

**Chinese herbal medicine (MaZiRenWan)
for functional constipation: a prospective,
double-blinded, double-dummy,
randomized, controlled study**

Zhaoxiang BIAN

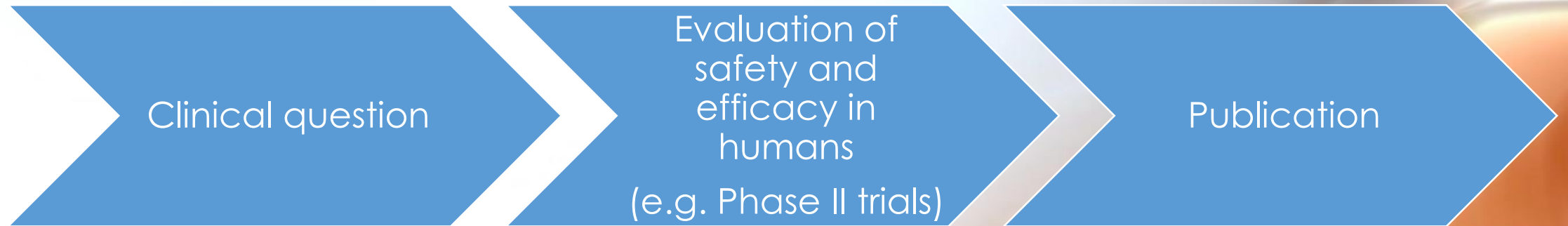
School of Chinese Medicine, Hong Kong Baptist University

Hong Kong Chinese Medicine Study Centre

Background

- Constipation: common chronic gastrointestinal disease
- Global prevalence: 0.7 – 79%, median 16%
- Rome III Criteria for functional constipation (FC):
 1. Must include at least two of the following:
 - a. Straining
 - b. Lumpy or hard stools
 - c. Sensation of incomplete evacuation
 - d. Sensation of anorectal obstruction/blockage
 - e. Manual maneuvers
 - f. <3 defecations/week
 2. Loose stools are rarely present
 3. Insufficient criteria for IBS

General approach of RCTs for TCM



Limitations:

Small sample size

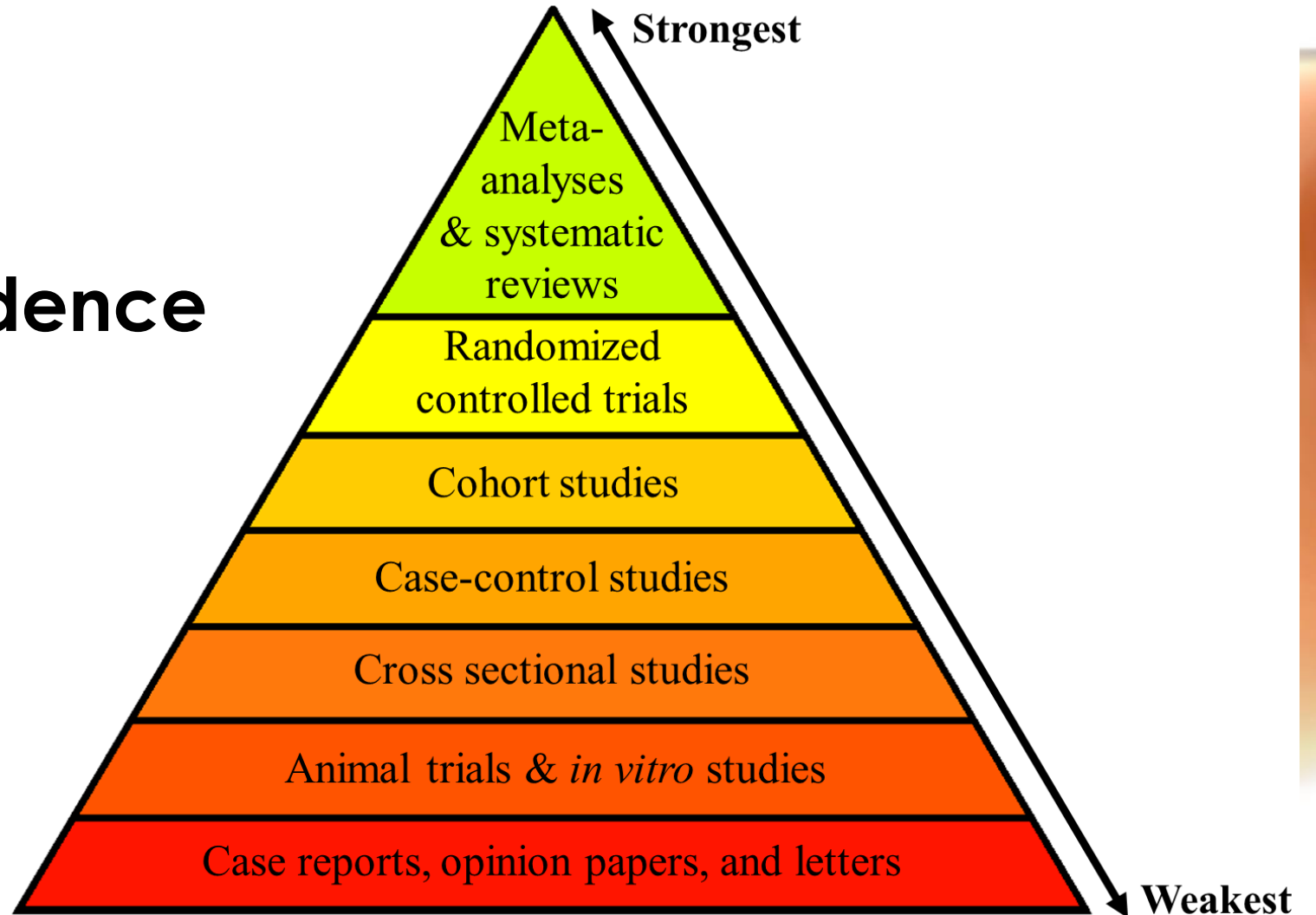
Lack of scientific background & explanation of rationale

