0.05.	Fair
Wu <i>et al</i> 2016 ⁴⁶	Retrospective cohort study	Hospital/ adults	420 (262/158)	September 2013– August 2014, September 2014– August 2015	Provided DI (eg, ADR), pharmaceutical monitoring; reviewed medical records to advise therapy	Partial economic evaluations	Cost of drugs	Total costs of drugs: intervention ¥5 581 228.8 versus ¥6 742 349.8. The average cost of drugs: intervention ¥21 302.4 per person versus ¥42 673.1 per person. P<0.05.	Fair
Jiang <i>et al</i> 2017 ⁴⁷	Prospective cohort study	Hospital/ adults	124 (63/61)	November 2014– October 2015	Attended rounds; provided pharmaceutical care, discharge education; reviewed medical records	Partial economic evaluations	Total costs of hospitalisation and drugs	The total costs of hospitalisation in the intervention group were significantly lower compared with the control group (¥8537.76±2835.09 vs ¥10 236.28±3043.82). Costs of drugs (¥4275.10±1123.67 vs ¥5339.77±1024.80). P<0.05.	Fair
Xin <i>et al</i> 2013 ⁴⁸	Before-and- after study	Hospital/ adults	944 (473/471)	January 2012– March 2012, October 2012– December 2012	Attended rounds; reviewed medical records to advise therapy	Partial economic evaluations	Cost of drugs	Drug: preintervention US\$347.15 versus US\$309.74. P=0.095.	Fair
Xin <i>et al</i> 2014 ⁴⁹	Before-and- after study	Hospital/ adults	849 (429/420)	January 2013– June 2013, July 2013–December 2013	Attended rounds; provided pharmaceutical consultation and monitoring; advised changes in therapy	Partial economic evaluations	Cost of drugs	The drug cost per patient day decreased from €254.74 to €219.85. P=0.095.	Fair
Long <i>et al</i> 2014 ⁵⁰	Before-and- after study	Hospital/ adults	101	March 2011–June 2011	Provided DI, pharmaceutical consultation and follow-up	Full economic evaluations	Cost-effectiveness analysis	The cost of pharmacy service: preintervention ¥1899.13 versus ¥1899.13. The C/E: 22.27 versus 21.98	Good
Chen and Zhao 2014 ⁵¹	Before-and- after study	Hospital/ adults	190	June 2011–June 2012	Provided DI, pharmaceutical consultation and follow-up; guided use of drugs for diabetes	Full economic evaluations	Cost-effectiveness analysis	C/E: the ratio of total effect, hypoglycaemic effect, antihypertensive effect and lipid-lowering effect after intervention was 275.4, 157.0, 240.9 and 184.5 respectively; there was a substantial decline than before the intervention.	Good

