Clinical practice guidelines in China

Yaolong Chen and coworkers analyse the situation and challenges for clinical practice guidelines in China and provide recommendations for their development and implementation.

Clinical practice guidelines are statements that include recommendations for the optimisation of patient care. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative options.[1] Such guidelines are an extremely important tool for healthcare delivery in China. Firstly, implementation of cost effective treatment and care will help to optimise resource use and patient outcomes for the country with the largest population in the world. Secondly, substantial variability in clinical practice exists among hospitals and in different districts across China, which can be minimised by the use of guidelines. Thirdly, China is the only country where Western medicine and traditional Chinese medicine are practised alongside each other at every level of the healthcare system; traditional Chinese treatments account for about 40% of the total.[2] Healthcare providers can use guidelines to identify and apply evidence based recommendations across both types of medicine in a complementary and safe manner. We analyse the situation and challenges for clinical practice guidelines in China and provide recommendations for their development and implementation.

Status of clinical practice guidelines developed in China

Between 1993 and 2010, 269 guidelines were produced by 256 Chinese developers and published in 115 Chinese medical journals,[3] and the number of guidelines is increasing annually (fig 1). Most were developed by the Chinese Medical Association and its branches, and one third focused on traditional Chinese medicine.[3] Chinese medical societies have released an even larger number of expert based consensus statements: one study identified 186 expert consensus statements but only 14 guidelines for managing cardiovascular disease.[4] These expert consensus statements were usually developed without any formal approach, did not use evidence systematically, and seldom dealt with conflicts of interest. However, for primary care, the most important type of care in China, few practice guidelines have been developed for general practitioners, particularly those in rural areas.[5]

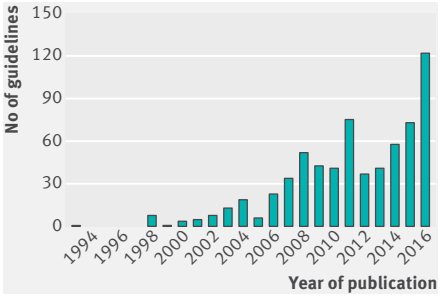

Fig 1 | Number of clinical practice guidelines published in Chinese medical journals between 1993 and 2016—a total of 664 guidelines. The data for 1993 to 2010 were derived from Chen et al[3]; the data for 2011 to 2016 are unpublished and available upon request from the corresponding author

Chinese guidelines are generally of lower quality than those from Western countries, as assessed with the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.[3 6 7] Chinese guideline developers seldom use systematic reviews to support their recommendations. The average number of references in Chinese guidelines is 36, whereas international guidelines have about 400.[8] Only 71 Cochrane reviews were cited in 172 Chinese guidelines,[8] whereas 731 Cochrane reviews were cited in 106 guidelines issued by the United Kingdom National Institute for Health and Care Excellence (NICE).[9]

Conflict of interest in developing guidelines has become a great concern in China. Chinese guideline developers receive far less financial support from government and non-profit agencies than developers in Western countries.[10] Thus, they inevitably seek support from industry, which may lead to bias and reduced credibility. Unfortunately, however, 88% of Chinese clinical guidelines provide no information about conflict of interest.[3]

No systematic data have been published on the implementation of, and adherence to, clinical guidelines in China. Two investigations showed that the adherence rate of clinicians to guidelines for

KEY MESSAGES

- China publishes a large number of clinical practice guidelines and expert consensus statements but the quality needs to be improved
- For Chinese guideline developers, adoption or adaptation of existing international guidelines, and de novo development of recommendations, are all options. Developers need to decide on a case by case basis which option, or combination of options, is most appropriate
- China can contribute both clinical practice guidelines and experiences and methods of guideline development, adaptation, and implementation to the global community

Box 1: Examples of adoption and adaptation of clinical practice guidelines in China

Adoption: Guidelines for the prevention, care, and treatment of people with chronic hepatitis B infection13 (World Health Organization, March 2015)

China has the world's largest number of patients with chronic hepatitis B. Chinese hepatologists participated in the development of this guideline and Chinese studies were included in the evidence used to support the recommendations. This guideline also has a Chinese translation and is endorsed by the Chinese government and by Chinese medical societies

Adaptation: HIV/AIDS clinical nursing practice guidelines14 (School of Nursing, Fudan University; Fudan University Centre for Evidence-based Nursing: Joanna Briggs Institute Centre of Excellence; Shanghai Public Health Clinical Centre, March 2014)

A large number of evidence based guidelines for managing people with HIV infection have been published. The HIV epidemic varies greatly across countries and settings. These international guidelines attempt to cover both generalised epidemics (mainly in sub-Saharan Africa) and the key populations that have a major role in concentrated epidemics. The HIV epidemic in China has some particular characteristics, such as the very low national prevalence and great variability across geographical regions in the affected key populations and routes of transmission. The guideline panellists considered it unnecessary to develop new guidelines in China after assessing the quality of the international guidelines, the applicability to China of the recommendations, and the time and cost of developing new guidelines. They followed the ADAPTE approach,[15] included international guidelines, updated the evidence, and made the final recommendations after several consensus meetings

