Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

Common Mechanism of Pathogenesis in Gastrointestinal Diseases Implied by Consistent Efficacy of Single Chinese Medicine Formula

A PRISMA-Compliant Systematic Review and Meta-Analysis

Wei Ling, MD, Yang Li, MD, Wei Jiang, MD, Yi Sui, MD, PhD, and Hai-Lu Zhao, PhD

Abstract: Gastrointestinal (GI) disorders often manifest similar symptoms with overlapping clinical diagnosis and unmet medical needs. Traditional Chinese medicine (TCM) has history-proven benefits for GI diseases; albeit language barrier prevents Western readers from accessing the original reports in Chinese. The TCM formula *Si-Ni-San* (SNS) consists of 4 herbs targeting on homeostatic disturbances characterized by ''reflux'' and ''irritable'' problems. Here we used SNS as a therapeutic tool to explore the common mechanisms of pathogenesis in non-neoplastic GI diseases.

Data sources from PUBMED, Chinese National Knowledge Infrastructure, and Wanfang databases were searched for clinical trials. Comparisons were SNS as intervention and Western conventional medicine as control, which treat patients with upper GI disorders (gastroesophageal reflux disease, peptic ulcer, chronic gastritis, duodenogastric reflux), lower GI diseases (irritable bowel syndrome, ulcerative colitis), and functional dyspepsia. Participants and studies in accordance with the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement were eligible. We used the Jadad scale to assess methodological qualities, the fixed or random-effect model to evaluate therapeutic efficacy, and the funnel plots to explore publication bias. Outcome was clinical efficacy defined by symptom relief with normal GI endoscopy, radiology, and pathology.

We included 83 studies involving 7762 participants: 1708 versus 1397 of the upper GI disorders in 34 studies, 901 versus 768 of the lower GI diseases in 19 studies, 1641 versus 1348 of functional dyspepsia in 30 studies, and 328 versus 287 of relapse rate in 8 studies. Six studies had a Jadad score >2 points and the rest were <2 points. Pooled data showed significant efficacy of SNS for the upper GI disorders (odds ratio [OR] = 3.9, 95% confidence interval [CI] = 3.09–4.92), lower GI diseases (OR = 4.91, 95% CI = 3.71–6.51), and functional dyspepsia (N = 2989; OR = 3.94, 95% CI = 3.17–4.90). The relapse rate was 12.9% for SNS, significantly <46.5% for conventional therapies (OR = 0.16, 95% CI = 0.11–0.25).

The consistent efficacy of the single TCM formula implicates common mechanisms of pathogenesis in GI disorders.

(*Medicine* 94(27):e1111)

Abbreviations: DGR = duodenogastric reflux, GERD = gastroesophageal reflux disease, IBS = irritable bowel syndrome, SNS = *Si-Ni-San*, TCM = traditional Chinese medicine.

INTRODUCTION

Individuals with digestive problems are often diagnosed on symptoms grounds alone. Dyspepsia, heartburn, non-cardiac chest pain, abdominal pain, chronic diarrhea, and constipation are common symptoms complained by individuals who have no histopathological explanation. Common digestive diseases such as gastroesophageal reflux disease (GERD), chronic gastritis, duodenogastric reflux, and irritable bowel syndrome (IBS) are clinically symptom-based diagnosis with considerable overlap and symptom fluctuation over time.[1] GERD symptoms in individuals with IBS are 4-fold that of individuals without IBS.[2,3] Similarly, IBS symptoms frequently co-exist with biopsy-proved celiac disease,[4] Crohn disease, and ulcerative colitis.[5] Furthermore, IBS individuals usually suffer from dyspepsia[6,7] and chronic idiopathic constipation.[8] It remains uncertain whether all these common digestive disorders share common mechanisms of pathogenesis.[2,9]

Traditional Chinese medicine (TCM) is typically symptoms-based approach with history-proven therapeutic efficacy. TCM physicians have used classic formula comprising of several ingredient herbs to achieve symptom relief,[10] sustain metabolic homeostasis,[11,12] and prolong patients' survival.[13] One of the classic formulas designed about 220 B.C. for relieving digestive symptoms is *Si-Ni-San* (SNS), consisting of 4 herbs *Radix Bupleuri*, *Radix paeoniae Alba*, *Fructus Aurantii Immaturus,* and *Radix Glycyrrhizae*. Most of the clinical studies of SNS have been reported in Chinese, not readable by any non-Chinese. Hereby, we conducted a systematic review and meta-analysis to evaluate the clinical efficacy of SNS on common digestive disorders, and to use TCM as a tool to validate the hypothesis that all common GI problems have shared mechanisms of pathogenesis.

Editor: Bulent Kantarceken.
Received: October 16, 2014; revised: May 8, 2015; accepted: June 8, 2015.
From the Center for Systems Medicine, Guilin Medical University, Guilin (WL, YL, WJ, YS, H-LZ); Department of Gastroenterology, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot (YL); Department of Traditional Chinese Medicine, The Affiliated Hospital of Guilin Medical University, Guilin (WJ); and Guangdong Hospital of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine, Guangzhou, China (YS).
Correspondence: Dr. Hai-Lu Zhao, Director, Center for Systems Medicine, Guangxi Key Laboratory of Excellence, Director, Institute of Basic Medical Sciences, Director, Metabolism and Translational Medicine, Guilin Medical University, Guilin 541004, China (e-mail: zhaohailu9@126.com; zhaohailu@glmc.edu.cn).
This work was supported by grants from the Guilin Medical University (KY2011002), Program for Innovative Research Team of Guilin Medical University (PIRTGMU), Guangxi Key Laboratory of Systems Medicine and National Natural Science Foundation of China (81270934).
WL and YL contributed equally to this study.
The authors report no conflicts of interest.
Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.
ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001111

METHODS

The present study was approved by the Ethics Committee Board of Guilin Medical University (GLMC030811HL) and conducted in accordance with the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. We had also reviewed each article and found 5 articles mentioned in the Method section that ethical approval and written informed consent were obtained.

Search Strategy and Databases

We searched up to March 2014 the following electronic databases: the Chinese National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database, the *Wanfang* Database and the PubMed. All potentially relevant articles including reference lists of retrieved articles were investigated as full text in English or Chinese. For ambiguous or missing information, we contacted the authors where possible. For duplicate publications, the original publication was used. Medical terms used in literature search were as follows: gastroesophageal reflux diseases, peptic ulcer, duodenogastric reflux disease, chronic gastritis, irritable bowel syndrome, functional dyspepsia, and ulcerative colitis, and in combination with "*Si-Ni-San (Sini San or sinisan)*". Figure 1 shows the ingredient herbs and their ratios of SNS.

Eligibility Criteria

Studies meeting the following criteria were included: randomized controlled trials stating the phrase "randomization" (no restriction was imposed on studies with respect to blinding and type of design such as parallel or cross-over); participants with GERD, peptic ulcer, duodenogastric reflux, functional dyspepsia, chronic gastritis, IBS, or ulcerative colitis, irrespective of age, sex, ethnic origin, and geography; the patients were diagnosed using the latest guideline by the year of the study conducted (pregnant, lactating women, and patients with serious medical conditions were excluded); and intervention was SNS, whereas control could be western conventional medicine, studies with co-intervention were excluded if they were given to both groups.

Studies meeting the following criteria were excluded: duplication (the same data of patients with the same authors published in different journals); information of diagnostic criteria, participants, interventions, or outcomes were not defined; observational studies, reviews, and case series reports; studies not meeting the inclusion criteria. Eligibility assessment was performed independently by 2 investigators (LW and JW), using pre-designed eligibility forms, with all questions resolved by consensus with other authors.