Lack of sufficient details to allow replication

Lack of authentication & quality control of CHM interventions

Can CHM relieve FC?

Hierarchy of Scientific Evidence



Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.4886



World J Gastroenterol
World Journal of
© 2009 The WJG Press

REVIEW

Systematic review of Chinese herbal medicine for constipation

Chung-Wah Cheng, Zhao-Xiang Bian, Tai-Xiang Wu

Abstract

Constipation is a common gastrointestinal complaint in clinical practice, affecting an estimated 27% of the population. Many patients are disappointed by current conventional treatments and, therefore, seek help from complementary and alternative medicine (CAM). Traditional Chinese medicine, is the most important part of CAM and has been practiced for treating diseases and promoting the health of humans for thousands of years, and has become a popular alternative choice. Although there are many Chinese herbal medicine (CHM) interventions available, and some have been verified by clinical trials, their efficacy and safety are still questioned by both patients and health care providers worldwide. The purposes of this review are, first, to appraise the qualities of individual study designs in the new Cochrane approach. Second, the benefits of individual CHM interventions or individual types of CHM intervention for the treatment of functional constipation are analyzed. Finally, valid and comprehensive conclusions are drawn, if applicable, in order to make clinical recommendations.

REVIEW

Chinese herbal medicine for constipation: *zheng* among herbs, formulae and herb–drug interactions

Linda L. D. Zhong^{1,2†}, Guang Zheng^{1,5†}, Li Da Gai^{1,2,4} and Zhao Xiang Bian^{1,2*}

Abstract

Background: As current symptomatic treatments of constipation are still unsatisfactory, an increasing number of patients seek help from Chinese medicine (CM), particularly Chinese herbal medicine (CHM). This study aimed to review the most frequently used CHM herbs and formulae, proprietary CHMs, and herb–drug interactions for functional constipation using *zheng* (syndrome)-based differentiation, and to determine the current practice of *zheng*-based CHM treatments for functional constipation.

Methods: We developed a search strategy to include all the related clinical studies of CHM for constipation and set inclusion and exclusion criteria as studies on subjects with constipation of all ages and both sexes, using objective measures from laboratory or imaging techniques. The interventions included single herbs, CM classical formulae, CM new formulae, and Chinese herb-derived products and combination products. The clinical study types included were quasi- or randomized controlled trials, observational clinical studies, case series or case reports, and other types of appropriate research methods. The data concerning study design, sample size, mode of recruitment, sampling and diagnostic procedure, inclusion and exclusion criteria, and participants' characteristics (including age, sex, and duration of constipation). CM patterns, CM treatment principles, treatment regimen, and CM treatment outcomes were recorded.