Box 2: Examples of factors necessitating de novo development of guidelines

Prioritisation of topics and questions

The health priorities in China may differ from those of other countries. Chinese guideline developers need to take this into account when identifying potential guideline topics. For instance, since 1 January 2016, Chinese couples have been allowed to have two children. One study shows that 70% of women of childbearing potential are older than 35 years in urban areas and 25-40% of them would like to have a second child.[16] On the other hand, evidence also indicates that advanced maternal age (>35 years) is associated with reduced fertility and a higher chance of miscarriage.[17] Evidence based recommendations on the diagnosis and treatment of infertility among women of advanced age were therefore needed. Since there were no such guidelines available in the world, the Chinese Medical Doctor Association's reproductive medicine specialised committee developed a guideline on this topic[18]

Diagnostic criteria

Around 95% of diagnostic criteria in China are estimated to come from Western countries.[19] This may cause inappropriate medical diagnoses and treatments for patients in China. For example, the World Health Organization defines overweight as a body mass index (BMI) ≥25 and obesity as a BMI ≥30 for adults. However, these diagnostic thresholds underestimate the prevalence of obesity in China. A meta-analysis of 239 972 Chinese adults showed that the risks of hypertension, type 2 diabetes, and dyslipidaemia increase dramatically with a BMI >24 .[20] The Chinese guidelines for prevention and control of overweight and obesity therefore define overweight as BMI ≥24 and obesity as BMI ≥28 [21]

Drug doses and treatment regimen

Some recommendations on drug dose and treatment regimens in international guidelines are not suitable for Chinese patients. For instance, US and European guidelines recommend 100 mg/2 h recombinant tissue-type plasminogen activator (rt-PA) for acute pulmonary thromboembolism.[22 23] However, high quality evidence from China showed that a 50 mg/2 h rt-PA regimen was as effective and possibly safer[24]

Adverse reactions

Chinese patients have a higher incidence and greater severity of adverse reactions to some drugs. Allopurinol was recommended for first line, urate lowering treatment in the 2017 British gout guideline because of its safety, effectiveness, and low cost.[25] The 2016 Chinese guideline on gout, however, assessed the strength of the recommendation for allopurinol use as weak[26] because it can induce severe cutaneous adverse reactions. These reactions correlate strongly with the allele human leucocyte antigen (HLA)-B*58:01,[27] which is much more common among Han Chinese (6-12%) than caucasians (<2%).[25] Because most Chinese hospitals cannot carry out genetic testing for this allele, the recommendation for allopurinol was not graded as strong

Values and preference

The values and preferences of patients and the general public may differ between China and Western countries because of different environments and cultures. For instance, in China, acupuncture has been traditionally used to prevent and treat disease, as well as to improve general health. Thus in a Chinese guideline, acupuncture is recommended for the treatment of overweight and obesity based on an investigation of the values and preferences of Chinese patients,[28] whereas pharmacotherapy is recommended as an adjunct to lifestyle treatment in US guidelines[29]

Market and profitability

Many drugs, including those on essential medicine lists, have disappeared in China in recent years because they are not seen as profitable by Chinese pharmaceutical companies. For instance, probenecid is recommended as the first choice drug to lower urate in the 2012 US gout guidelines.[30] However, because of its low price, very few drug companies in China produce it. Additionally, Chinese rheumatologists generally do not have experience with this drug. Thus, although the 2004 version of the Chinese gout guidelines mentioned probenecid, it is not discussed in subsequent versions (2011 and 2016)

Local policy, insurance coverage, and resource implications

Different medical insurance plans and policies can lead to different recommendations for the same intervention. For instance, febuxostat is first line treatment for urate lowering in gout in US guidelines,[30] where the annual cost per person for a dose of 80 mg daily is about $500 (£380, €430). In China, however, the annual cost is $2500 and this drug is not covered by health insurance. For this reason, the 2016 Chinese gout guidelines gave a weak recommendation for the use of febuxostat[26]

Approval by China Food and Drug Administration

Benzbromarone is a highly effective, well tolerated treatment for gout and is recommended in 2017 British guidelines.[25] In contrast, benzbromarone is not recommended in US guidelines and is not available in the USA owing to potential hepatotoxicity.[30] The China Food and Drug Administration approved the drug in 2000, and the 2016 Chinese gout guidelines include a weak recommendation after balancing its benefits, harms, and cost.[26] The market share of benzbromarone in China in 2017 is larger than the share of febuxostat plus allopurinol, mainly because benzbromarone is cheaper than febuxostat and is not associated with severe cutaneous adverse reactions. On the other hand, some effective drugs cannot be used in China because they have not been approved by the China Food and Drug Administration; for example, macitentan and riociguat are strongly recommended for pulmonary arterial hypertension in the 2015 European Society of Cardiology and the European Respiratory Society guidelines[31] but are not included in Chinese guidelines

traditional Chinese medicine was 50%[11] and the adherence rate of patients in gout treatment was 20-40%.[12]

Adoption, adaptation, and de novo development of clinical practice guidelines in China

Given the low quality of Chinese guidelines and the limited resources available, China needs to be strategic and pragmatic in developing new guidelines, and carefully prioritise its population's needs. The adoption or adaptation of existing high quality international guidelines is a potentially efficient and cost effective approach (see box 1).

