

# *Advances in the Use of Combined Chinese and Western Medicine in Opioid-Associated Constipation*

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**Abstract:** As the incidence of malignancy continues to rise, cancer pain is one of the most prevalent symptoms throughout the course of cancer treatment. Currently, opioid-related constipation (OIC) is a major obstacle to patients' tolerance of opioid medication, but how to correct the persistent opioid-induced constipation and improve the medical compliance of cancer pain patients. The limitations of traditional Chinese medical (TCM) and Western medicine should not be ignored. This is a brief review of the combination of Chinese and Western medicine in the prevention and treatment of OIC in recent years, with a view to providing reference for clinical colleagues.

## 1. Introduction

According to A Cancer Journal for Clinicians the latest statistics: an estimated 19.3 million new cases of cancer will be diagnosed worldwide in 2020, and the number of cancer deaths will soon exceed the 10 million mark. Cancer pain is the most common symptom in cancer patients throughout the course of cancer treatment, and the most widely used drugs for cancer pain are opioids, but opioids often cause nausea, vomiting, drowsiness and other adverse effects.<sup>[2]</sup> This has a significant impact on the quality of life of patients and the subsequent treatment of their tumours. How to effectively address opioid-induced constipation and improve patient compliance is one of the most pressing issues in the clinical management of malignancies today.

## 2. Understanding of OIC in Chinese and Western Medicine

### 2.1 TCM Understanding of OIC

Constipation was first recorded in the Yellow Emperor's Classic of Internal Medicine, where it was referred to as “difficulty in passing stool” and “posterior discomfort”. The Ji Sheng Fang classifies constipation into five main types: wind, qi, damp, cold and heat, with the disease mainly located in the large intestine and closely related to the lungs, spleen and kidneys. Opium originated from the capsule of the poppy plant and was introduced to China as early as the Han Dynasty. The

Chinese medicine believes that opioids are pungent and aromatic, easily depleting fluids and damaging the body's vital energy, and that tumour patients have a deficient body and cancer toxins have been internalized for a long time. Therefore, Chinese medicine believes that the pathogenesis of OIC is mostly due to the deficiency of Qi, blood and fluids, and the deficiency of fluids is the most important type of evidence. For constipation caused by opioids, TCM practitioners mostly use methods that benefit Qi and nourish Yin, moisten the bowels and open the bowels.<sup>[3-5]</sup>

## 2.2 Modern Medical Understanding of OIC

Since opioid-related constipation is very similar to other causes of constipation, there are no clear diagnostic criteria for OIC. (The main mechanism of OIC may be related to the binding of opioids to the mu-opioid receptor (MOR), which binds to the  $\mu$ ,  $\delta$  and  $\kappa$  opioid receptors, resulting in analgesic, anxiolytic, and diaphoretic effects. These three types of opioid receptors are used to produce analgesic and euphoric effects. These three types of opioid receptors are distributed throughout the body, including the central nervous system, peripheral nervous system and non-neural tissues. These include the central nervous system, peripheral nervous system and non-neural tissues. The binding of  $\mu$  receptors, which are expressed in enteric neurons and affect intestinal nociception, motility and secretion, delays gastric emptying and intestinal transport through the involvement of the central and enteric nervous systems, and inhibits intestinal water and electrolyte secretion and bile excretion, leading to dry stools and difficult defecation. This leads to dry stools and difficult bowel movements.

## 3. Current Status of Chinese and Western Medicine in the Treatment of OIC

### 3.1 Chinese Medicine for OIC

① Internal administration of Chinese herbal medicine is the most common clinical treatment for constipation. Since constipation caused by OIC is mostly deficiency, while using laxative and diuretic herbal medicine, according to the dialectical evidence, either to benefit qi and nourish yin, or to move qi and regulate qi, or to benefit qi and warm yang, add or subtract the medicine so as to achieve the purpose of treating constipation. Yu Haiyan<sup>[9]</sup> formulated his own hemp seed and nut soup, which had a significant advantage in the improvement of constipation symptoms compared with oral lactulose (96% vs. 70%). According to Deng W.<sup>[10]</sup> the underlying pathogenesis of OIC lies in “fire stagnation in the Xuanfu and heat nodulation into solidity”, and the treatment was based on elevation and dispersion, with oral Fusong granules (polyethylene glycol 4000) as the control group. constipation-related symptoms also showed significant improvement. ② Acupuncture in Chinese medicine: opium is pungent and dry, astringent and acidic, which depletes qi and injures fluid, resulting in poor qi flow in the large intestine, inaccessibility of internal qi, depletion of fluid, internal stagnation of dregs, and closure and inaccessibility. Therefore, acupuncture points are often taken from Tianshu, Feosanli, Shangjuxu, and Yu of the large intestine. Wang Wenwen<sup>[11]</sup> included 60 patients with OIC, the observation group was treated with acupuncture and the control group was treated with oral lactulose solution alone, and the improvement of defecation time, stool shape, and abdominal distension in the observation group was significantly better than that in the control group, while acupuncture also effectively improved appetite, fatigue, and other symptoms. ③ Chinese herbal enemas: Chinese herbal enemas were detailed as early as in the Treatise on Typhoid Fever, and most of them were used clinically with rhubarb, or other herbal prescription preparations for enemas. Li Pei Kan, Li Pei Ying<sup>[12]</sup> and Lv Baodi<sup>[13]</sup> have used the enema with the addition and subtraction of “Jia Wei Cheng Qi Tang”, which has achieved remarkable efficacy on the symptoms