Results: A total of 29,832 relevant records were found, of which 8541 were duplicate records and 20,639 were excluded for reasons of irrelevance. The full text of 965 articles was retrieved for detailed assessment, following which 480 articles were excluded for various reasons. From the included articles, we retrieved 190 different CM *zheng* diagnoses from 485 individual studies. The most common *zheng* was *dual deficiency of qi and blood* ($N = 48$), which was diagnosed in 948 out of 15,740 subjects. The most frequently used classical formula was *Ma-Zi-Ren-Wan* (MZRW) ($N = 75$) and the most frequently used proprietary CHM was *Run-Chang-Wan* ($N = 87$). The most frequently used combined medication was *Da Huang* with sodium bicarbonate tablets (frequency across all studies, $n = 23$), followed by *Fan Xie Ye* with lactulose oral solution ($n = 8$), *Ma-Ren-Ruan-Jiao-Nang* with lactulose oral solution ($n = 6$) and *Liu-Wei-An-Xiao-Jiao-Nang* ($n = 6$) with mosapride citrate tablets.

MaZiRenWan (MZRW) 麻子仁丸

- English name: hemp seed pills
- Origination: Discussion of Cold-induced Disorders (*Shang Han Lun*) in Han Dynasty (A.D. 200)
- Functions: moisten the intestines, drain heat, promote movement of Qi & unblock the bowel

➔ Potential treatment for FC



What is the optimal dose of MZRW?

→ Dose determination study



Is MZRW a myth of placebo effect?

→ Placebo-controlled RCT

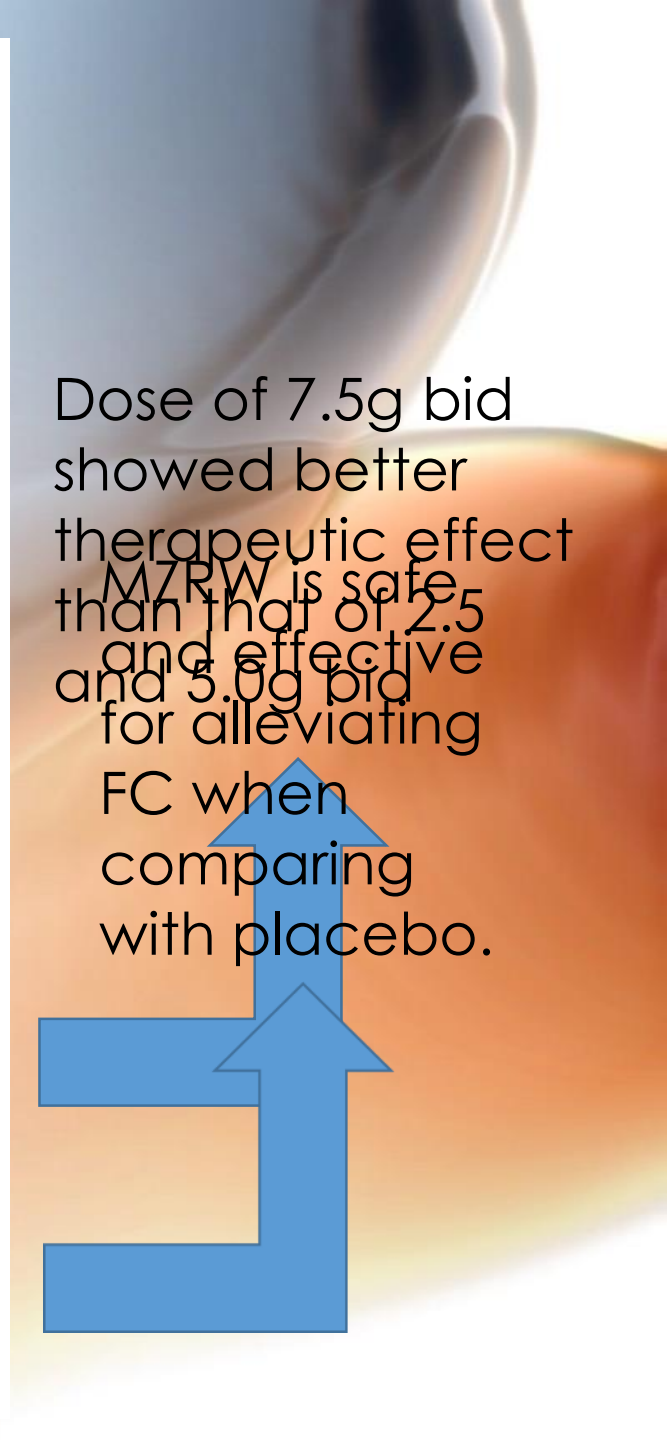
Placebo and Placebo Effect



Efficacy of a Chinese Herbal Proprietary Medicine (Hemp Seed Pill) for Functional Constipation

Chung-Wah Cheng, Mphil¹, Zhao-Xiang Bian, PhD¹, Li-Xing Zhu, PhD², Justin C.Y. Wu, MD³ and Joseph J.Y. Sung, MD, PhD³