International guidelines also have limitations, however: they may have methodological flaws, and different guidelines for the same topic may have inconsistent recommendations. Some factors that are relevant to China may be neglected, such as traditional Chinese medicine. Even if the recommendations are credible, consistent, and relevant, some critical factors remain that must be considered before they are implemented.

In many cases, therefore, China needs to develop guidelines de novo to meet the needs of its populations (see box 2).

Recommendations for Chinese guideline developers, methodologists, and policy makers

Based on the above discussions of guidelines in China, we propose the following recommendations to improve their quality and implementation.

Recommendation 1: examine existing guidelines

Chinese guideline developers should comprehensively review existing national and international guidelines before starting new guidelines. Once relevant guidelines are identified, developers should evaluate their quality, analyse included recommendations, and assess the evidence that supports each recommendation. To avoid unnecessary primary research, no new studies should be done without a systematic review of existing evidence.[32] Similarly for clinical practice guidelines, developers need to survey what has already been published. To facilitate this, the Guidelines International Network (G-I-N) database lists more than 6300 guidelines (http://www.g-i-n.net/library) and the US National Guideline Clearinghouse contains over 1600 (https://www.guideline.gov/browse/clinical-specialty).

Recommendation 2: determine local suitability

After a systematic review of existing guidelines, Chinese guideline developers should consider whether adoption, adaptation, or de novo development of guidelines is indicated. If the decision is for a de novo guideline, developers should follow well established processes and methods. Over the past decade, handbooks and methodological papers on guideline evaluation, development, and implementation have been translated into Chinese. The Chinese Medical Association, the largest and oldest non-governmental medical organisation in China, also released its first official guidance on how to develop and update evidence based guidelines.[33]

Recommendation 3: focus on guideline methods and implementation

Chinese guideline developers and methodologists should work together on guideline development and also on guideline methods and implementation research. Chinese researchers have published a number of guidelines and methodological papers in international medical journals. For example, they are taking a lead role in research on the reporting quality of guidelines and have developed a tool—RIGHT (Reporting Items for Practice Guidelines in Healthcare) checklist.[34] They are also focusing on registration of practice guidelines, managing a multilingual international practice guidelines registration platform (IPGRP).[35] As does the international clinical trials registry platform (ICTRP) and the international platform of prospective registrations of systematic reviews (PROSPERO), the IPGRP aims to improve transparency in guideline development and prevent duplication, as well as promote the collaboration, dissemination, and implementation of guidelines. In addition, Chinese guideline developers and methodologists can make major contributions to Chinese medical research as they highlight priorities and unanswered clinical questions in the section on research gaps that should be part of all clinical practice guidelines.

Recommendation 4: establish a national guideline system

Chinese guideline developers and policy makers should establish a national system to collect, disseminate, and implement guidelines, strengthen the management of conflict of interest, and provide quality assurance and control. Several newly formed institutions and collaborations are working to deal with these matters. For example, the National Health and Family Planning Commission of China opened a new agency in 2015: the National Center for Medical Service Administration. One of its key functions is to provide quality assurance and promote the use of guidelines. An ongoing programme of the agency is to build the China National Guideline Clearinghouse in collaboration with the WHO Collaborating Centre for Guideline Implementation and Knowledge Translation. Chinese clinicians and patients will have free access to this searchable database.

Recommendation 5: international collaboration

Chinese guideline developers and methodologists should enhance communication and cooperation with international guideline and evidence based healthcare organisations. For example, Cochrane China was established in 1999 and the Chinese GRADE (Grading of Recommendations Assessment, Development and Evaluation) Centre in 2011. These two centres are each part of an international network, and provide methodological training and produce systematic reviews to support the adaptation and development of guidelines in China. G-I-N Asia, cofounded by China, Japan, Korea, and Singapore in 2016, aims to lead, strengthen, and support collaboration across Asia.

In conclusion, the successful development, adaptation, and implementation of clinical practice guidelines in China depends on many factors, including the existence of high quality, relevant primary research studies from China; robust methods; efficient processes; adequate resources; quality assurance; widespread dissemination; implementation in health systems and by healthcare providers; and appropriate monitoring and feedback for quality improvement. Efforts are well underway to deal with all these factors and significant progress has been made. Trustworthy guidelines are an invaluable tool for helping Chinese patients and clinicians prevent and manage disease.

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