Data Extraction and Quality Assessment

Two reviewers (LY and LW) independently conducted the literature search, study selection, and data extraction. The extracted data included authors, title of the study, publication date, study design, characteristics of participants, details of intervention, outcome measures, intervention durations, adverse events, and any relapse of uncomfortable symptoms. Disagreement was resolved by discussion and consensus with the TCM experts (SY and JW). The quality assessment of the trials selected for inclusion was evaluated using the Jadad score.[16] The final Jadad score ranged from 0 to 5 points, with high scores indicating high quality. Studies with a Jadad score of 2 or less were considered to have low quality and those with a Jadad score of $\geq$3 were considered to have high quality.[17]

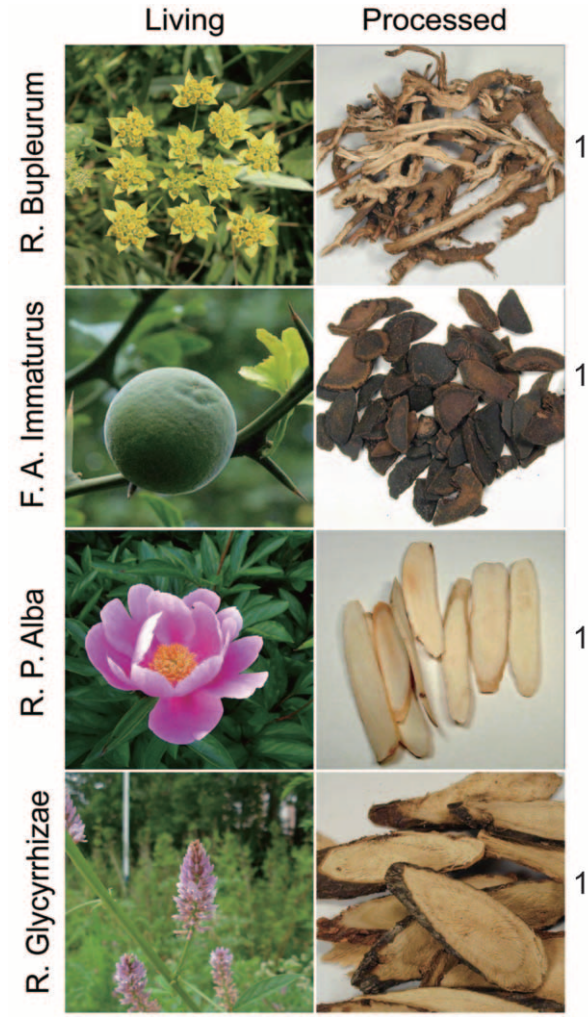

FIGURE 1. Ingredient herbs and their ratio for *Si-Ni-San* formula.

Outcome Measures

Outcome was clinical efficacy defined by symptom relief with normal endoscopies results: relief of the clinical symptoms according to the latest guidelines implemented by the year the study conducted; normalization of GI endoscopies, radiology, and pathology.

For functional dyspepsia diagnosed on symptoms grounds alone, we strictly followed the Rome III criteria. The formula to calculate the clinical effect index (EI) is as follows: EI = (pre-(pretreatment scores – post-treatment scores)/pretreatment scores × 100%, whereas the treatment scores were calculated by the degree of clinical symptoms.

Relapse rate and adverse events were extracted for the evaluation of sustained effectiveness and safety concern.

Data Synthesis

Revman 5.1 software provided by the Cochrane Collaboration was used to combine results from >2 separate trials to generate forest plots of pooled efficacy rates, pooled odds ratio (OR), and 95% confidence interval (CI). Before the results of the studies were combined, statistical heterogeneity among studies was estimated using the chi-square test and I^2 test ($P > 0.05$ and $I^2 < 50\%$ indicate acceptable heterogeneity between the pooled

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

studies). Fixed-effect model can be appropriate when there is statistical homogeneity ($P > 0.1$, $I^2 < 50\%$) among the studies, and random-effect model has to be pursued when statistical heterogeneity ($P < 0.1$, $I^2 > 50\%$) exists in the trials. Intervention effects were expressed OR and the associated 95% CI as calculated for dichotomous outcomes. The funnel plot was used for publication bias. A symmetric inverted funnel indicates that publication bias is unlikely, whereas an asymmetric funnel signifies the possibility of either publication bias or a systematic difference between smaller and larger study effects.

RESULTS

Study Description

A total of 859 articles were initially identified and eventually 83 randomized controlled studies, involving 7763 patients (4,250 in SNS groups and 3,513 in control groups) were in accordance with our inclusion criteria (Figure 2). Among the 83 studies, listed in the Appendix, http://links.lww.com/MD/A331, 6 studies were postgraduate candidate thesis, and 77 journal articles. All the 83 studies were conducted in China. Trials treating GERD were observed in 7 studies, peptic ulcer in 6 studies, functional dyspepsia in 30 studies, chronic gastritis in 6 studies, duodenogastric reflux in 15 studies, IBS in 15 studies, and ulcerative colitis in 3 studies. The duration of all studies ranged from 15 days to 90 days. Eight RCTs had reported the relapse rate after treatment discontinuation (615 patients, 328 in SNS groups and 287 in control groups). Clinical characteristics are summarized in Table 1.

Outcome of Interventions

Effects of SNS Versus Conventional Therapy on Upper GI Diseases

Thirty-four independent trials (SNS: 1708; control, 1397 patients) reported SNS-treated GERD, peptic ulcer, chronic gastritis, and duodenogastric reflux with homogeneity in the consistency of the trial results ($P = 1.00$, $I^2 = 0\%$); therefore, fixed-effects model was used for statistical analysis. As shown in Figure 3A, higher efficacy rate was attributed to SNS than conventional therapy for duodenogastric reflux (OR = 3.83, 95% CI = 2.71–5.41), GERD (OR = 3.93, 95% CI = 2.42–6.38), chronic gastritis (OR = 5.09, 95% CI = 2.83–9.14), and peptic ulcer (OR = 2.99, 95% CI = 1.65–5.43). The combined OR was 3.90 (95% CI = 3.09–4.92) with significant overall effect ($Z = 11.44$, $P < 0.001$). The funnel plot was roughly symmetric, indicating little publication bias for the 4 diseases (Figure 3B).

Effects of SNS Versus Conventional Therapy on Lower GI Diseases

SNS-treated 901 patients and 768 control subjects were included in 19 studies of lower GI diseases (16 in IBS, 3 in ulcerative colitis). Fixed-effects model was used for statistical analysis ($P = 0.81$, $I^2 = 0\%$). Consistently, SNS showed higher efficacy rates than conventional treatment (IBS: OR = 4.81, 95% CI = 2.71–5.41; ulcerative colitis: OR = 2.40, 95% CI = 1.21–4.75). Pooled results showed an OR as 4.91 (95% CI = 3.71–6.51) with overall effect as 2.50 ($P < 0.001$) (Figure 4A). The funnel plot demonstrated no apparent asymmetry, suggesting publication bias unlikely (Figure 4B).

Effects of SNS Versus Conventional Therapy on Functional Dyspepsia

Thirty studies of functional dyspepsia involving 2989 participants (1641 in SNS group) were qualified for the comparison with significant heterogeneity in the 2 groups ($P = 0.99$; $I^2 = 0\%$); thus, fixed-effects model was used for statistical analysis. The outcomes favored SNS group by pooled data (OR = 3.94, 95% CI = 3.17–4.90) and test for overall effect ($Z = 12.39$, $P < 0.001$) (Figure 5A). The funnel plot was roughly symmetric, indicating little publication bias of the studies (Figure 5B).

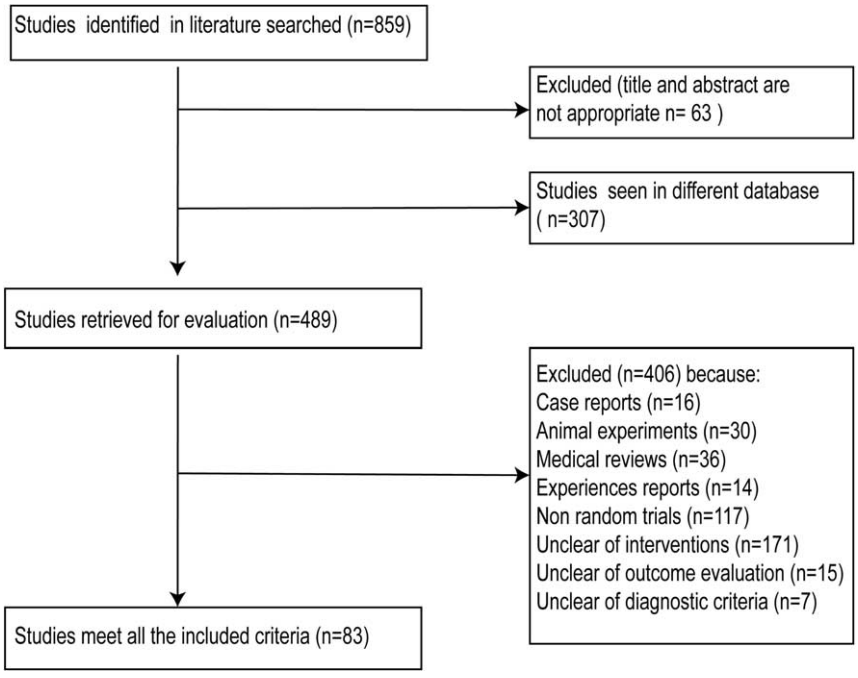

FIGURE 2. Flow chart of the study selection process.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 1. Summary of the Characteristics of the Included Trials