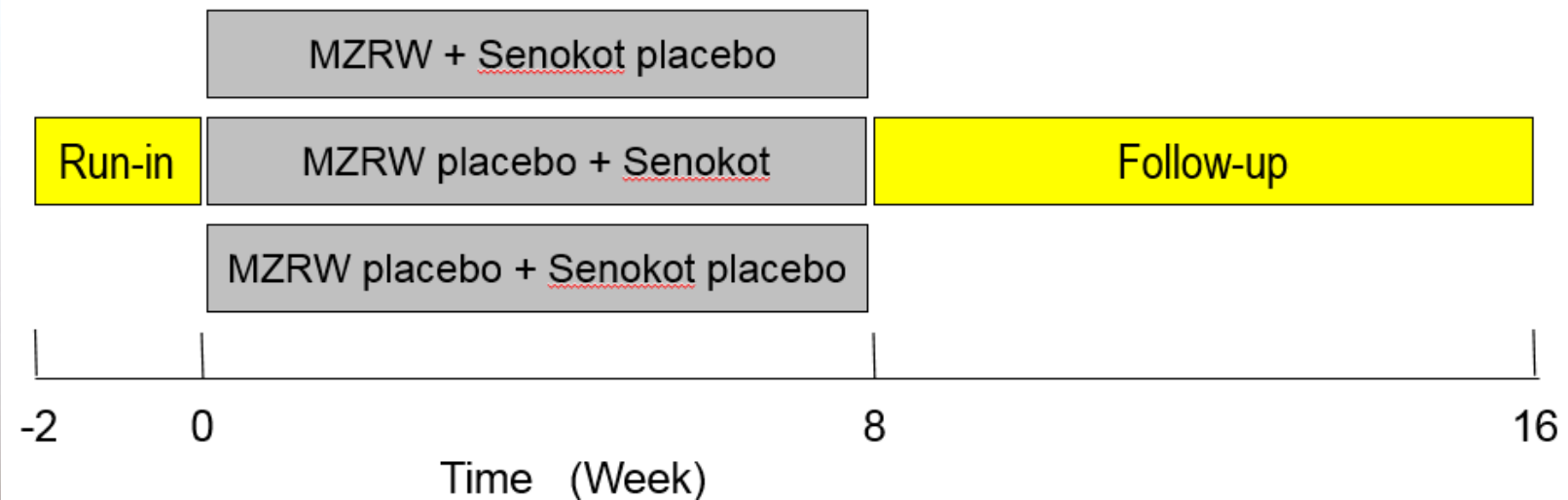
- OBJECTIVES:** Functional constipation (FC) is a common clinical complaint. Despite a lack of consolidated evidence, Chinese herbal medicine (CHM) has become a popular alternative treatment for this condition. The aim of this study was to assess, with a rigidly designed study, the efficacy and safety of a CHM proprietary medicine, Hemp Seed Pill (HSP), in optimal dosage for treating FC.
- METHODS:** This study comprised two parts: trial I, a dose determination study, and trial II, a placebo-controlled clinical study. In trial I, the optimal dosage of HSP was first determined from among three doses (2.5, 5.0, and 7.5 g b.i.d.). In trial II, a randomized double-blind study, the efficacy and safety of HSP for FC patients (Rome III criteria) in excessive syndrome as defined by traditional Chinese medicine (TCM) theory were compared with placebo. All participants in trials underwent a 2-week run-in, an 8-week treatment, and an 8-week follow-up. The primary end point was the responder rate for complete spontaneous bowel movement (CSBM) during treatment. Participants with a mean increase of CSBM ≥ 1 /week compared with their baselines were defined as responders. Secondary outcome measures included responder rate during follow-up, individual and global symptom assessments, and reported adverse effects (AEs).
- RESULTS:** The dose of 7.5 g b.i.d. showed better therapeutic effect than that of 2.5 and 5.0 g b.i.d. among 96 subjects (32 per arm) in trial I and was therefore selected for comparison with placebo in trial II. In trial II, 120 subjects were randomized into two arms (60 per arm). Responder rates for the HSP and placebo groups were 43.3 and 8.3% during treatment and 30.0 and 15.0% in the follow-up period, respectively ($P < 0.05$). Those in the HSP group showed benefit in terms of increased CSBM, relief in the severity of constipation and straining of evacuation, and effective reduction in the use of rescue therapy when compared with placebo. No serious AE was reported.
- CONCLUSIONS:** HSP (7.5 g b.i.d.) is safe and effective for alleviating FC for subjects in excessive syndrome. Optimal dose determination may be crucial for all CHM studies.



