Reviewer Comments

This manuscript addressed some major problems with prescription during clinical practice. I have some suggestions for the authors.

Abstract

Background

Suggestion:

1. Using prescribing appropriateness instead of prescribing normality.

Reply 1: We have modified our text as advised (see Page 5 Line 105)

Changes in the text: There are some criteria about prescription appropriateness, such as Beers Criteria, which is the mainstay to characterize the potentially inappropriate prescription in geriatric population.

2. Suggest modifying the sentence of "there are no relevant domestic and international guidelines…..". The Beers criteria is one of the standards to be applied for judgment of potentially inappropriate medications and it was developed by the American Geriatric Society. Otherwise, the authors should specify which clinical problems were not be mentioned in these criteria.

Reply 2: We have modified our text in Page 3 to 4 Line 87 and 88.

Changes in the text: There are no relevant domestic and international guidelines, principles and standards which can help us to solve the problem.

3. "Abnormal prescriptions" was not usually used in literature. Suggest using prescription errors or other MeSH terms in the manuscript. Otherwise, the authors can define abnormal prescription.

Reply 3: Abnormal prescriptions also be regarded as Irrational prescriptions, which include non-standard prescription, inappropriate prescription and abnormal prescription.

Objective

There were too many "prescription" and "for" in the sentence. Suggest modifying the sentence briefly.

Reply 4: We have modified our text as advised (see Page 3 Line64 and 65)

Changes in the text: Objective: To develop the guideline for evaluation of prescriptions appropriateness in clinical practice.

Methods

Suggest modifying the sentence briefly or reducing the length of sentence.

Reply 5: We have modified our text as advised (see Page 3 Line66 to 69)

Changes in the text: Methods: The Pharmaceutical Affairs Commission of Chinese Hospital Association formed the guideline working group with multidisciplinary. Experts. The guideline working group summarized clinical questions in evaluation of prescription, searched support evidences and reached consensus for recommendations.

Conclusions

It was redundant to describe that the guideline could provide guidance. Suggest modifying the sentence.

Reply 6: We have modified our text as advised (see Page 3 Line73 and 74)

Changes in the text: Conclusions: Evaluation of Prescription appropriateness assessment could be more systematic and transparent based on this guideline.

Highlights

What is already known about the topic?

The first sentence should be modified for the subjects with plural nouns.

Reply 7: We have modified out text as advised(see Page 3 Line 87 and 88)

Changes in the text: There are challenges for professionals at hospital medical management department, clinician and pharmacist in clinical questions from inappropriate prescription and abnormal prescription identified by the electronic evaluation system of prescription.

Also, the Beers criteria is one of the standards to be applied for judgment of potentially inappropriate medications and it was developed by the American Geriatric Society. Otherwise, the authors should specify which clinical problems were not be mentioned in these criteria.

Reply 8: We have alreadt modified our text as advised(see Page 3 Line 85 to 87)

Changes in the text: However, if guidelines have different recommendation about an off-label prescription or guidelines have no recommendation, how should we evaluate the prescription appropriateness?

What does the paper add to existing knowledge?

The subjects in the second sentence might be changed to plural nouns.

Reply 9: We have modified out text in Page 4 Line 93 and 94.

Changes in the text:Introduced evidence synthesis of clinical practice guidelines systematic reviews and primary studies in the evaluation of prescription.

Background

There were explicit (Beers and STOPP, etc.) and implicit criteria (medication appropriateness index and pharmaceutical care network Europe-classification) for evaluating the appropriateness of prescription. Suggest adding the shortage of these criteria and why these could not be applied for irrational prescription or prescription appropriateness.

Reply 10: We have modified as advised(see Page 5 Line 103 to 110)

Changes in the text: There are some criteria about prescription appropriateness, such as Beers Criteria, which is the mainstay to characterize the potentially inappropriate prescription in geriatric population. But these criteria only focus on the appropriateness of several prescription in some population. The evaluation of prescription has to solve the questions about appropriateness of every prescription in the entire population. It's necessary to establish a process or a procedure to guide the professionals at hospital medical management department, clinician and pharmacist to search the best evidence to confirm the prescription appropriateness.

Method section

On page 6, second paragraph, line 125, what's the prescription comment system? Suggest describe the system briefly and the readers would know which problems might not be solved by this system.

Reply 11: We have modified our text in Page 6 Line 129to 131, 135 to 137

Changes in the text: There are some prescriptions that the electronic evaluation system of prescription cannot judge.