Multidimension clinical pharmaceutical services

Continued

Table 1 Continued

Author/year	Study design	Setting/ patients	Simple size (I/C)	Study period	Pharmacist's intervention(s)	Type of economic evaluation	Outcomes measure	Results	Quality of economic method
Li <i>et al</i> 2015 ⁵²	Randomised controlled trial	Hospital/ adults	120 (60/60)	January 2012– January 2014	Optimised therapy; provided pharmaceutical monitoring	Partial economic evaluations	Total costs of hospitalisation and drugs	The cost of drugs in the intervention group was lower than control group (¥3343.2±1833.3 vs ¥3462.1±1929.2). Cost of hospitalisation (¥5117.1±2739.1 vs ¥5234.4±2480.9), P>0.05.	Fair
Wang 2016 ⁵³	Randomised controlled trial	Clinical/adults	198 (99/99)	October 2013– January 2016	Optimised therapy; provided pharmaceutical monitoring	Partial economic evaluations	Total costs of hospitalisation	The cost of hospitalisation and the cost of drugs as a percentage of total hospitalisation cost were not statistically significant.	Fair
Qi <i>et al</i> 2016 ⁵⁴	Randomised controlled trial	Hospital/ adults	240 (120/120)	April 2015–April 2016	Suggested therapy	Partial economic evaluations	Cost of treatment	The cost of treatment in the observation group was significantly lower than control group. Saved ¥36.25±2.51 versus ¥1.24±0.03, P<0.05.	Fair
Han <i>et al</i> 2017 ⁵⁵	Before-and- after study	Hospital/ adults	87 (46/41)	2015 and 2016	Advised therapies of antibiotics, analgesics, economic adjunct drugs, anticoagulant and anticoagulants	Partial economic evaluations	Total costs of hospitalisation and drugs	Hospitalisation: observation group ¥40 661.82±5489.48 versus ¥46 797.7±4848.61. Drugs: observation group ¥8465.19±2168.54 versus ¥12 290.88±3396.18, P<0.05.	Fair
Liu <i>et al</i> 2016 ⁵⁶	Before-and- after study	Hospital/ adults	173 (92/81)	September 2015– November 2015, December 2015– February 2016	Reviewed prescriptions to suggest therapy adjustments	Partial economic evaluations	Cost of TPN	TPN: preintervention ¥1021±218 versus ¥860±176, P<0.001.	Fair
Zhang <i>et al</i> 2012 ⁵⁷	Randomised controlled trial	Hospital/ paediatrics	160 (80/80)	December 2010– March 2011	Attended rounds; provided DI, pharmaceutical consultation; reviewed prescriptions to advise therapy	Partial economic evaluations	Cost of hospitalisation and drugs	Cost of drugs and hospitalisation in the two groups were not statistically different.	Fair
Jiang <i>et al</i> 2012 ⁵⁸	Before-and- after study	Hospital/ adults	825 (416/409)	December 2010– March 2011, March 2011–June 2011	Attended rounds; provided pharmaceutical consultation, ADRM; reviewed medical records to advise therapy	Partial economic evaluations	Cost of drugs	Saved US\$40.07/d; the drug cost per patient-day decreased from US\$347.43 to US\$307.36, P=0.095.	Fair

ADR, adverse drug reaction; ADRM, adverse drug reaction monitoring; DI, drug information; TPN, total parenteral nutrition.

Table 2 Risk of bias for randomised controlled trials

Study ID	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other bias
Shen <i>et al</i> 2011 ¹⁹	U	L	H	L	L	L	L
Yang <i>et al</i> 2016 ²⁰	U	U	U	U	L	L	L
Xu 2017 ²¹	L	U	H	U	L	L	L
He <i>et al</i> 2017 ²²	L	L	H	U	L	L	L
Wang 2017 ²³	U	L	H	U	L	L	L
Kadier and Tan 2016 ²⁴	U	U	H	U	L	U	L
Li <i>et al</i> 2011 ⁴²	U	U	U	U	L	L	L
Chen 2016 ⁴³	L	L	H	U	L	L	L
Huang and Hu 2013 ⁴⁴	L	U	H	U	L	U	L
Li <i>et al</i> 2015 ⁵²	L	L	H	U	L	L	L
Wang 2016 ⁵³	U	U	H	U	L	L	L
Qi <i>et al</i> 2016 ⁵⁴	L	L	H	U	L	L	L
Zhang <i>et al</i> 2012 ⁵⁷	L	L	H	L	L	L	L

H, high risk; ID, identification; L, low risk; U, unknown.

risk-of-bias assessments in the cohort and before-and-after studies are shown in [table 3](#).

Clinical pharmacy interventions

The type of CPS was classified as one of the three following areas: (1) antimicrobial management services^{19–41} (23 (57.5%)) that primarily focused on antimicrobial use and may have included predefined guidelines for the provision of dosing recommendations or the preferred drug; (2) chronic disease state management services^{42–51} (10 (25%)) that were primarily directed at patients with a specific disease state or diagnosis, such as a diabetes management programme; and (3) multidimensional clinical pharmaceutical services^{52–58} (7 (17.5%)) that encompassed a broad range of activities based on the need of patients. The content of the interventions included the adjustment of dosages; the provision of advice regarding therapeutic drug monitoring; the evaluation of drug history; the provision of drug information to physicians and patients to prevent pharmacological and physicochemical interactions, prescribing and transcription errors and ADEs; the participation in physician rounds; and the implementation and tracking of the use of guidelines regarding the correct use of drugs. In these studies, interventions were generally undertaken by clinical pharmacists and did not involve dispensing services.