Dose of 7.5g bid showed better therapeutic effect than that of 2.5 and 5.0g bid for alleviating FC when comparing with placebo.

MZRW vs Active Control

- Design: multicenter, double-blind, double dummy RCT
- Interventions: MZRW, Senokot (first-line remedy) or placebo
- Participants: 291 FC patients in excessive pattern
- Study period: June 2013 to August 2015
- Clinical Trial Reg No: NCT01695850



Packages and appearances of MZRW, Senokot and their placebos



- I. The one-week course package of MZRW
- II. The appearances of MZRW & placebo
- III. The clear appearance of MZRW granules

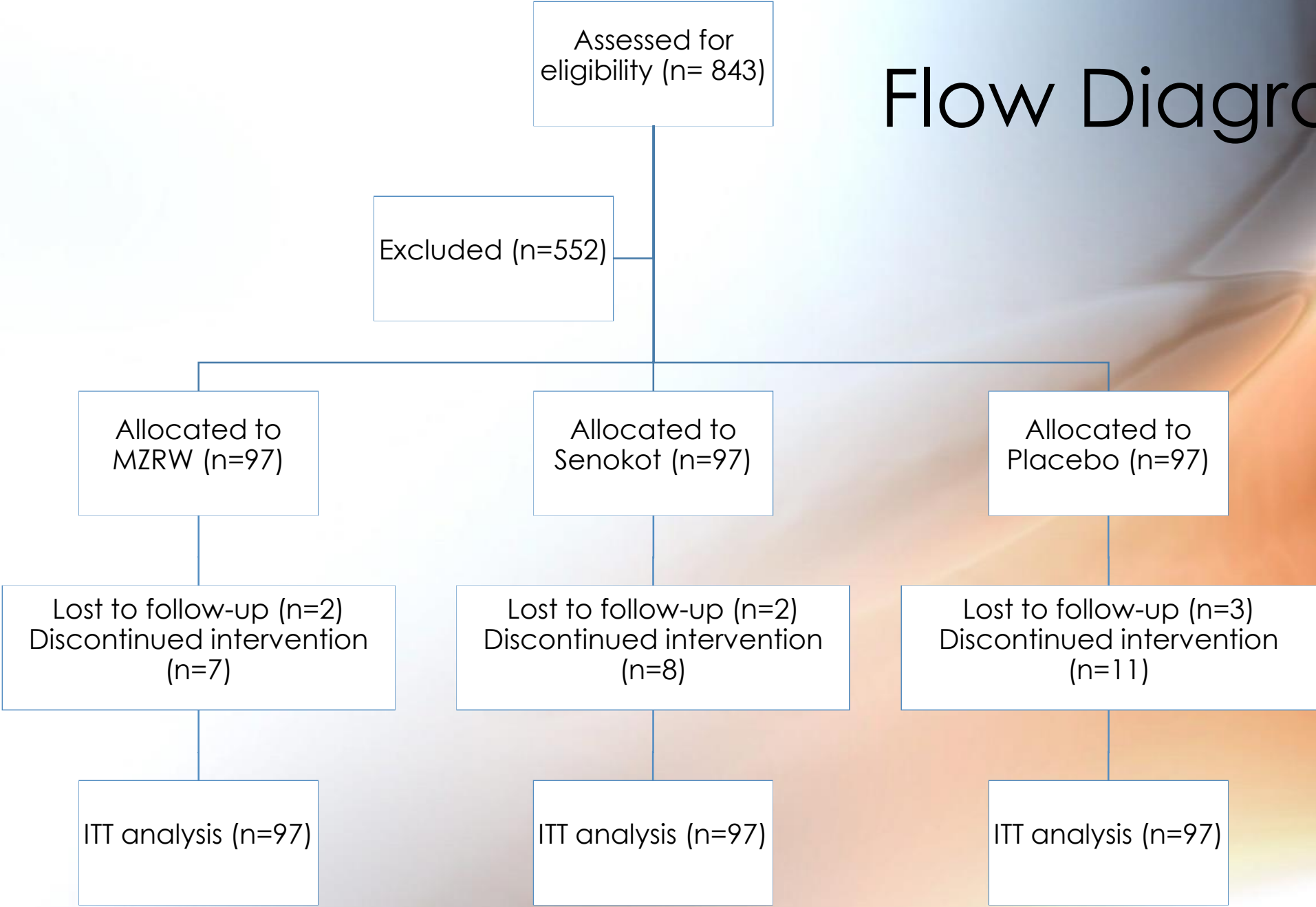
- I. The 4-week course package of Senokot & placebo
- II. The appearances of Senokot & placebo
- III. The appearance of Senokot