All the prescriptions were first evaluated by the electronic evaluation system of prescription, which contain label information of commonly used medicines of different manufacturers and guideline information of authoritative associations.

On page 7, first paragraph, line 145, the information in Google or Baidu were not reviewed by peers, suggest remove these websites and use information which was published on the website of the government.

Reply 12: We have modified as advised(see Page 7 Line 152 and 153)

Changes in the text: Remove Google and Baidu websites. 4) other sites such as the National Health Commission, National Medical Products Administration (NMPA) for relevant notices, standards and regulations.

Results

In clinical question 2, the other disease of the same type was vague. The drug to treat the off-label disease means that the disease was not listed in the drug indication in the instruction. Most instructions are specified for a certain class of disease. Therefore, the disease in the instruction might not always be classified as the same type of disease as off-label disease. Suggest modifying the description.

Reply 13: We have modified our text on Page 9 and Page 10 Line 204 to 213

Changes in the text: Two different diseases have with similar pathogenesis. Can the usage and dosage of the drug used to treat one disease of the drug instruction be used to treat another disease? Recommendation: Clinicians should provide evidence of effectiveness and safety of the prescribing drug to treat another disease. If there is a high or moderate level evidence supporting the treatment the disease with similar pathogenesis, the prescription is appropriate; otherwise, it should be judged as irrational. Explanation: Evidence of efficacy and safety should be provided for the treatment of any off-label disease. According to the 5S model of evidence-based medicine 5, the evidence levels of clinical practice guidelines, SR, RCT and observational studies were successively reduced. As the level of the evidence reduces, the likelihood of evaluating prescription as irrational increases.

In clinical question 3, the issue of this question might not have been listed in all guideline which was published by an authoritative authority. Therefore, the recommendation and explanation for this question might not give a guide for readers to answer question 3. A specific suggestion might be added to direct the practice when clinicians encounter this question.

Reply 14: We have modified our text on Page 10 Line 216 to 224

Changes in the text: For the following: the frequency or dose of the prescription exceeds the drug instruction; the diagnosis of the prescription not included in the indication of the drug instruction; the diagnosis of the prescription included in the contraindications of the drug, but the domestic guideline recommend the drug. How to judge the appropriateness of the

prescription? Recommendation: Clinicians should evaluate the domestic guideline that the prescription are based. A prescription may be deemed appropriate if the guideline is issued by an authority organization (national medical and health administration, association or society).Explanation: Guidelines issued by authority organization with access to rigorous methodological guidance and expert review are generally of higher quality.

In clinical question 4, difference frequency and dose between the Chinese and other population would be suggested for clinical practice for certain classes of drugs. The difference in weight, drug metabolism, and renal function would contribute to these differences. Suggest adding that clinicians should confirm the dose or frequency that the instruction listed for certain special populations, such as older adults or patients with chronic kidney disease.

Reply 15: We have modified our text on Page 11 Line 227 to 237

Changes in the text: If the indication, frequency or dose of the prescription does not comply with the drug instruction, which is also not recommended in domestic guidelines or guidelines for the special populations(such as overweight, diabetic, and renal hypofunction patients et, al.), but there are international guidelines or guidelines for normal populations to support the prescription, is the prescription appropriate ?Recommendation: Clinicians should search for evidence of the efficacy and safety of this drug in the domestic population or special populations, analyze whether it has been widely used in clinical practice, evaluate whether it is consistent with national or special conditions, elaborate the reasons for prescribing and form relevant research evidence, on this basis to judge whether the prescription is appropriate.Explanation: International guidelines and guidelines for normal populations generally lack supporting evidence on the drug usage in domestic and special population, so clinicians need to comprehensively elaborate on the necessity of prescribing this drug.

In the Discussion section, it was mentioned that the Delphi vote was used to establish these guidelines. The detailed process should be described in the method section. And the preliminary 27 clinical questions would provide information for readers about major problems encountered in the system and regraded as important ones by the experts. Also, the authors declared that "We also used the GRADE approach to rate the quality of evidence", but the 6 recommendations did not have been graded.

However, it needs major revision before publication. This manuscript seems to be the principle for prescribing in China. If authors want to publish as a guideline, suggest adding an evidence-grading system, such as quality of evidence and strength of recommendation for each recommendation. Also, how the experts decided these questions were included in this guideline? The results of the Delphi survey should be presented in the manuscripts.

Generally, there were many grammatical mistakes and repeating sentences. The manuscript should be edited by native English speakers before it is finally published.