Economic impact assessment

Three studies were full economic evaluations, using the method of cost-effectiveness analysis.^{43 50 51} Others conducted partial economic evaluations that were limited to the direct healthcare costs, estimating the

drug and hospitalisation cost savings only. Most studies (97.5%) did not calculate the pharmacist's labour costs. In addition, only two studies (5%) conducted a sensitivity analysis to account for uncertainty in the estimates of the costs and consequences.^{43 51} An incremental cost-benefit ratio or incremental cost-effectiveness ratio (ICER) was presented in one study.⁵⁰ The transferability of results to other settings or countries was not discussed in all the studies' results.

A positive economic benefit associated with pharmacy services was noted in 80% (n=32) of these studies. The other studies (n=8, 20%) also showed lower medical costs due to pharmacist intervention; however, these trials did not find statistically significant differences in the medication costs saved. In the following discussion, we provide a detailed description of these studies categorised by the type of clinical pharmacy intervention.

Economic impact of antimicrobial management

Twenty-three studies on CPS included antimicrobial management, and the interventions were conducted in hospitals.^{19–41} All of these assessments were partial economic evaluations; among them, 21 studies with a control group applied statistics to compare the two groups, with economic outcomes showing that pharmacists providing antimicrobial management services led to overall cost savings (including the cost of antibacterial drugs, hospitalisation expenses and total treatment costs) in the intervention groups, and the results showed a significant difference ($p < 0.05$).^{19–39} Another two studies also showed that antibiotic costs decreased but were not reported as a statistically significantly different.^{40 41}



Table 3 Risk of bias for cohort and before-and-after studies

Study ID	Selection				Comparability			Outcome		Total number of stars
	Representativeness of the exposed cohort*	Selection of the no exposed cohort†	Ascertainment of exposure‡	Demonstration that outcome of interest was not present at start of study§	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome**	Was follow-up long enough for outcomes to occur††	Adequacy of follow-up of cohorts‡‡		
Peng 2017 ²⁵	b	a	a	b	b	b	a	c	★★★★★	
Cai <i>et al</i> 2015 ²⁶	b	a	a	b	b	b	a	c	★★★★★	
Ren and Pu 2016 ²⁷	b	a	a	b	c	b	a	a	★★★★★	
Zhang <i>et al</i> 2013 ²⁸	b	a	a	b	b	b	b	a	★★★★★	
Du 2016 ²⁹	b	a	a	a	b	b	a	a	★★★★★	
Xu 2016 ³⁰	b	a	a	b	c	b	a	a	★★★★★	
Lv <i>et al</i> 2011 ³¹	b	a	a	b	c	b	a	a	★★★★★	
Huang <i>et al</i> 2014 ³²	b	a	a	b	b	b	b	a	★★★★★	
Liu <i>et al</i> 2011 ³³	b	a	a	b	c	b	a	b	★★★★★	
Hao 2016 ³⁴	b	a	a	b	b	b	b	b	★★★★★	
Li and Yang 2014 ³⁵	b	a	a	b	c	b	a	a	★★★★★	
Feng 2014 ³⁶	b	a	a	b	c	b	a	a	★★★★★	
Chu 2016 ³⁷	b	a	a	b	c	b	a	a	★★★★★	
Gan 2016 ³⁸	b	a	a	b	c	b	a	d	★★★★★	
Tao and Hu 2014 ³⁹	b	a	a	a	c	b	a	a	★★★★★	
Guo 2015 ⁴⁰	b	a	a	b	c	b	a	a	★★★★★	
Zhou <i>et al</i> 2015 ⁴¹	b	a	a	b	b	b	a	c	★★★★★	
Chen and Su 2016 ⁴⁵	b	a	a	b	c	b	a	c	★★★★★	
Wu <i>et al</i> 2016 ⁴⁶	b	a	a	b	b	b	a	a	★★★★★	
Jiang <i>et al</i> 2017 ⁴⁷	b	a	a	b	c	b	b	a	★★★★★	
Xin <i>et al</i> 2013 ⁴⁸	b	a	a	b	c	b	a	a	★★★★★	
Xin <i>et al</i> 2014 ⁴⁹	b	a	a	b	b	b	a	d	★★★★★	
Long <i>et al</i> 2014 ⁵⁰	b	a	a	b	c	b	a	b	★★★★★	
Chen and Zhao 2014 ⁵¹	b	a	a	b	b	b	a	a	★★★★★	
Han <i>et al</i> 2017 ⁵⁵	b	a	a	b	c	b	a	a	★★★★★	
Liu <i>et al</i> 2016 ⁵⁶	b	a	a	b	c	b	a	a	★★★★★	
Jiang <i>et al</i> 2012 ⁵⁸	b	a	a	b	b	b	a	a	★★★★★	