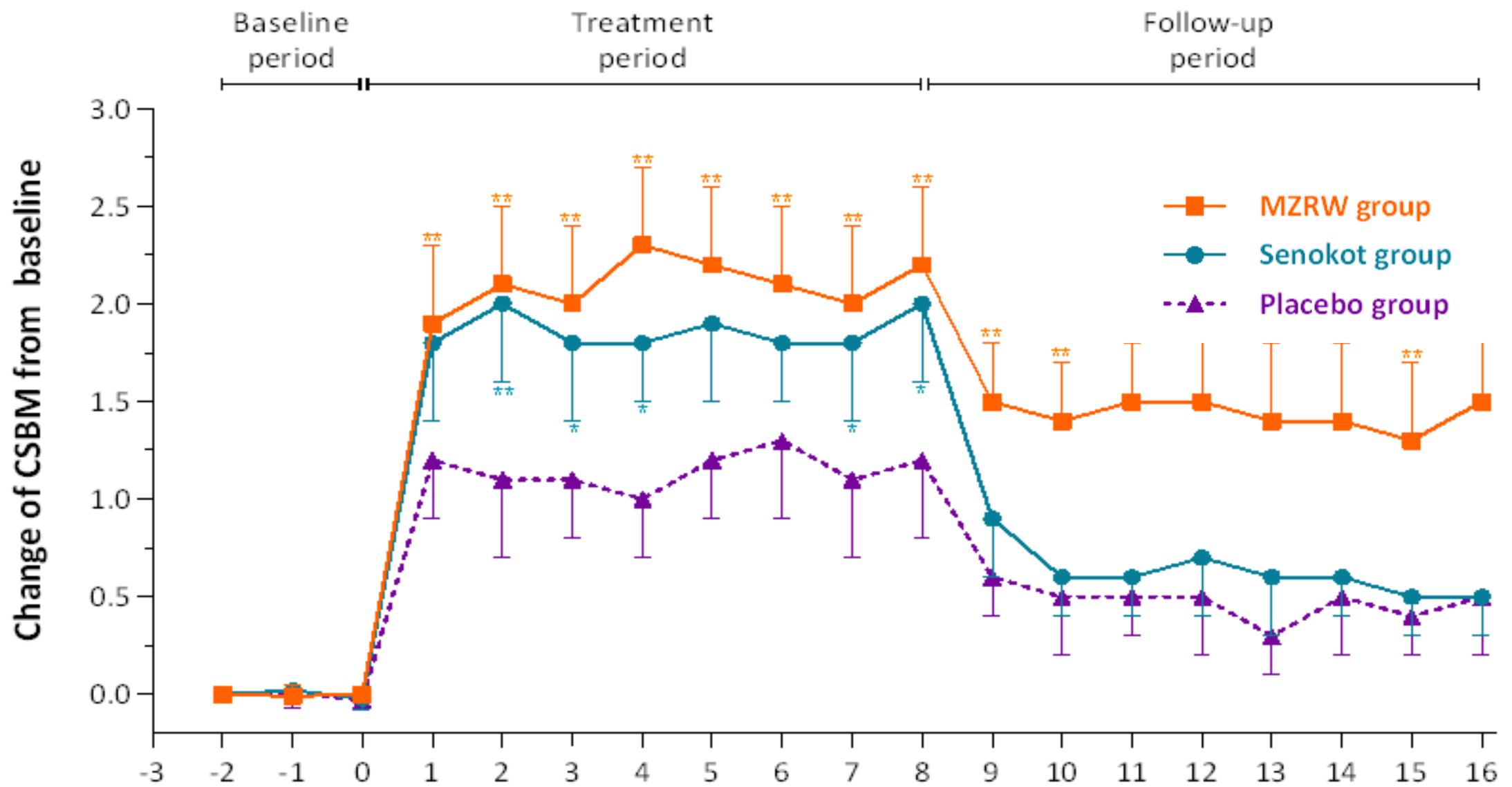
Outcome measures

- Primary outcome
 - Responder rate during treatment
 - Responders: mean increase ≥ 1 complete spontaneous bowel movement (CSBM) per week from baseline
- Secondary outcomes
 - Responder rate in follow-up
 - Colonic transit
 - Individual and global symptom assessments
 - SF-36
 - Adverse events

