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Chinese Medicine Treatment in Functional Gastrointestinal Disorders

中醫藥治療功能性胃腸病

中药研發研討會，10-11 Sept 2015
《内径》云：饮入于胃，游溢精气，上输于脾，脾气散精，上归于肺，通调水道，下输膀胱，水精四布，五经并行。

Jean Anthelme Brillat-Savarin (1755 – 1826)

"Tell me what you eat, and I will tell you what you are."
李东垣（1180-1251）《脾胃论》中指出："内伤脾胃，百病由生。" 《Treatise on the Stomach and Spleen: All diseases begin in the gut!}
Common disorders of the gastrointestinal (GI) tract account for about 50 million visits per year to physicians trained in traditional allopathic or osteopathic medicine.

In the United States, the overall expenditure for complementary and alternative medicine (CAM) is in the tens of billions of dollars per year.

Aaron J. Michelfelder MD, Kit C. Lee MD and Eva M. Bading MD
Primary Care: Clinics in Office Practice, 2010-06-01, Volume 37, Issue 2, Pages 25
胃腸病的種類
Gastrointestinal Disorders

器質性病變(Organic disorders)
Ex: 消化道腫瘤(Gastrointestinal tumor)、炎症性腸病(IBD)、消化道潰瘍(peptic ulcer)......

功能性病變(Functional disorders)
Ex: 功能性消化不良(Functional dyspepsia)、功能性便秘(Functional constipation)、腸易激綜合征(IBS)、功能性腹瀉，功能性腹痛等......
胃肠道疾病的病因远未清晰
Not fully understood about diseases causes

pH--Hp
Colon Cancer and Polyp

社會心理因素
Social psychological factors
食物耐受不良
Food intolerance
生活習慣改變
Altered life habits
遺傳因素
Genetics
功能性胃腸病的病理生理基礎
Pathophysiology of FGIDs

- 内臟運動感覺功能異常 (Sensory-motor function disorder)
- 腦腸軸功能異常 (Brain-gut axis dysfunction)
- 心理應激 (Psychosocial stress)
  - ……
功 能 性 胃 腸 病 的 臨 床 表 現

Clinical Manifestations of FGIDs

胃腸道外症狀
Extra-gastrointestinal symptoms

- 頭痛 headache
- 呼吸困難 dyspnea
- 心悸 palpitation
- 肌痛 muscle pain
- ......

胃腸道症狀

GI symptoms

- 腹痛
- 腹瀉或便秘
- 腹脹
- 消化不良
功能性胃腸病的現代治療靶點
Treatment Targets for FGIDs

對症治療
Symptomatic treatment

• 便秘 constipation
  – 瀉藥 laxative
  – 促分泌藥 prosecretory agents

• 腹瀉 diarrhea
  – 止瀉藥 antidiarrheals
  – 5-HT\textsubscript{3}受體拮抗劑 5-HT\textsubscript{3} receptor antagonist

• 腹痛 abdominal pain
  – 解痙藥 antispasmodics
  – 抗抑鬱藥 antidepressants
### Current treatment methods have certain efficacy, but the efficacy was not good enough.

- **Ex. 1** 糞便蓬鬆劑、解痙藥、抗抑鬱薬治療IBS的系統綜述
- **Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome**

<table>
<thead>
<tr>
<th>Outcome: Comparing nr(%) of successfully treated patients with IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
</tr>
<tr>
<td>Total events: 164 (Bulking agent), 136 (Placebo)</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.03; \hat{h}^2 = 15.49, df = 10 (P = 0.17); I^2 = 39%$</td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.00 (P = 0.32)$</td>
</tr>
<tr>
<td>Test for subgroup differences: $Ch_1^2 = 2.10, df = 1 (P = 0.15), I^2 = 52%$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>糞便蓬鬃剂</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
</tr>
<tr>
<td>Total events: 579 (Spasmolitics), 382 (Placebo)</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.03; \hat{h}^2 = 51.37, df = 21 (P = 0.0002); I^2 = 64%$</td>
</tr>
<tr>
<td>Test for overall effect: $Z = 4.46 (P &lt; 0.0001)$</td>
</tr>
<tr>
<td>Test for subgroup differences: $Ch_1^2 = 38.38, df = 9 (P = 0.00), I^2 = 69%$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>解痙藥</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
</tr>
<tr>
<td>Total events: 151 (Antidepressants), 86 (Placebo)</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.12; \hat{h}^2 = 17.41, df = 7 (P = 0.01); I^2 = 60%$</td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.23 (P = 0.03)$</td>
</tr>
<tr>
<td>Test for subgroup differences: $Ch_1^2 = 1.16, df = 1 (P = 0.26), I^2 = 1%$</td>
</tr>
</tbody>
</table>
僅有利那洛肽用於IBS-C的推薦等級為強，其餘藥物的推薦等級均為弱(有條件的)

Only linaclotide was strongly recommended in treatment of IBS-C, the recommendation levels of other drugs were conditional.