		Sample Size	Sex			Intervention	Effectiveness	Ineffectiveness	Duration
First Author	Diagnosis	EG/CG	M (EG/CG)	F (EG/CG)	EG	CG	EG/CG	EG/CG	(d)
Yu 2012[1]	FD	41/41	23/22	18/19	SNS	Domperidone	37/29	4/12	15
Deng 2011[2]	FD	30/30	12/11	28/27	SNS	Domperidon, cimetidine	28/21	2/9	30
Wang 2011[3]	FD	33/32	15/32	17/16	SNS	Domperidone	31/29	2/3	28
Han 2011[4]	FD	30/30	11/9	19/21	SNS	Deanxit, domperidone	29/27	1/3	28
Dang 2011[5]	FD	40/40	12/11	28/27	SNS	Domperidone	36/28	4/12	28
Chen 2010[6]	FD	38/37	13/16	25/21	SNS	Domperidone	35/31	3/6	28
Pei 2010[7]	FD	45/40	21/19	24/21	SNS	Mosapride	42/31	3/9	28
Wang 2010[8]	FD	25/25	10/12	15/13	SNS	Domperidone	21/19	4/6	28
Li 2009[9]	FD	50/50	21/18	29/32	SNS	Domperidone	46/38	4/12	28
Wang 2009[10]	FD	30/40	18/16	22/24	SNS	Domperidone	29/25	1/15	28
Zou 2009[11]	FD	35/35	15/16	25/19	SNS	Domperidone	31/23	4/12	28
Zhuang 2009[12]	FD	78/60	36/32	42/28	SNS	Domperidone	75/41	3/19	28
Jin 2008[13]	FD	120/118	58/54	62/64	SNS	Domperidone	108/80	12/38	30
Song 2008[14]	FD	32/32	13/19	12/20	SNS	Domperidone, omeprazole	30/25	2/7	28
Zhou 2008[15]	FD	32/32	11/21	14/20	SNS	Domperidone	29/24	3/8	28
Yao 2008[16]	FD	76/50	32/22	44/28	SNS	Domperidone	71/39	5/11	28
Sun 2008[17]	FD	40/40	/	/	SNS	Domperidone	36/28	4/12	28
Guo 2007[18]	FD	56/34	24/14	32/20	SNS	Domperidone	51/25	5/9	28
Shu 2007[19]	FD	76/60	30/24	46/36	SNS	Domperidone, oryzanol	68/44	8/16	28
Zhen 2007[20]	FD	40/26	16/10	24/16	SNS	Cisapride	39/20	1/6	28
Wang 2007[21]	FD	180/120	84/54	96/66	SNS	Mosapride	167/92	13/28	30
Gao 2006[22]	FD	60/60	28/26	32/34	SNS	Domperidone	54/41	6/19	28
Wang 2005[23]	FD	90/30	44/14	46/16	SNS	Domperidone	83/22	7/8	28
Shu 2004[24]	FD	86/80	25/24	61/56	SNS	Domperidone	80/60	6/20	28
Shen 2004[25]	FD	38/37	11/10	27/27	SNS	Domperidone	35/29	3/8	28
Liu 2004[26]	FD	50/30	17/10	33/20	SNS	Domperidone	47/21	3/9	28
Xue 2001[27]	FD	52/48	23/21	29/27	SNS	Domperidone	49/39	3/9	28
Hu 2001[28]	FD	58/30	22/13	36/17	SNS	Domperidone	52/24	6/6	28
Chen 2001[29]	FD	30/30	18/17	12/13	SNS	Domperidone	28/22	2/8	28
Jiang 2000[30]	FD	40/30	18/13	22/17	SNS	Domperidone	39/26	1/4	30
Huang 2012[31]	DGR	120/60	79/40	41/20	SNS	Itopride, hydrotalcite	111/48	9/12	28
Chen 2012[32]	DGR	38/36	18/17	20/19	SNS	Omeprazole, domperidone	35/25	3/11	48
Lin 2011[33]	DGR	41/41	/	/	SNS	Omeprazole, domperidone	39/34	2/7	48
Li 2011[34]	DGR	30/30	12/14	18/16	SNS	Pantoprazole, domperidone	27/21	3/9	32
Tian 2010[35]	DGR	48/48	21/19	27/29	SNS	Domperidone, hydrotalcite	43/35	5/13	28
Li 2010[36]	DGR	30/30	16/16	14/14	SNS	Domperidone, hydrotalcite	26/25	4/5	58
Chu 2010[37]	DGR	46/45	24/23	22/22	SNS	Metoclopramide, cisapride	43/36	3/9	60
Liu 2009[38]	DGR	30/30	12/10	18/20	SNS	Ranitidine, domperidone	29/25	1/5	28
Jin 2009[39]	DGR	43/42	/	/	SNS	Domperidone	40/33	3/9	15
Fan 2009[40]	DGR	72/60	32/26	40/34	SNS	Domperidone	68/49	4/11	28
Ling 2008[41]	DGR	38/37	21/20	17/17	SNS	Metoclopramide	36/29	2/8	56
Li 2008[42]	DGR	95/61	/	/	SNS	Domperidone	92/51	3/10	30
Hu 2008[43]	DGR	65/40	28/17	37/23	SNS	Urso, sucralfate	60/31	5/9	28
Liu 2007[44]	DGR	56/50	26/22	30/28	SNS	Ranitidine	54/39	2/11	30
Ma 2003[45]	DGR	40/35	28/25	12/1	SNS	Domperidone	38/29	2/6	90
Liu 2012[46]	IBS	59/56	21/19	38/37	SNS	Pinaverium bromide	55/32	4/24	28
Li 2012[47]	IBS	68/57	/	/	SNS	Trimebutine	58/38	10/19	28
Xiong 11[48]	IBS	35/20	/	/	SNS	Omeprazole	33/14	2/6	28
Wang 2011[49]	IBS	29/29	12/13	17/16	SNS	Berberine, oryzanol	26/18	3/11	28
Tang 2011[50]	IBS	25/25	14/12	11/13	SNS	Changtai heji	22/16	3/9	28
Peng 2011[51]	IBS	94/90	48/46	46/44	SNS	Smectite powder	84/62	10/28	90
Liu 2011[52]	IBS	60/40	20/16	40/24	SNS	Loperamide hydrochloride	55/30	5/10	28
Du 2011[53]	IBS	34/28	15/12	19/16	SNS	Arnold siqiong	30/19	4/9	28
Weng 2009[54]	IBS	32/32	14/10	18/14	SNS	Dicetel	30/24	2/8	28
Lao 2009[55]	IBS	38/34	20/18	18/16	SNS	Bifico	33/20	5/14	28
Zhang 2008[56]	IBS	68/54	30/24	38/30	SNS	Dicetel	61/37	7/17	30
Lan 2008[57]	IBS	32/24	12/8	20/16	SNS	Pinaverium bromide	28/20	4/4	28
Wang 2007[58]	IBS	50/40	22/18	28/22	SNS	Trimebutine maleate	48/30	2/10	30
Song 2007[59]	IBS	45/31	26/14	19/17	SNS	Bifidobiogen	42/17	3/14	60
Huang 2007[60]	IBS	52/52	25/24	27/28	SNS	Nifedipine, oryzanol	50/38	2/14	90
Jia 2006[61]	IBS	45/45	15/16	30/29	SNS	Bifidobiogen, oryzanol	42/30	3/15	10
Xu 2006[62]	GERD	50/50	27/25	23/25	SNS	Domperidone	47/39	3/11	28
Zhu 2007[63]	GERD	50/30	34/20	18/10	SNS	Domperidone	47/23	3/7	28
Ou 2007[64]	GERD	42/38	/	/	SNS	Domperidone	38/26	4/12	28