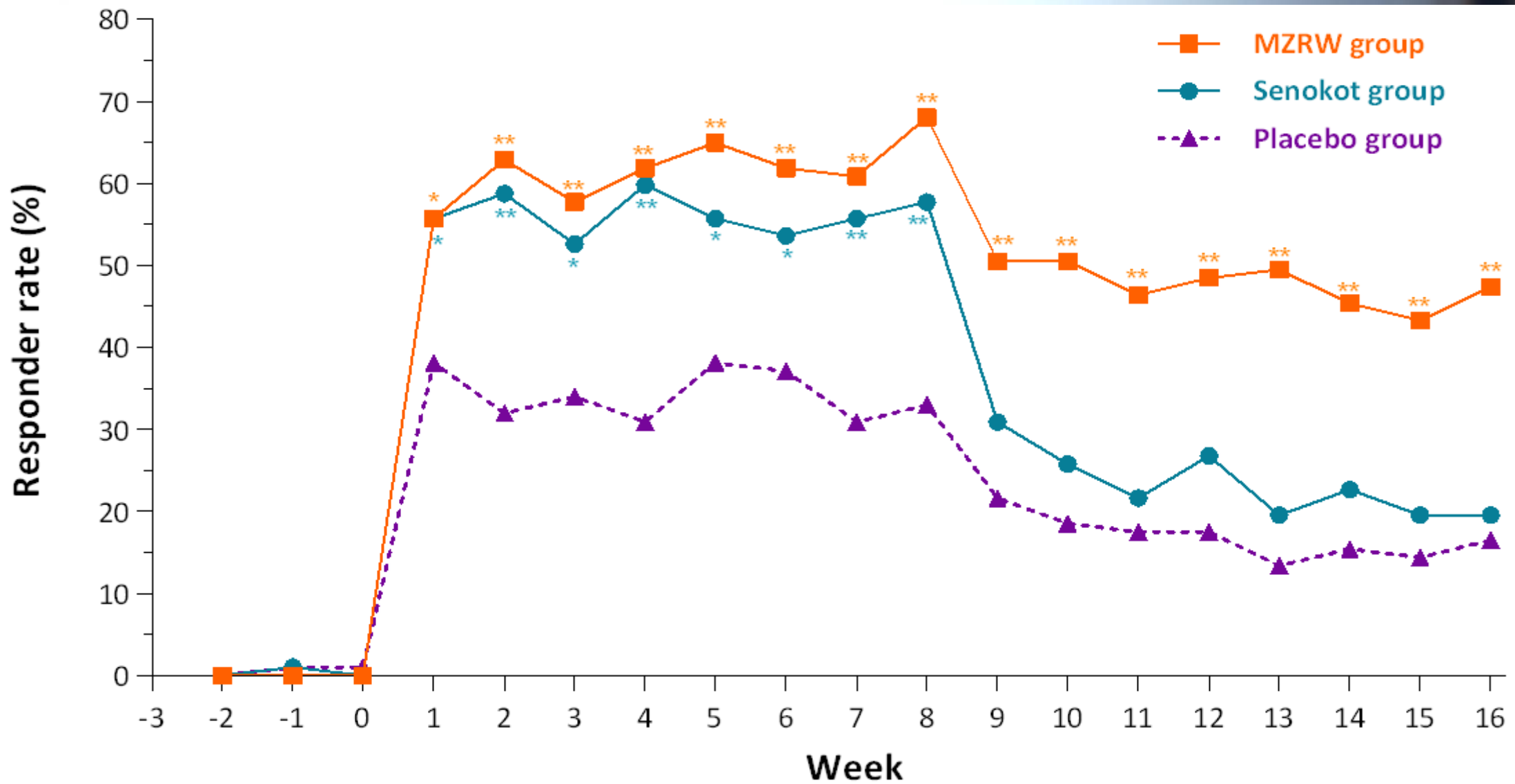


Flow Diagram





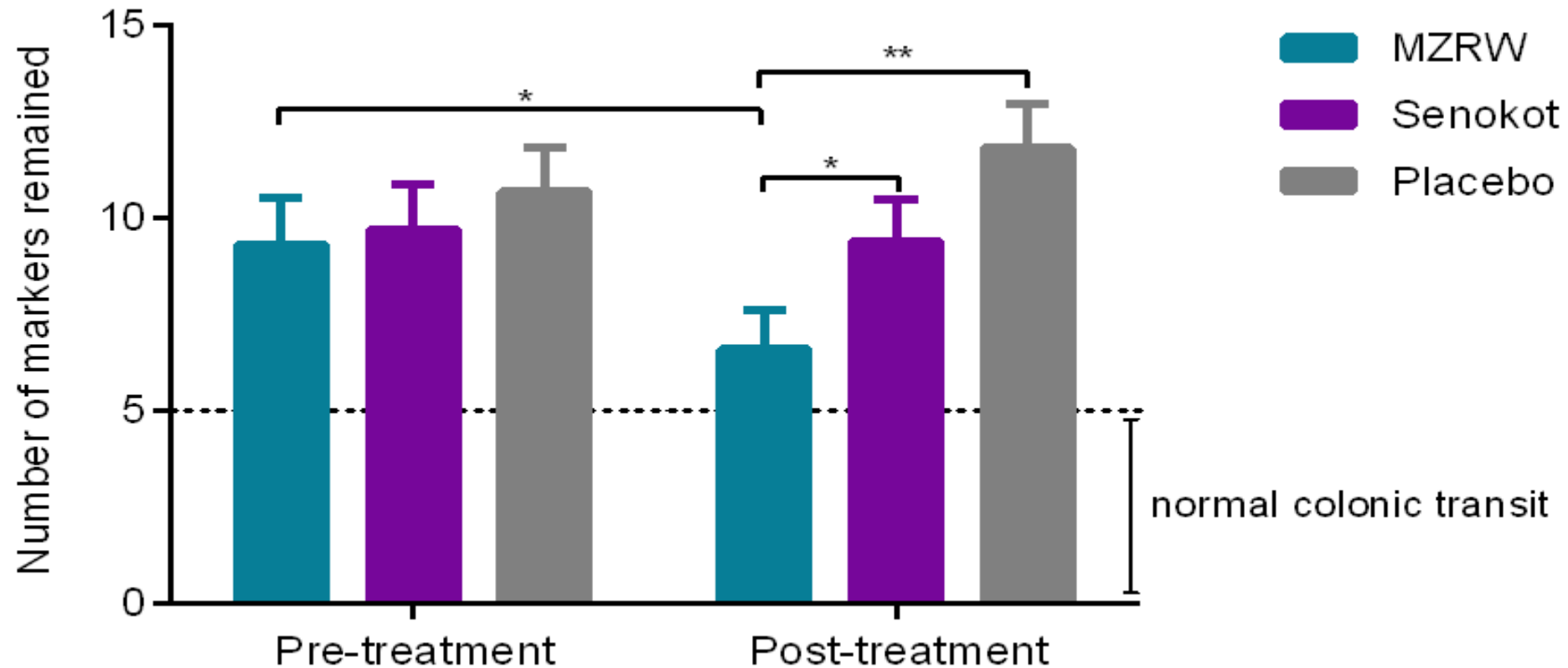
MZRW and Senokot increased 2.2 and 2.0 mean CSBM/wk during treatment, respectively ($P > 0.05$). Mean CSBM/wk of MZRW was 1.6 during follow-up, which was significantly higher than Senokot (0.6 CSBM/wk) and placebo (0.5 CSBM/wk), with $P < 0.0005$. *, $P < 0.05$, **, $P < 0.01$



Responder rate: mean increase ≥ 1 CSBM/wk from baseline.

During treatment: MZRW (68.0%) was comparable to Senokot (57.7%), $P=0.14$, and superior to placebo (33.0%), $P<0.005$. A sustained effect was in favor of MZRW over Senokot and placebo in the follow-up period ($P<0.0005$). MZRW (47.4%) vs Senokot (20.6%) vs placebo (16.5%). (*, $P<0.05$; **, $P<0.01$)

Changes of colonic transit



Prolonged colonic transit was found in all groups with 9.3 (SD: 9.3) in MZRW, 9.7 (SD: 9.1) in Senokot and 10.7 (SD: 8.7) in placebo ($P > 0.05$).

After treatment, MZRW significantly improved the colonic transit to 6.6 (SD: 8.0) when comparing with Senokot 9.4 (SD: 8.4), with $p = 0.036$; and placebo 11.8 (SD: 9.0), with $P = 0.004$. *, $P < 0.05$; **, $P < 0.01$

Summary

- Responder rate: MZRW comparable to Senokot during treatment, but superior than Senokot & placebo in follow-up.
- MZRW showed benefit in:
 - increased CSBM
 - improved colonic transit
 - relief severity of constipation, straining & incomplete evacuation
 - relief global constipation symptom
- Patients well tolerance & no serious AEs

Conclusion

- MZRW granules in 7.5g bid is safe & effective for alleviating FC in excessive pattern by comparing with Senokot and placebo.
- MZRW can be an alternative remedy for FC in clinical practice.
- Study model of MZRW can be a reference for other CHM.

Practical approach of CHM study



High quality clinical evidence yielded by:

- Rigid Study Design
- Rigorous Implementation
- Transparent Reporting