The AGA recommends using linaclotide (over no drug treatment) in patients with IBS-C. (Strong recommendation; High-quality evidence)

Comments: Patients who place a high value on avoiding diarrhea and avoiding higher out-of-pocket expenses associated with linaclotide may prefer alternate treatments.
Complementary and Alternative Medicine Use Is Prevalent Among Patients with Gastrointestinal Diseases

Adelina Hung · Nancy Kang · Andrea Bollom · Jacqueline L. Wolf · Anthony Lembo

Table 1 Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of CAM users (n = 118)</th>
<th>% of CAM non-users (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, range)</td>
<td>45 (19–78)</td>
<td>48 (17–87)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 %</td>
<td>44 %</td>
</tr>
<tr>
<td>Female</td>
<td>81 %†</td>
<td>56 %†</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78 %</td>
<td>83 %</td>
</tr>
<tr>
<td>African-American</td>
<td>9 %</td>
<td>8 %</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>5 %</td>
<td>3 %</td>
</tr>
</tbody>
</table>

Table 1 continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of CAM users (n = 118)</th>
<th>% of CAM non-users (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>54 %</td>
<td>52 %</td>
</tr>
<tr>
<td>Indigestion</td>
<td>26 %</td>
<td>22 %</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>16 %</td>
<td>21 %</td>
</tr>
<tr>
<td>Bloating/gas</td>
<td>59 %†</td>
<td>40 %†</td>
</tr>
<tr>
<td>Difficulty or pain with swallowing</td>
<td>8 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Heartburn</td>
<td>31 %</td>
<td>24 %</td>
</tr>
<tr>
<td>Did not respond</td>
<td>6 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux (GERD)</td>
<td>30 %</td>
<td>22 %</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>32 %</td>
<td>23 %</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>3 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Liver disease</td>
<td>3 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Pancreatic disease</td>
<td>3 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>13 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>16 %</td>
<td>22 %</td>
</tr>
<tr>
<td>Stomach/bowel cancer</td>
<td>0 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Did not respond</td>
<td>24 %</td>
<td>30 %</td>
</tr>
</tbody>
</table>
symptoms between the two groups. Users reported “wish to feel generally better” as main reason for utilization, and a majority of patients (62%) experienced improved GI symptoms. Among patients who did not discuss CAM with their physicians (30%), they cited physician failure to ask about CAM as the major reason (82%).

Conclusion CAM is prevalent among patients attending a GI clinic, particularly among women and those who are dissatisfied with conventional therapies and “wish to feel better.” Greater awareness and understanding of CAM among GI physicians is necessary.
概要
Outlines

• 功能性胃腸病的現代治療
  Modern treatment in FGIDs

• 中醫藥是治療功能性胃腸病的良好補充
  CM is a favorable supplement in FGIDs treatment

• 中醫藥治療理念有助於優化臨床診療
  Concept of CM is helpful to optimizing clinical practice
中醫藥治療功能性胃腸病

Chinese Medicine Treatment in FGIDs

• 中醫藥的背景
  – 超過2000年的應用歷史
  – 獨特的理論體系
  – 多元化的治療手段
• 中醫藥治療胃腸病的經驗
  – 治瀉九法
  – 經典便秘方劑：麻子仁丸、大承氣湯、小承氣湯
• 中醫藥的優勢
  – 長期的用藥經驗
  – 治療成本低
  – 不良反少
  – ......

• Background of Chinese Medicine
  – History of more than 2000 years
  – Different theoretical system
  – Various forms of treatment
• Experience of CM treatment
  – Nine methods of treating diarrhea
  – Classical prescriptions for constipation: Maziren pills, Dachengqi decoction, Xiaochengqi decoction
• Advantages of CM
  – Long-term medication experience
  – Low cost
  – Less adverse events
  – ......
中醫藥治療的困境
Barrier of CM Treatment

- 截止到2015年8月，在CDSR數據庫中，僅有11篇系統性綜述關於中醫治療胃腸病，其中:
  - 中草藥: 9篇
  - 針灸: 2篇

需要進行基於循證醫學的高質量中醫臨床研究
It is compulsory to conduct high-quality CM clinical trail on the foundation of evidence-based medicine
如何开展有效的药物研发？
How to develop a new drug based on TCM?