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

		Sample Size	Sex			Intervention	Effectiveness	Ineffectiveness	Duration
First Author	Diagnosis	EG/CG	M (EG/CG)	F (EG/CG)	EG	CG	EG/CG	EG/CG	(d)
Lin 2012[65]	GERD	80/80	/	/	SNS	Domperidone	78/66	2/14	28
Yang 2003[66]	GERD	50/50	28/30	22/20	SNS	Domperidone	45/35	5/15	28
Wang 2008[67]	GERD	50/40	24/26	16/14	SNS	Domperidone	35/32	5/8	28
Bi 2013[68]	GERD	20/20	11/10	9/10	SNS	Pantoprazole	18/12	2/8	28
Wang 2012[69]	PU	63/52	47/36	16/16	SNS	Omeprazole	58/43	5/9	40
Yao 2010[70]	PU	38/38	28/29	10/9	SNS	Ranitidine	36/33	2/5	180
Tu 2010[71]	PU	56/30	38/21	18/19	SNS	Omeprazole	54/28	2/2	80
Li 2010[72]	PU	120/60	90/42	30/18	SNS	Omeprazole	116/56	4/4	56
He 2010[73]	PU	40/40	30/28	10/12	SNS	Ranitidine	39/32	1/8	40
Zhong 2009[74]	PU	64/32	52/26	12/6	SNS	Ranitidine	59/25	5/7	90
Zhao 2012[75]	CHG	40/36	22/23	18/13	SNS	Wei fu chun	35/21	5/15	90
Zeng 2010[76]	CHG	38/35	22/19	16/14	SNS	Triple therapy	33/24	5/11	90
Liu 2010[77]	CHG	30/30	18/16	12/14	SNS	Hericium	30/20	0/10	60
Zhang 2007[78]	CHG	30/30	13/14	17/16	SNS	Triple therapy	28/23	2/7	60
Wang 2007[79]	CHG	34/31	22/20	12/11	SNS	Hericium	30/19	4/12	150
Wang 2005[80]	CHG	29/27	/	/	SNS	Triple therapy	28/25	1/2	/
Xu 2012[81]	UC	42/30	25/18	17/12	SNS	Sulfasalazine	37/22	5/8	56
Hu 2010[82]	UC	60/51	36//29	24/22	SNS	Sulfasalazine	58/42	2/9	30
Zhang 2002[83]	UC	33/30	/	/	SNS	Sulfasalazine	32/18	1/12	90

''/'' = not mentioned, CG = control group, CHG = chronic gastritis, DGR = duodenogastric reflux disease, EG = experimental group, F = female, FD = function dyspepsia, GERD = gastroesophageal reflux disease, IBS = irritable bowel syndrome, M = male, PU = peptic ulcer, SNS = *Si-Ni-San*, UC = ulcerative colitis. Note: All the Refs (1–83) appearing in this table are listed in the Appendix, http://links.lww.com/MD/A331.

Relapse Rate of SNS Versus Conventional Therapy on Treating GI Diseases

Among the 83 studies, 8 have addressed the relapse problems (3 studies in IBS, 2 in functional dyspepsia, 2 in peptic ulcer, 1 in GERD). The observation period ranged from 3 months to 6 months. As shown in Figure 6A, meta-analysis of the 8 studies strongly favored SNS than conventional therapy for clinical efficacy (OR = 3.54, 95% CI = 2.29–5.47). In contrast, relapse rate was more common in conventional group than the SNS-treated subjects (OR = 0.16, 95% CI = 0.11–0.25), with overall effect of 8.11 ($P < 0.001$); the relapse rate was 12.9% for SNS, significantly lower than 46.5% for conventional therapy (Figure 6A). Funnel plot provided evidence of publication bias (Figure 6B, C).

None of the included 83 studies reported mortality or acute incidents such as hemorrhage and perforation.

Methodological Quality and Adverse Effects

Based on randomization, blinding and description of withdrawal, the Jadad score varied greatly from 1 to 4 points, whereas 6 studies (7.2%) were classified as high quality. Seven mentioned randomization, 1 described blinding, and 5 (6.0%) provided information of dropout or withdrawal. Seven studies reported adverse events: 3 reported no adverse events and 4 reported more frequent adverse effects in the SNS-treated groups than control groups. The adverse effects were gastrointestinal symptoms, such as nausea, vomit, and abdomen uncomfort. All the adverse effects were mild and tolerable and did not result in treatment withdrawal. Table 2 summarizes the results of the methodological quality item for each included studies.

DISCUSSION

Summary of Main Findings

This is the first attempt to synthesize clinical data of single formula for 7 different GI disorders. In this systematic review, SNS was used as a tool to validate the common pathogenesis of the 7 GI disease entities. The efficacy of the single TCM formula SNS is consistently validated for functional dyspepsia and the other 6 GI disorders, indicating that all the 7 GI disorders may have shared mechanisms of common pathogenesis.

Common Mechanisms of Pathogenesis

GI symptoms often manifest similar symptoms and diagnosed on symptoms ground alone. A vast number of treatment strategies were introduced to relieve the symptoms of GI diseases.[18,19] However, few of them could provide complete control of reflux symptoms,[20] indigestion, abdominal pain,[21] diarrhea, and constipation. Several studies have demonstrated the overlaps among different GI diseases;[1,2,6] multiple mechanisms such as abnormal GI motility,[22] visceral hypersensitivity,[23] impaired GI mucosa barrier,[24] and central nervous system factors[25] are likely involved to explain the phenomenon, yet few are holistic and reasons for overlaps remain speculative. Consequently, the definitions of non-neoplastic GI disorders remain confounding with unmet clinical needs.

The consistent efficacy of this single Chinese formula SNS on 7 GI diseases may provide a novel insight and alternative prospective. In this study of synthesized data of SNS, TCM serves as a tool to validate the common mechanisms of digestive disorders. The first potential reason for the apparently increased risk of overlaps in GI disorders may link to ''reflux.'' ''Reflux,'' on one hand, could be defined as the regurgitation of the lower digestive track contents into upper organs.[26] Researchers found disturbed motility in functional dyspepsia and IBS.[27,28] Many reports have also demonstrated specific association between GERD and functional dyspepsia,[29,30] IBS,[2,31] and ulcerative colitis.[32] However, the bacterial dysbiosis and relocation might be an important etiology factor for reflux disorders.[33,34] Walker review article highlights the upper gastrointestinal bacteria and associations with disease such as IBS and coeliac disease.[35] Yang and colleagues' findings also

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

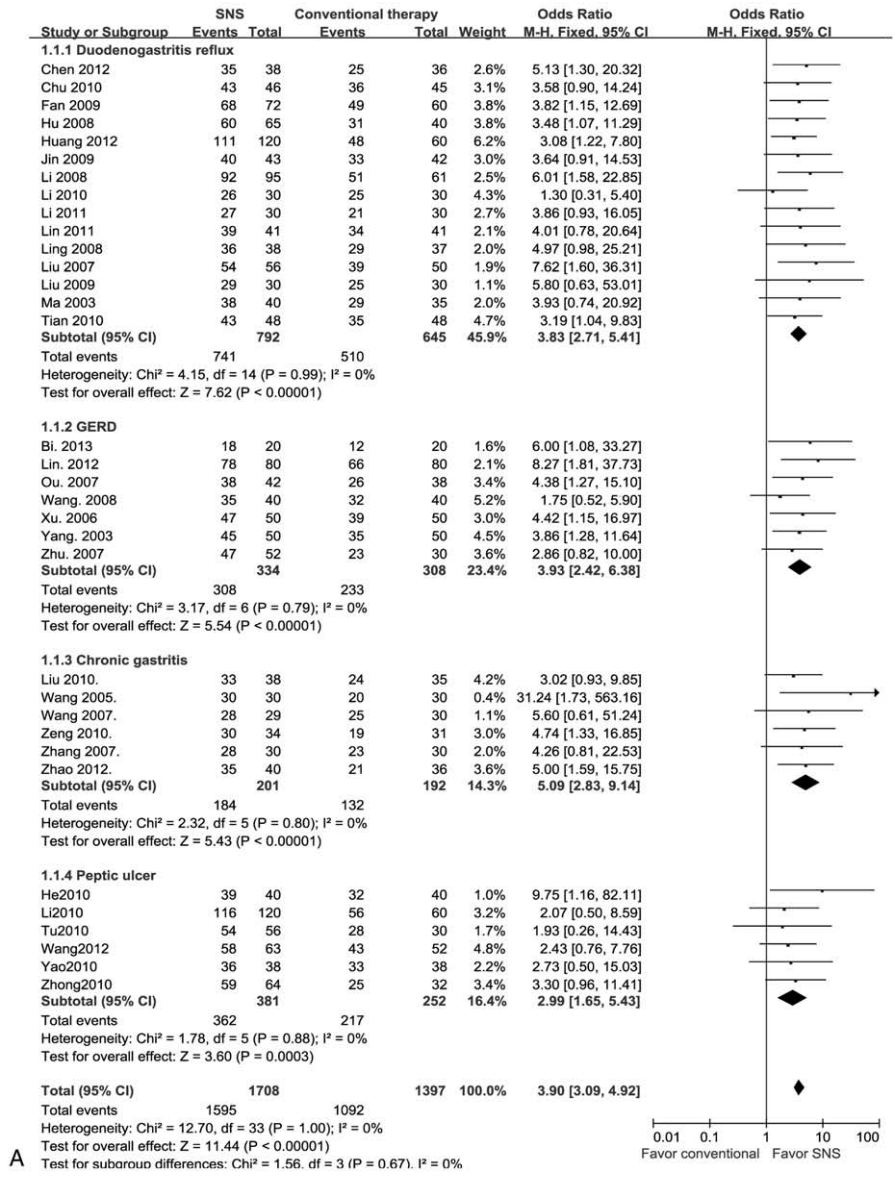

FIGURE 3. Efficacy rates and publication bias of the included 34 studies on upper gastrointestinal diseases. (A) Meta-analysis of the efficacy rate of *Si-Ni-San* versus conventional therapy in the treatment of upper GI diseases. (B) Publication bias of the included studies.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