*a: truly representative of the average (describe) in the community; b: somewhat representative of the average in the community; *: selected group of users, for example, nurses, volunteers; d: no description of the derivation of the cohort.
 †a: drawn from the same community as the exposed cohort; *: b: drawn from a different source; c: no description of the derivation of the non-exposed cohort.
 ‡a: secure record (eg, surgical records); *: b: structured interview; *: c: written self-report; d: no description.
 §a: yes; *: b: no.
 ||a: study controls for age (select the most important factor); *: b: record linkage; *: c: self-report; d: no description.
 **a: independent blind assessment; *: b: record linkage; *: c: self-report; d: no description.
 ††a: yes (select an adequate follow-up period for outcome of interest); *: b: no.
 †††a: complete follow-up—all subjects accounted for; *: b: subjects lost to follow-up unlikely to introduce bias—small number lost follow-up, or description provided of those lost; *: c: follow-up rate <40% (select an adequate %) and no description of those lost; d: no statement.

Economic impact of chronic disease state management

Ten studies described three disease state management programmes (tuberculosis, diabetes and hypertension).^{42–51} Among them, three studies were full economic evaluations, and all of them used cost-effectiveness analyses.^{43 50 51} The pharmacist provision of education to patients with diabetes resulted in a cost-effectiveness ratio (CER) of 21.98 in comparison with the control group (22.27) and the ICER was 21.02, which showed a positive economic outcome based on the estimated cost of providing the service.⁵⁰ A stewardship programme provided for hypertension was investigated, and the study reported a reduction in the CER (pharmacist present 1627.0 vs no pharmacist 2654.6, $p < 0.05$) when pharmacists were included as a part of a multidisciplinary team.⁴³ Another study showed a substantial decline in the CER compared with before an intervention occurred (intervention 275.4 vs no intervention 384.5), and the CPS improved the effect of the treatment on patients with diabetes mellitus in the community, thereby reducing the cost of treatment.⁵¹ Other studies were partial economic evaluations, and they only reported the cost of treatment (including drug charges and hospitalisation expenses), which were reduced after intervention. Service costs were considered in one study,⁵⁰ but the other studies omitted them.

Economic impact of multidimensional CPS

There were seven studies on such pharmaceutical services. All of them were partial economic evaluations, which only reported decreased medical costs, and four of the studies showed no statistically significant differences, although medical costs decreased due to pharmaceutical interventions in the results.^{52 53 57 58} The cost of providing the service was not stated in all studies.

The detailed economic results of each study are shown in [table 1](#).

DISCUSSION

In this systematic review, a positive economic benefit associated with CPS was noted in 80% ($n=32$) of the articles, showing that CPS were associated with cost savings. The context of CPS has been expanding from medication dispensing towards providing individualised care in China. The types of services include antimicrobial management, chronic disease state management and multidimensional clinical pharmaceutical services, and the interventions are concentrated in hospitals and community clinics. However, compared with studies from other countries, the types of services provided in China and the settings of the interventions show a lack of diversity. For example, an economic assessment of the CPS in the USA by the ACCP showed that types of CPS also included health screening services, laboratory testing services, wellness programmes, immunisation services and medication therapy management. In addition, studies in the USA evaluated interventions in community settings, clinics,

long-term monitoring institutions, rehabilitation organisations and so on.^{3 9} Faced with China's current healthcare reform, increasing numbers of hospitals are paying more attention to the development of CPS with the hope that pharmacists can provide more correct guidance regarding drug use, thereby saving medical resources. By expanding the breadth of CPS, further economic savings could be garnered; however, the evaluation of services in other settings, such as the community, will be needed to determine if similar savings are obtained.