目標：
1、
New approaches for TCM drug development

- 药效作用的物质基础
- 作用机理
- 配伍规律

- 探索名方优化大方衍生新方
- 中药二次开发
- 新型复方中药疗效确切成分相对明确机理相对清楚质量可控

推动研究

新型复方中药品种研制

促进
中醫藥治療功能性便秘
CM Treatment in Functional Constipation

- 中醫病因病機
- Etiology and pathogenesis in CM

![Diagram showing etiology and pathogenesis in CM]

- 鬱熱 (Heat stagnation)
- 氣滯 (Qi stagnation)
- 寒凝 (Cold inducing stagnation)
- 陽氣虧虛 (Qi and yang deficiency)
- 陰虧 (Yin deficiency)

邪滯大腸、腑氣不通
Pathogens lingering in large intestine, Obstruction of Fu-qi

腸失温濁，傳導失常
Loss of warm and moistening, disorder of bowel movement

便秘
Constipation
中醫藥治療功能性便秘

CM Treatment in Functional Constipation

- 中醫治則治法
- Therapeutic principles and methods in CM

### 實證

**Sthenia pattern**

- 祛邪為主
  - Eliminating pathogens at first
  - Purging heat, warming and dissipating, and regulating qi for heat, cold, and qi constipation, respectively

### 虛證

**Deficiency pattern**

- 养正為先
  - Strengthening vital energy at first
  - Nourishing yin and blood, and invigorating qi and warming yang according to the deficiency of qi, blood, yin and yang

### 邪去便通

Relieved after pathogens gone

### 正盛便通

Relieved after vital energy abundance
Systematic review of Chinese herbal medicine for functional constipation

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.
MaZiRenWan for Functional Constipation

- Study 1: Optimal Dose Determination
  - Prospective 18wk study
  - Single blinded
  - Dosage controlled
  - Study period: 10/2006-10/2007

<table>
<thead>
<tr>
<th>Run-in</th>
<th>MZRW 5.0g bid (MD) (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZRW 2.5g bid (LD) (n=32)</td>
</tr>
<tr>
<td></td>
<td>MZRW 7.5g bid (HD) (n=32)</td>
</tr>
</tbody>
</table>

- 研究一: 劑量優化研究
  - 為期18周的前瞻性研究
  - 單盲
  - 劑量對照
MaZiRenWan for Functional Constipation

- High-dose group showed benefit in terms of increased CSBM, constipation-related symptoms and global symptom improvement when compared with other two groups (P<0.05)

![Bar chart showing changes in number of CSBM over time with pairwise comparisons performed for each treatment group with its baseline.](image)

• Study 2: Randomized Placebo-controlled Trial
  – Prospective 18wk study
  – Double blinded
  – Placebo controlled
  – Registration (ID: NCT00741936)

<table>
<thead>
<tr>
<th>Time(Week)</th>
<th>MZRW 7.5g bid (n=60)</th>
<th>Placebo 7.5g bid (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Run-in</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MaZiRenWan for Functional Constipation

- Responder rates for the MZRW 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).

On going studies of MZRW for constipation

MZRW formula proved by clinical studies

Study 1. GI-motility related drug targets
Done and Manu In preparation

Study 2. MOST: Naïve Bayes model for target prediction
Done

Study 3. Identifying major active compounds in MZRW for constipation
Manu In preparation

Study 4. Design drug combination from MZRW for constipation
On going

Compounds Identified in MZRW by LC-MS
Published

Drug combination for constipation
On going

Unpublished data
Major approaches for identifying the major active compounds of MZRW by combined approach

Chinese Herb Medicine MZRW

MZRW Extract

LC-MS Identification

Animal Studies plasma, feces

In silico target prediction by MOST

Identified compounds from MZRW in rat plasma and feces

Generate Candidates

Validation

Major active compounds in MZRW

Computer

GI motility related target panel

Unpublished data
麻子仁丸研究的思考

- 疾病的针对性
- 临床需求的紧迫性
- 循证证据可获得性
- 注册的可能性
- 新型中藥與二次開發
  - 療效確切
  - 成分相對明确
  - 機理相對清楚
  - 質量可控
概要

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中醫藥治療理念
Treatment Concept of Chinese Medicine

- 整體觀念
- Treatment based on holism concept
整體觀念與臨床實踐
Holism Concept and Clinical Practice

整體觀念
Holism Concept

病理上相互影響
Interaction in pathology

與自然環境的統一性
Unify of nature

與社會環境的統一性
Unify of society

臨床實踐
Clinical Practice

干預合併疾病
Treating combined disease

飲食及生活方式干預
Dietary and lifestyle modification

心理及行為療法
Psychological and behavior therapy
例：腸易激綜合征的綜合管理
Ex. Comprehensive Management of IBS

對症治療
Symptomatic treatment

飲食調整
Dietary modification
- 避免不規律飲食
- Avoid irregular diet

心理療法
Psychological therapy
- 避免焦慮情緒
- Avoid anxiety

生活方式干預
Lifestyle intervention
- 合理運動
- Proper physical exercise

綜合治療理念在藥物設計中必須體現！
未來展望
Future Expectation

有效的治療藥物，成為健康生活調整的一個環節，守護健康！
Thank you!