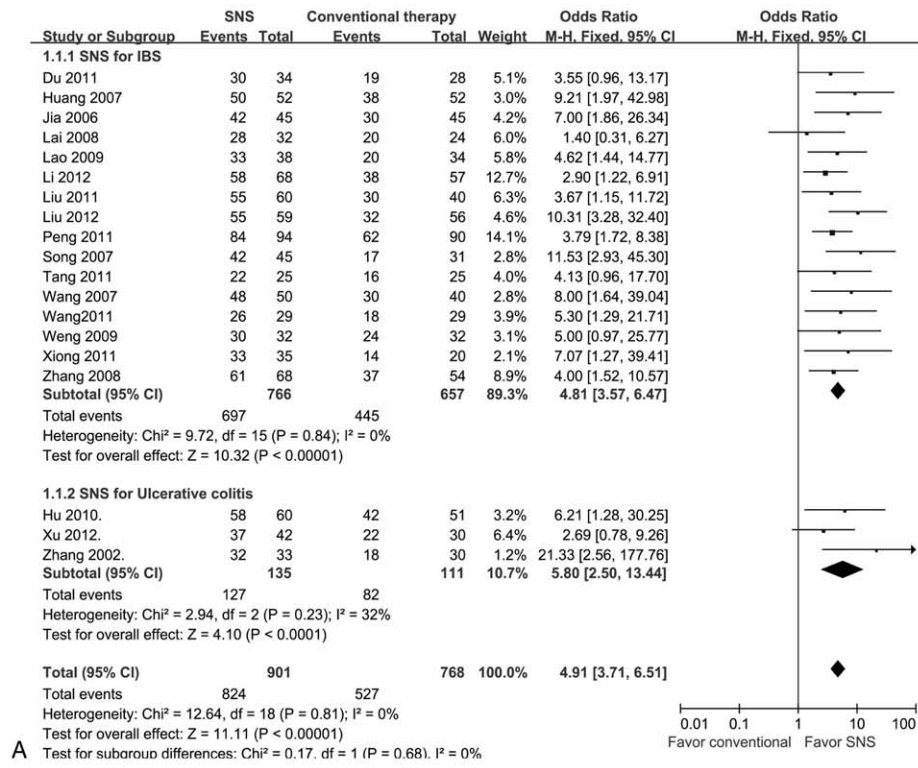

FIGURE 4. Efficacy rates and publication bias of the included 19 studies on lower GI diseases. (A) Meta-analysis of efficacy rate of *Si-Ni-San* versus conventional therapy in the treatment of lower GI diseases. (B) Publication bias of the included trials.

raise the issue of a possible role for microbiome dysbiosis in the pathogenesis of reflux-related GI disorders.[36]

It is well-known that there are several annulus muscles functioning as ''gates'' or one-way moving ''check-points'' along the GI tract. These muscles include the orbicularis oris muscle, preventriculus, pylorus, oddi sphincters, ileocecal valve, orifice of vermiform appendix, and the anus. All the ''gates'' are fixed with sphincter or smooth muscle as barriers, which can resist effacement and opening when challenged by lower contents. Failure to do so results in episodes of lower gut juice refluxing into upper digestive tracts.[37,38] Therefore, one shared mechanism relies on the ''reflux'' because of the inability of such sphincters and smooth muscles. Sphincters are important to GI functions.[39–41] A manometric study has

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

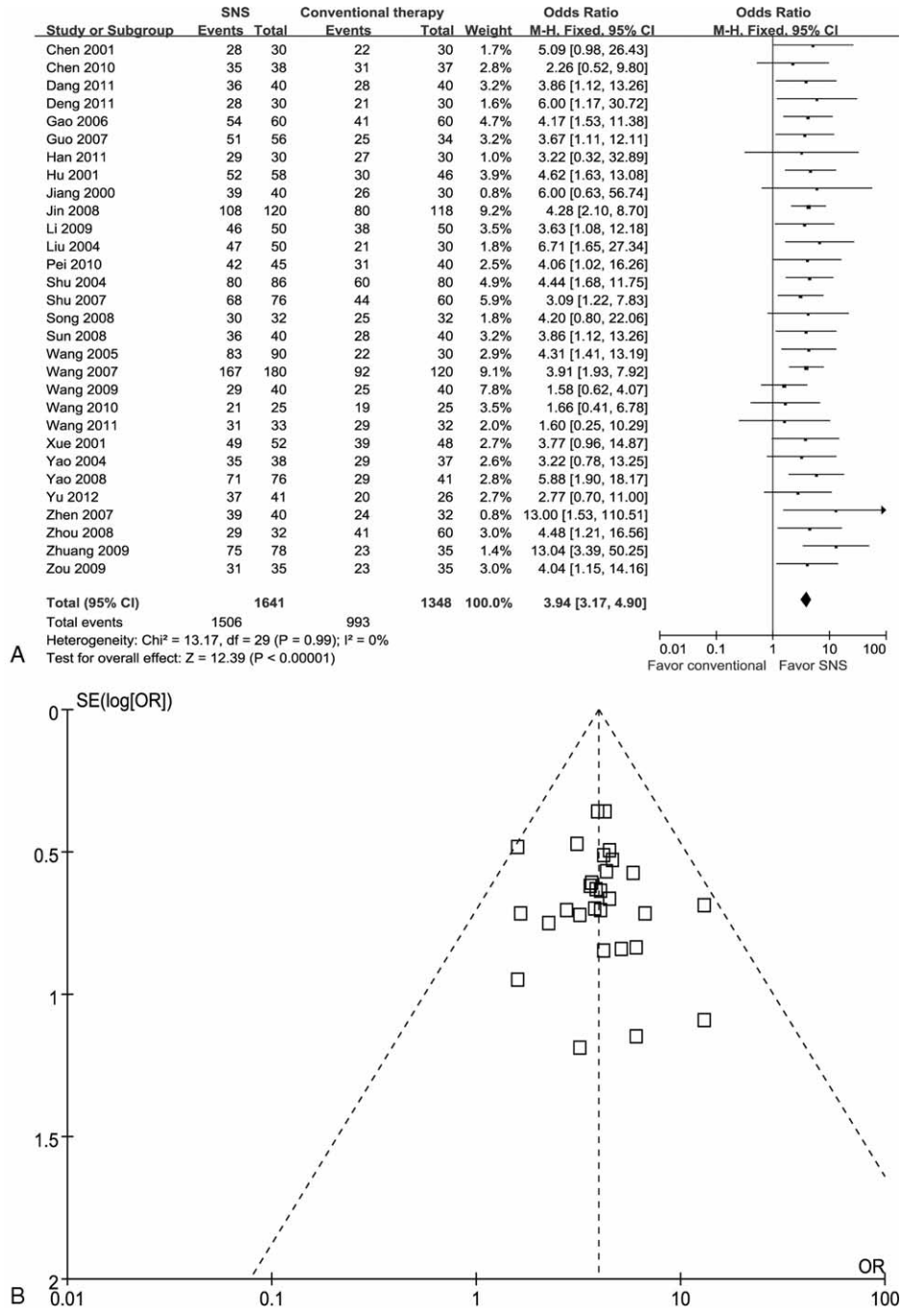

FIGURE 5. Efficacy rates and publication bias of the included 30 studies on functional dyspepsia. (A) Meta-analysis of efficacy rate of *Si-Ni-San* versus conventional therapy in the treatment of functional dyspepsia. (B) Publication bias of the included trials.

found that IBS patients exhibited significantly lower esophageal sphincter pressures compared with age and sex-matched controls.[39] Other researchers reveal a fluctuation among GI hormones,[42] glucose,[43,44] and oxidative free radicals[24] in patients with damages to the sphincters and smooth muscles. Interestingly, TCM formulae such as SNS exhibit consistent efficacy for maintaining the normal function of the sphincters, and thus may correct most, if not all, reflux-associated disorders.[45,46]

The second common mechanism of pathogenesis refers to irritable stimulation. Irritable comorbidity, including emotional irritation, anger, and depression, is prevalent in GI diseases. GI patients with persistent emotional irritation, especially anger and anxiety, are usually suffering from GI disorders.[47] Epidemiologic, psychophysiological, and functional neuroimaging studies have partially elucidated the mechanisms underlying the relation between cognitive-affective processes on the one hand and GI function and symptom reporting on the other. A