CPS are still in the early stages of development in China, and the number of studies on the economic evaluation of pharmaceutical services has only gradually increased since 2010. Most of the included studies focused on adults. Among the included studies, 80% reported a positive economic benefit associated with CPS, but only four (10%) of the studies were 'good quality'. Most of the studies were partial economic evaluations that cited clinical effects as the main outcome, and the economic outcome was added as an afterthought; these studies only reported direct cost savings, for example, hospitalisation and drug-related cost savings. In addition, these studies did not calculate hidden costs and potential savings; only one study took into account the pharmacist's labour costs and time input. When input costs are not appropriately estimated, it leads to the overestimation of the cost savings, rendering it impossible to make an informed decision regarding the true value of CPS. Future economic evaluations should pay more attention to paediatric populations and conduct full economic evaluations in which all relevant direct healthcare costs and the indirect costs of productivity loss are considered and measured, including pharmacist employment costs.

CPS have existed in China for more than 20 years, and there is a vast body of original research about the economic impact of pharmacy services. However, to the best of our knowledge, the present study is the first to systematically review the economic evaluation literature on CPS in China. The results of this study showed that CPS have resulted in beneficial outcomes for patients, such as reducing drug costs, the length of stay and the cost of treatment; in addition, one pilot programme showed that nearly all directors of hospitals, doctors, pharmacy directors and patients surveyed ($n=207$) supported the role of clinical pharmacists.⁵⁹ However, whether and how to 'pay pharmacists for patient care' is still an area of debate. Our research provides information that can be used by healthcare administrators regarding the potential return on investment afforded by CPS. This information can help guide those responsible for allocating medical resources when faced with reforms of the healthcare system and skyrocketing healthcare costs. This work further highlights the gaps in knowledge where further research is needed, forming the foundation for designing future economic evaluations of pharmacy interventions in the region.

This review has some limitations. First, in the process of study selection, some grey articles were unavailable and not included in this review. Second, this study might be

affected by publication bias, as negative or non-significant results may have remained unpublished. Third, the literature search was conducted until January 2018; next, we will update the literature review every 3 years. Fourth, the included studies were conducted in different hospitals, with different kinds of patient and various interventions, making it difficult to compare the results and preventing the performance of a meta-analysis. Therefore, we qualitatively analysed the results. In addition, most included studies were partial economic evaluations and had a risk of bias. Among the included RCTs, 46.2% (n=6) had selection bias (random sequence generation and allocation concealment). Many articles reported that they used randomisation methods; however, some of them did not clearly report the randomisation approach, which may reduce the credibility of the evaluation findings. Furthermore, sensitivity analyses were not considered in many studies because the changes in parameter values could result in different results and conclusions. All cohort studies used retrospective experimental designs with the recommended methods for collecting and reporting economic information. Future studies should adopt full economic evaluations in which all relevant costs and outcomes are considered and measured. Furthermore, efforts should be made to improve the quality of the studies to decrease the risk of bias. All guidelines available regarding the design and reporting of economic evaluations should be used by authors when developing the economic portion of their studies.⁶⁰

CONCLUSION

Clinical pharmacy interventions are associated with cost savings. However, most studies had limitations in their methodological quality and applicability to current practice. Compared with CPS and the evaluations of CPS in other countries, the types of pharmaceutical services in China were limited, and most studies adopted partial economic evaluations. It is suggested that new pharmaceutical services be included in future studies and that full economic evaluations capturing both expenses and cost savings be conducted to promote the development of pharmaceutical care.

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