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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10413-review.doc).

Title: Xiaoyao pill in treatment of functional dyspepsia associated with depression of perimenopausal women

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1)In this study, the patients with depression were included as FD. However, the dyspeptic symptoms in the patients with depression should be treated as a part of depression.

patients with depression are usually accompanied with FD and comply with FD diagnostic criteria and depression scale estimation. Mental factor is often regarded as the predisposing factor. Depression state can cause changes of secretion of some hormones and changes of vegetative nerve function, thus leading to FD. Current researches consider causal relationship between depression and FD is unclear. From the perspective of traditional Chinese medicine, liver catharsis malfunction affects the functions of the spleen and stomach.

(2)In this study, it is not clear whether the patients underwent upper endoscopy or not. FD should be diagnosed in the patients without organic diseases.

The diagnostic criteria were based on the Rome III criteria. Rome III criteria mention the definition of FD: one or more dyspepsia symptoms in the middle area of the upper abdomen last for 3 months without structural or metabolic diseases. No structural or metabolic diseases mean all are normal through endoscopy. No special description in the paper. I have modified this.

(3)The authors measured the levels of MOT and GAS, however, unfortunately, this finding was not discussed in the discussion well.

the discussion part of this research puts particular emphasis on expounding therapeutic mechanism of Xiaoyao pill to treat women patients with FD and depression in perimenopause. MOT and GAS indexes are supplemented in the discussion part.

(4)The authors followed up the patients after 6 months. However, it is not clear the criteria to measure the symptomatic scores.

Follow-up visit was conducted after 6-month treatment. The criteria of symptom scores are evaluated by referring to Standards on diagnosing and treating functional dyspepsia with traditional Chinese medicine.

(5)Please describe the ingredient and each dose of Xiaoyao pill in detail and possible side effects.

main ingredients of Xiaoyao pill contain: 200g Radix bupleuri, 200g angelica sinensis, 200g radix paeoniae alba, 200g bighead atractylodes rhizome (stir-baking with bran), 200g poria cocos (removing the peel), 50g mint and 50g liquorice. At present, there is no report on adverse effect.

(6)The authors mentioned that the symptoms of depression may be related to the concentration of serum 5-HT and estrogen. Is it more realistic to study their concentration in serum whether depression improvement is related to serum 5-HT and estrogen change, thus further affecting the FD?

Some researchers determined the expression of 5-hydroxytryptophan decarboxylase and 5-HT_{1A} receptor mRNA in the proximal gastric mucosal tissue of FD patients and normal person by RT-PCR semiquantitative method respectively and it was found that the expression of 5-hydroxytryptophan decarboxylase and 5-HT_{1A} receptor mRNA in the proximal gastric mucosa of FD patients was obviously higher than that of normal group and control group, thus, it was thought that the gastric hypersensitivity was related to the increase of 5-HT synthesis and 5-HT_{1A} receptor expression in the proximal gastric mucosa. The research showed that the estrogen could relax the lower esophageal sphincter (LES). After the joint treatment of the estrogen, progesterone and progesterone of opossum by Fisher et al, it was observed in the in vivo experiment that the reaction of LES to the gastrin and acetyl choline was reduced and the relaxation of LES of three groups was increased gradually. The clinical research showed that the LES pressure of women that took the contraceptive pill decreased significantly and 30%-50% of pregnant women were of gastroesophageal reflux disease, with heartburn as the main symptom. In addition, it is hoped that whether women's serum estrogen level in perimenopause and 5-HT content will further influence FD occurrence rate will be further discussed in future experiments.

(7)In “Inclusion and exclusion criteria”, were the patients of perimenopausal with hormone replacement or psychiatric consultation excluded from this study? the patients of perimenopausal with hormone replacement or psychiatric consultation should be excluded from this study. This has been modified in the exclusion criteria.

(8)The authors often used WPFd rather than MPFD (perimenopausal functional dyspepsia). Please define WPFd or unify to MPFD. Also, ‘TCM syndrome’ in Introduction was not defined. Please add explanation.

MPFD refers to functional dyspepsia in perimenopause. In the paper, MPFD is uniformly used. Traditional Chinese medicine considers that this disease is related to blocked emotion and weak spleen and stomach. The disease location is the stomach. The disease is closely related to liver and spleen, i.e. liver depression and spleen deficiency syndrome. It refers to the syndrome dominated by gastral cavity swelling pain due to liver qi stasis, stomach invasion and stomach imbalance. supplementary explanation has been made in Introduction.

(9)In Table 2, HAMD scores ‘before’ and ‘after 8 weeks’ should be statistically compared. In Table 3, statistic symbols are missing. According to Results, p value should be < 0.05. Furthermore, comparison between ‘before’ and ‘after’ as well

as ‘control’ and ‘treatment’ should be described.

for HAMD scores, the data of the two groups before and after 8-week treatment have been statistically compared. The mistakes of statistic symbols in Table 3 have been modified. Before and after the treatment, the treatment group and the control group have been described.

(10)Please correct spelling; compate --- compare, M receptor --- muscarinic receptor (I this you meant?)

the spelling mistakes have been corrected. M receptor refers to muscarinic receptor. This has been modified in the paper.

(11)‘Liver depression and spleen deficiency syndrome’ based on Chinese Medicine concept ‘liver qi’ is unclear, although describing in Discussion. The authors may cite some review articles explaining this concept.

the concept of liver qi in the paper is not expressed clearly. Liver qi refers to a manifestation of physiological function of the liver, mainly reflected in adjusting spirit and emotion and promoting digestion and absorption. Further explanation is made through citing literatures.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

Han-Guang Du