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

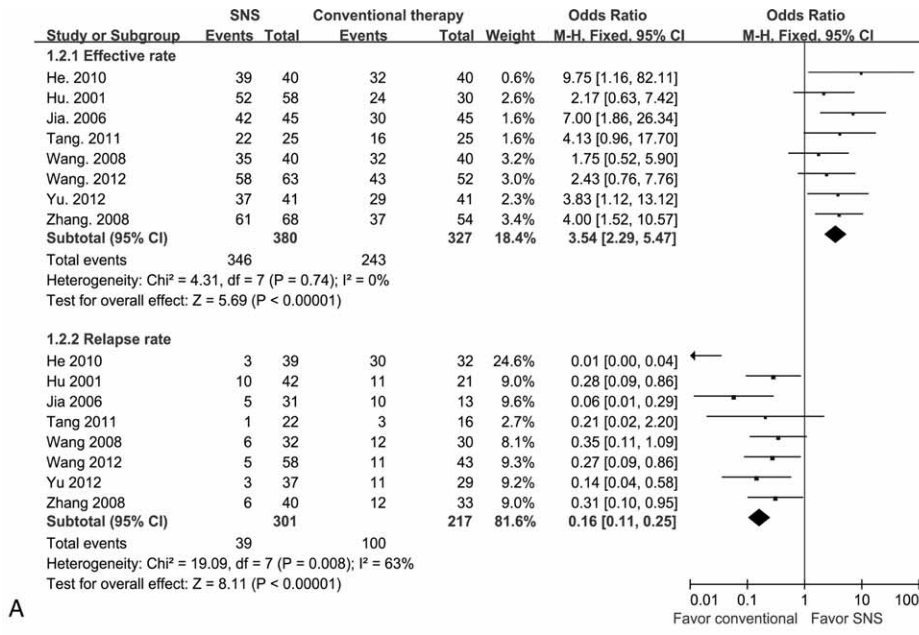

FIGURE 6. Relapse and efficacy rates of the included 8 studies on gastrointestinal diseases. (A) Relapse and efficacy rates of *Si-Ni-San* versus conventional therapy in the 8 studies. (B) Publication bias of the 8 studies on the relapse rate. (C) Publication bias of the 8 studies on the efficacy rate.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 2. The Methodological Quality of the Included Trials

First author	Diagnosis	Jadad Score	Randomization	Double Blinding	Dropout or Withdrawal	Adverse Effect	Allocation Concealment	Baseline Similarity	Overall Evaluation
Yu 2012[1]	FD	2	Y	N	N	Y	N	Y	Y
Deng 2011[2]	FD	1	N	N	N	N	N	Y	Y
Wang 2011[3]	FD	2	Y	N	N	N	N	Y	Y
Han 2011[4]	FD	4	Y	Y	N	N	Y	Y	Y
Dang 2011[5]	FD	1	N	N	N	N	N	Y	Y
Chen 2010[6]	FD	1	N	N	N	N	N	Y	Y
Pei 2010[7]	FD	1	N	N	N	N	N	Y	Y
Wang 2010[8]	FD	1	N	N	N	N	N	Y	Y
Li 2009[9]	FD	1	N	N	N	Y	N	Y	Y
Wang 2009[10]	FD	1	N	N	N	N	N	Y	Y
Zou 2009[11]	FD	1	N	N	N	N	N	Y	Y
Zhuang 2009[12]	FD	1	N	N	N	N	N	Y	Y
Jin 2008[13]	FD	1	N	N	N	N	N	Y	Y
Song 2008[14]	FD	1	N	N	N	N	N	Y	Y
Zhou 2008[15]	FD	1	N	N	N	N	N	Y	Y
Yao 2008[16]	FD	1	N	N	N	N	N	Y	Y
Sun 2008[17]	FD	1	N	N	N	N	N	Y	Y
Guo 2007[18]	FD	1	N	N	N	N	N	Y	Y
Shu 2007[19]	FD	1	N	N	N	N	N	Y	Y
Zheng 2007[20]	FD	1	N	N	N	N	N	Y	Y
Wang 2007[21]	FD	1	N	N	N	N	N	Y	Y
Gao 2006[22]	FD	1	N	N	N	N	N	Y	Y
Wang 2005[23]	FD	1	N	N	N	N	N	Y	Y
Shu 2004[24]	FD	1	N	N	N	N	N	Y	Y
Shen 2004[25]	FD	1	N	N	N	N	N	Y	Y
Liu 2004[26]	FD	1	N	N	N	N	N	Y	Y
Xue 2001[27]	FD	1	N	N	N	N	N	Y	Y
Hu 2001[28]	FD	1	N	N	N	N	N	Y	Y
Chen 2001[29]	FD	3	Y	N	Y	Y	N	Y	Y
Jiang 2000[30]	FD	1	N	N	N	N	N	Y	Y
Huang 2012[31]	DGR	1	N	N	N	N	N	Y	Y
Chen 2012[32]	DGR	1	N	N	N	N	N	Y	Y
Lin 2011[33]	DGR	1	N	N	N	N	N	Y	Y
Li 2011[34]	DGR	3	Y	N	Y	N	Y	Y	Y
Tian 2010[35]	DGR	1	N	N	N	N	N	Y	Y
Li 2010[36]	DGR	2	Y	N	N	N	N	Y	Y
Chu 2010[37]	DGR	1	N	N	N	N	N	Y	Y
Liu 2009[38]	DGR	1	N	N	N	N	N	Y	Y
Jin 2009[39]	DGR	1	N	N	N	N	N	Y	Y
Fan 2009[40]	DGR	1	N	N	N	N	N	Y	Y
Ling 2008[41]	DGR	1	N	N	N	N	N	Y	Y
Li 2008[42]	DGR	1	N	N	N	N	N	Y	Y
Hu 2008[43]	DGR	1	N	N	N	N	N	Y	Y
Liu 2007[44]	DGR	1	N	N	N	N	N	Y	Y
Ma 2003[45]	DGR	1	N	N	N	N	N	Y	Y
Liu 2012[46]	IBS	1	N	N	N	N	N	Y	Y
Li 2012[47]	IBS	1	N	N	N	N	N	Y	Y
Xiong 11[48]	IBS	1	N	N	N	N	N	Y	Y
Wang 2011[49]	IBS	1	N	N	N	N	N	Y	Y
Tang 2011[50]	IBS	3	Y	N	Y	Y	N	Y	Y
Peng 2011[51]	IBS	1	N	N	N	N	N	Y	Y
Liu 2011[52]	IBS	1	N	N	N	N	N	Y	Y
Du 2011[53]	IBS	1	N	N	N	N	N	Y	Y
Weng 2009[54]	IBS	3	Y	N	Y	N	N	Y	Y
Lao 2009[55]	IBS	1	N	N	N	N	N	Y	Y
Zhang 2008[56]	IBS	3	Y	N	Y	Y	N	Y	Y
Lai 2008[57]	IBS	1	N	N	N	N	N	Y	Y
Wang 2007[58]	IBS	1	N	N	N	N	N	Y	Y
Song 2007[59]	IBS	1	N	N	N	N	N	Y	Y
Huang 2007[60]	IBS	1	N	N	N	N	N	Y	Y
Jia 2006[61]	IBS	1	N	N	N	N	N	Y	Y
Xu 2006[62]	GERD	1	N	N	N	N	N	Y	Y
Zhu 2007[63]	GERD	1	N	N	N	N	N	Y	Y
Ou 2007[64]	GERD	1	N	N	N	N	N	Y	Y
Lin 2012[65]	GERD	1	N	N	N	N	N	Y	Y

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

First author	Diagnosis	Jadad Score	Randomization	Double Blinding	Dropout or Withdrawal	Adverse Effect	Allocation Concealment	Baseline Similarity	Overall Evaluation
Yang 2003[66]	GERD	1	N	N	N	N	N	Y	Y
Wang 2008[67]	GERD	1	N	N	N	N	N	Y	Y
Bi 2013[68]	GERD	1	N	N	N	N	N	Y	Y
Wang 2012[69]	PU	1	N	N	N	N	N	Y	Y
Yao 2010[70]	PU	2	Y	N	N	N	N	Y	Y
Tu 2010[71]	PU	1	N	N	N	N	N	Y	Y
Li 2010[72]	PU	1	N	N	N	N	N	Y	Y
He 2010[73]	PU	1	N	N	N	N	N	Y	Y
Zhong 2009[74]	PU	2	Y	N	N	N	N	Y	Y
Zhao 2012[75]	CHG	1	N	N	N	Y	N	Y	Y
Zeng 2010[76]	CHG	1	N	N	N	N	N	Y	Y
Liu 2010[77]	CHG	1	N	N	N	N	N	Y	Y
Zhang 2007[78]	CHG	1	N	N	N	N	N	Y	Y
Wang 2007[79]	CHG	1	N	N	N	N	N	Y	Y
Wang 2005[80]	CG	1	N	N	N	N	N	Y	Y
Xu 2012[81]	UC	1	N	N	N	N	N	Y	Y
Hu 2010[82]	UC	1	N	N	N	Y	N	Y	Y
Zhang 2002[83]	UC	1	N	N	N	N	N	Y	Y

CHG = chronic gastritis, DGR = duodenogastric reflux disease, FD = function dyspepsia, GERD = gastroesophageal reflux disease, IBS = irritable bowel syndrome, N = not mentioned, PU = peptic ulcer, UC = ulcerative colitis, Y = mentioned. Note: All the Refs (1–83) appearing in this table are listed in the Appendix, http://links.lww.com/MD/A331.

nationwide cohort study in Taiwan suggests that psychiatric patients using antidepressant agents have increased risk of upper GI bleeding.[48] In IBS, 50% to 90% of those seeking treatment have comorbidity of lifetime psychiatric disorders, especially depressive and anxiety disorders.[49] In another systematic review and meta-analysis, patients with IBS had significantly higher levels of anxiety and depression than healthy controls.[50] Furthermore, irritable GI causes visceral hypersensitivity. GI patients demonstrated lower sensory thresholds for diarrhea, constipation, and abdominal pain[51,52] when taking ice foods[23] and experiencing climate change of weather. Intriguingly, SNS has history-proven beneficial effects on reliving GI irritability.[53–55]

The third common mechanism underlying the apparent overlaps of GI diseases is the stasis of GI microcirculation. Previous researches have demonstrated catecholamine and dopamine fluctuation in function dyspepsia,[56] IBS,[57,58] and peptic ulcer.[59] Elikowski et al[60] and Mitsuyama et al[61,62] found a disturbed blood viscosity in IBS and colitis, causing the imbalance of myogenic homeometric autoregulation and resulting in a stasis of abdominal circulation. Accordingly, *radix paeoniae Alba*, one component of SNS, has benefits on artery pressure,[63] inflammation, allergy,[64] and smooth muscle dilation,[65] and consequently improves GI microcirculation. The abnormal contractions of abdominal vascular smooth muscle and the inappropriate hormone secretion constitute rationale for the SNS-induced efficacy on abnormal motility, visceral hypersensitivity, bowel irritability, and mucosal barrier disruption.[66–68]

Overlap of functional gastrointestinal disorders, GERD, peptic ulcer, and IBD may exist more than by chance. But pathogenesis of these diseases is very complex and multifactorial. Such as *Helicobacter pylori* is one of the most important causes of GU, but no for GERD. Intriguingly, the effects of TCM, herbal formula such as SNS in particular, are also multiple and plural. Therefore, the multiple effects of SNS might target the multifactorial pathogenesis in common digestive disorders.

CONCLUSION AND LIMITASIONS

In this study, we have used synthesized clinical data of the single TCM formula as a tool indirectly to validate the common mechanisms of pathogenesis of GI disorders. The findings are positive for common GI disorders implicated by similar pathogenesis. The present study has limitations such as inherited risk bias and low quality of some included trials. Validation of our findings warrants high-quality clinical studies based on different geographic locations or using different therapeutic agents.

ACKNOWLEDGMENTS

We would like to thank Yu-Zhong OU YANG for his assistance for preparing the figures and Mr. Kishore for his helpful English editing.

REFERENCES

1. Agreus L, Svardsudd K, Nyren O, et al. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. *Gastroenterology.* 1995;109:671–680.
2. Lovell RM, Ford AC. Prevalence of gastro-esophageal reflux-type symptoms in individuals with irritable bowel syndrome in the community: a meta-analysis. *Am J Gastroenterol.* 2012;107:1793–1801quiz 1802.
3. Cheung TK, Lam KF, Hu WH, et al. Positive association between gastro-oesophageal reflux disease and irritable bowel syndrome in a Chinese population. *Aliment Pharmacol Ther.* 2007;25:1099–1104.
4. Ford AC, Chey WD, Talley NJ, Malhotra A, Spiegel BM, Moayyedi P. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. *Arch Intern Med.* 2009;169:651–658.
5. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol.* 2012;107:1474–1482.
6. Ford AC, Forman D, Bailey AG, Axon AT, Moayyedi P. Fluctuation of gastrointestinal symptoms in the community: a 10-year longitudinal follow-up study. *Aliment Pharmacol Ther.* 2008;28:1013–1020.
7. Ford AC, Marwaha A, Lim A, Moayyedi P. Systematic review and meta-analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. *Clin Gastroenterol Hepatol.* 2010;8:401–409.
8. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol.* 2011;106:1582–1591quiz 1581, 1592.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

9. Halder SL, Locke GR 3rd, Schleck CD, Zinsmeister AR, Melton LJ 3rd, Talley NJ. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. *Gastroenterology.* 2007;133:799–807.
10. Zhao HL, Tong PC, Chan JC. Traditional Chinese medicine in the treatment of diabetes. *Nestle Nutr Workshop Ser Clin Perform Programme.* 2006;11:15–25discussion 25–29.
11. Sui Y, Zhao HL, Wong VC, et al. A systematic review on use of Chinese medicine and acupuncture for treatment of obesity. *Obes Rev.* 2012;13:409–430.
12. Zhao HL, Sui Y, Qiao CF, et al. Sustained antidiabetic effects of a berberine-containing Chinese herbal medicine through regulation of hepatic gene expression. *Diabetes.* 2012;61:933–943.
13. Zhao HL, Sun CZ, Jiang WP, et al. Eight-year survival of AIDS patients treated with Chinese herbal medicine. *Am J Chin Med.* 2014;42:1–14(DOI: 10.1142/S0192415X14500177).
14. Vergnes JN, Marchal-Sixou C, Nabet C, Maret D, Hamel O. Ethics in systematic reviews. *J Med Ethics.* 2010;36:771–774.
15. Neupane D, McLachlan CS, Sharma R, et al. Prevalence of hypertension in member countries of South Asian Association for Regional Cooperation (SAARC): systematic review and meta-analysis. *Medicine.* 2014;93:e74.
16. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1–12.
17. Savovic J, Weeks L, Sterne JA, et al. Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. *Syst Rev.* 2015;3:37.
18. Ganz RA, Peters JH, Horgan S, et al. Esophageal sphincter device for gastroesophageal reflux disease. *N Engl J Med.* 2016;368:719–727.
19. Brun R, Kuo B. Functional dyspepsia. *Ther Adv Gastroenterol.* 2010;3:145–164.
20. Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med.* 2008;359:1700–1707.
21. Halling K, Kulich K, Carlsson J, Wiklund I. An international comparison of the burden of illness in patients with dyspepsia. *Dig Dis.* 2008;26:264–273.
22. Cremonini F, Locke GR 3rd, Schleck CD, Zinsmeister AR, Talley NJ. Relationship between upper gastrointestinal symptoms and changes in body weight in a population-based cohort. *Neurogastroenterol Motil.* 2006;18:987–994.
23. Bredenoord AJ, Chial HJ, Camilleri M, Mullan BP, Murray JA. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. *Clin Gastroenterol Hepatol.* 2003;1:264–272.
24. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiol Rev.* 2014;94:329–354.
25. Vandenberghe J, Dupont P, Van Oudenhove L, et al. Regional cerebral blood flow during gastric balloon distention in functional dyspepsia. *Gastroenterology.* 2007;132:1684–1693.
26. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2016;108:308–328quiz 329.
27. Haag S, Talley NJ, Holtmann G. Symptom patterns in functional dyspepsia and irritable bowel syndrome: relationship to disturbances in gastric emptying and response to a nutrient challenge in consulters and non-consulters. *Gut.* 2004;53:1445–1451.
28. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology.* 1998;115:1346–1352.
29. Yarandi SS, Christie J. Functional dyspepsia in review: pathophysiology and challenges in the diagnosis and management due to coexisting gastroesophageal reflux disease and irritable bowel syndrome. *Gastroenterol Res Pract.* 2013;2013:351086.
30. Lee SY, Lee KJ, Kim SJ, Cho SW. Prevalence and risk factors for overlaps between gastroesophageal reflux disease, dyspepsia, and irritable bowel syndrome: a population-based study. *Digestion.* 2009;79:196–201.
31. De Vries DR, Van Herwaarden MA, Baron A, Smout AJ, Samsom M. Concomitant functional dyspepsia and irritable bowel syndrome decrease health-related quality of life in gastroesophageal reflux disease. *Scand J Gastroenterol.* 2007;42:951–956.
32. Kuriyama M, Kato J, Morimoto N, Fujimoto T, Okada H, Yamamoto K. Specific gastroduodenoscopic findings in Crohn's disease: Comparison with findings in patients with ulcerative colitis and gastroesophageal reflux disease. *Dig Liver Dis.* 2008;40:468–475.
33. Theisen J, Nehra D, Citron D, et al. Suppression of gastric acid secretion in patients with gastroesophageal reflux disease results in gastric bacterial overgrowth and deconjugation of bile acids. *J Gastrointest Surg.* 2000;4:50–54.
34. Tamboli CP, Neut C, Desreumaux P, Colombel JF. Dysbiosis in inflammatory bowel disease. *Gut.* 2004;53:1–4.
35. Walker MM, Talley NJ. Review article: bacteria and pathogenesis of disease in the upper gastrointestinal tract–beyond the era of Helicobacter pylori. *Aliment Pharmacol Ther.* 2014;39:767–779.
36. Yang L, Lu X, Nossa CW, Francois F, Peek RM, Pei Z. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. *Gastroenterology.* 2009;137:588–597.
37. Ayazi S, Tamhankar A, DeMeester SR, et al. The impact of gastric distension on the lower esophageal sphincter and its exposure to acid gastric juice. *Ann Surg.* 2016;252:57–62.
38. Oberg S, Peters JH, DeMeester TR, et al. Inflammation and specialized intestinal metaplasia of cardiac mucosa is a manifestation of gastroesophageal reflux disease. *Ann Surg.* 1997;226:522–530. discussion 530–522.
39. Smart HL, Nicholson DA, Atkinson M. Gastro-oesophageal reflux in the irritable bowel syndrome. *Gut.* 1986;27:1127–1131.
40. Sivarao DV, Mashimo H, Goyal RK. Pyloric sphincter dysfunction in nNOS-/- and W/Wv mutant mice: animal models of gastroparesis and duodenogastric reflux. *Gastroenterology.* 2008;135: 1258–1266.
41. Sivarao DV, Mashimo HL, Thatte HS, Goyal RK. Lower esophageal sphincter is achalasic in nNOS(-/-) and hypotensive in W/W(v) mutant mice. *Gastroenterology.* 2001;121:34–42.
42. Korimilli A, Parkman HP. Effect of atilmotin, a motilin receptor agonist, on esophageal, lower esophageal sphincter, and gastric pressures. *Dig Dis Sci.* 2010;55:300–306.
43. El-Salhy M, Sitohy B. Abnormal gastrointestinal endocrine cells in patients with diabetes type 1: relationship to gastric emptying and myoelectrical activity. *Scand J Gastroenterol.* 2001;36:1162–1169.
44. Samsom M, Smout AJ. Abnormal gastric and small intestinal motor function in diabetes mellitus. *Dig Dis.* 1997;15:263–274.
45. Tang Y, Liao Y, Kawaguchi-Sakita N, et al. Sinisan, a traditional Chinese medicine, attenuates experimental chronic pancreatitis induced by trinitrobenzene sulfonic acid in rats. *J Hepatobiliary Pancreat Sci.* 2011;18:551–558.
46. Yamakage M, Hattori J, Satoh J, Namiki A. Effects of the Chinese herbal medicines Bupleuri radix, Ginseng radix, and Zingiberis rhizoma on lymphatic vessel activity in rats. *Am J Chin Med.* 2006;34:1063–1068.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

47. Van Oudenhove L, Vandenberghe J, Demyttenaere K, Tack J. Psychosocial factors, psychiatric illness and functional gastrointestinal disorders: a historical perspective. *Digestion.* 2010;82:201–210.
48. Lee YC, Shau WY, Chang CH, Chen ST, Lin MS, Lai MS. Antidepressant use and the risk of upper gastrointestinal bleeding in psychiatric patients: a nationwide cohort study in Taiwan. *J Clin Psychopharmacol.* 2012;32:518–524.
49. Lydiard RB, Falsetti SA. Experience with anxiety and depression treatment studies: implications for designing irritable bowel syndrome clinical trials. *Am J Med.* 1999;107 (5A):65S–73S.
50. Fond G, Loundou A, Hamdani N, et al. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci.* 2014;6:.
51. Trimble KC, Farouk R, Pryde A, Douglas S, Heading RC. Heightened visceral sensation in functional gastrointestinal disease is not site-specific. Evidence for a generalized disorder of gut sensitivity. *Dig Dis Sci.* 1995;40:1607–1613.
52. Costantini M, Sturniolo GC, Zaninotto G, et al. Altered esophageal pain threshold in irritable bowel syndrome. *Dig Dis Sci.* 1993;38:206–212.
53. Ninomiya F. Clinical evaluation of perspiration reducing effects of a kampo formula, Shigyaku-san, on palmoplantar hidrosis. *Evid Based Complement Alternat Med.* 2008;5:199–203.
54. Li Y, Sun Y, Ma X, et al. Effects of Sini San used alone and in combination with fluoxetine on central and peripheral 5-HT levels in a rat model of depression. *J Tradit Chin Med.* 2014;33: 674–681.
55. Wang YT, Tan QR, Sun LL, et al. Possible therapeutic effect of a Traditional Chinese Medicine, Sinisan, on chronic restraint stress related disorders. *Neurosci Lett.* 2009;449:215–219.
56. Braak B, Booij J, Klooker TK, van den Wijngaard RM, Boeckxstaens GE. The dopaminergic system in patients with functional dyspepsia analysed by single photon emission computed tomography (SPECT) and an alpha-methyl-para-tyrosine (AMPT) challenge test. *Eur J Nuclear Med Mol Imag.* 2016;39:642–650.
57. Hall KT, Lembo AJ, Kirsch I, et al. Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. *PloS One.* 2016;7:e48135.
58. Cheng P, Shih W, Alberto M, et al. Autonomic response to a visceral stressor is dysregulated in irritable bowel syndrome and correlates with duration of disease. *Neurogastroenterol Motil.* 2016;25:e650–e659.
59. Frenkel ID. Catecholamine and DOPA excretion in peptic ulcer patients. *Vopr Med Khim.* 1973;19:518–523.
60. Elikowski W, Malek M, Lewandowska M, Kawczynski S, Dobrowolska-Zachwieja A, Psuja P. Massive pulmonary embolism in a patient with ulcerative colitis and hyperhomocysteinaemia – a case report. *Kardiol Pol.* 2006;64:405–409discussion 410.
61. Mitsuyama K, Andoh A, Masuda J, et al. Mobilization of bone marrow cells by leukocytapheresis in patients with ulcerative colitis. *Ther Apher Dial.* 2008;12:271–277.
62. Mitsuyama K, Sata M. Therapeutic leukocytapheresis in inflammatory bowel disease: clinical efficacy and mechanisms of action. *Cytotherapy.* 2009;11:229–237.
63. Qian G, Cao J, Chen C, et al. Paeoniflorin inhibits pulmonary artery smooth muscle cells proliferation via upregulating A2B adenosine receptor in rat. *PloS One.* 2016;8:e69141.
64. Yamahara J, Yamada T, Kimura H, Sawada T, Fujimura H. Biologically active principles of crude drugs. II. Anti-allergic principles in ''Shoseiryu-To'' anti-inflammatory properties of paeoniflorin and its derivatives. *J Pharmacobiodyn.* 1982;5:921–929.
65. Jin SN, Wen JF, Wang TT, Kang DG, Lee HS, Cho KW. Vasodilatory effects of ethanol extract of Radix Paeoniae Rubra and its mechanism of action in the rat aorta. *J Ethnopharmacol.* 2016;142:188–193.
66. Xu FH, Uebaba K. Effect of Kampo formulations (traditional Chinese medicine) on circulatory parameters. *Acupunct Electrother Res.* 1999;24:11–28.
67. Sun Y, Cai TT, Shen Y, Zhou XB, Chen T, Xu Q. Si-Ni-San, a traditional Chinese prescription, and its active ingredient glycyrrhizin ameliorate experimental colitis through regulating cytokine balance. *Int Immunopharmacol.* 2009;9:1437–1443.
68. Sun Y, Chen T, Xu Q. Si-Ni-San, a traditional Chinese prescription, and its drug-pairs suppress contact sensitivity in mice via inhibition of the activity of metalloproteinases and adhesion of T lymphocytes. *J Pharm Pharmacol.* 2003;55:839–846.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.