of moderate to severe constipation caused by opioids. ④ Chinese herbal compresses: For OIC patients who cannot tolerate oral Chinese medicine, acupuncture or enemas, Chinese herbal acupuncture provides another possibility for this group of patients. Ma Liang et al<sup>[14]</sup> used herbal compresses with Shen Que as the acupuncture point to remove heat and laxity, and after 1 week of treatment, the efficiency of the treatment group (acupuncture point compresses) was significantly higher than that of oral phenolphthalein tablets (92.68% vs. 75.61%). Tang Xin and Wang Xiaoyan selected Shenqu acupuncture point with the guidance of “Ziwu Liu jue theory”. After treatment, the observation group (herbal acupuncture point patching) had better efficiency and relief of constipation than the control group (oral lactulose), and was also significantly better than the control group in improving the quality of life of OIC patients.⑤ Chinese patent medicines: “Ma Ren Soft Capsule” and “New Compound Aloe Vera Capsule” are the more widely used Chinese patent medicines for constipation treatment in clinical practice. Wu Lin-Man<sup>[15]</sup> found that oral administration of hemp seed soft capsule could effectively improve the time of defecation, stool shape and quality of life of OIC patients, and the constipation of patients could be improved continuously after stopping the medicine.

### 3.2 Modern Medical Treatment of OIC

Modern medical treatment of constipation in OIC is mainly divided into the following categories:

① Prokinetic drugs: mosapride, trimebutine, etc. Ji ,S.W. et al<sup>[16]</sup> found that mosapride may have potential use in constipation, gastroesophageal reflex disease and gastroparesis, Zhong L.P. et al<sup>[17]</sup> clinical use of mosapride in combination with lactulose for OIC achieved some efficacy, but there is no mosapride alone for However, there are no clinical trials on the use of mosapride alone in OIC. The mechanism of these two types of drugs is mainly to increase the absorption of water and liquid in the stool, make the stool swell, stimulate the intestinal wall, and induce the defecation reflex. patients with constipation and improve the quality of life. ②Volumetric laxative: magnesium sulfate, cellulose, agar, etc and Hyperosmotic laxative: lactulose, polyethylene glycol, etc. The mechanism of these two types of drugs is mainly to increase the absorption of water and liquid in the stool, make the stool swell, stimulate the intestinal wall, and induce the defecation reflex<sup>[18]</sup>. Zhang Jianzhu<sup>[19]</sup> found that the use of lactulose can effectively relieve constipation and improve the quality of life of OIC patients compared with those who only took senna leaves through clinical observation of 78 OIC patients. ③Lubricant: mainly represented by glycerol preparation, Zhou Beiyun<sup>[20]</sup>. applied glycerol enema combined with warm saline enema by modified enema method, and found that the modified enema method can effectively improve the constipation caused by opioid drugs by clinical observation. ④Microecological agents: common ones are lactobacilli, bifidobacteria, etc. Ye Jianhong<sup>[21]</sup> established a constipation model with compound difenoxanthin tablets, and through this study, it can be found that opioid drug-induced constipation may have a potential relationship with the dysbiosis of intestinal flora. By giving *Lactobacillus plantarum* preparation to the constipated group of mice, Peng Zhirong<sup>[22]</sup> showed a significant increase in food intake and fecal volume in mice after one week of administration. ⑤ Opioid receptor antagonists: naloxone, naltrexone, due to the high first-pass metabolism of naloxone, its main effect is limited to the intestine, inhibiting  $\mu$  opioid receptors in the gastrointestinal tract without significantly altering the analgesic effect of opioids<sup>[23]</sup>. In two large studies, it was found that nearly half of the OIC patients (40%, 44%) taking naloxone had increased active bowel movements, 10-15% higher compared to the placebo group, and this efficiency rate rose to 47-49% for laxative-refractory patients. The most common adverse events were: abdominal pain (19%), diarrhea (9%), nausea (9%), and flatulence (6%)<sup>[24]</sup>, so the clinical application of these drugs requires close attention to their adverse effects. In recent years, “biofeedback therapy” has also received more and more

attention. Biofeedback therapy is the use of modern physiological scientific instruments, according to the human body biofeedback mechanism, through some images or sounds, consciously exercise “intention” to control the body, learn to self-regulate internal physiological and psychological changes, so as to treat or prevent some specific diseases. Zhang Yue <sup>[25]</sup> established a biofeedback group and a conventional treatment group (oral lactulose) and found that the total effective rate of biofeedback therapy for improving chronic functional constipation was 95.7%, which was significantly higher than that of the oral lactulose group alone. However, there are no clinical studies on biofeedback therapy for OIC, and its efficacy on opioid-associated constipation needs to be further investigated.

### 3.3 Combination of Chinese and Western Medicine

#### 3.3.1 Chinese Herbal Medicine Combined with Western Medicine

Chinese medicine combined with Western medicine: Fang Zixin <sup>[26]</sup> applied “Plus flavor Zengliang Chengqi Tang” combined with lactulose to treat OIC, and the constipation improved better than oral Chinese medicine or lactulose only. Xue Jun et al <sup>[27]</sup> showed that the long-term efficacy of constipation was better with the combination of hemp-rem pill and lactulose than with only oral hemp-rem pill or lactulose. Wan Xiaoyun and Liu Chunqi <sup>[28]</sup> showed an increase in the apparent rate of improvement of constipation (96.6% vs. 62.9%) and a decrease in the incidence of adverse events compared with the control group by combining the application of “Zengliang Chengqi Tang” and lactulose. Zhao Wan et al and Wu Qian <sup>[29-30]</sup> both applied the combination of Ma Ren Wan and lactulose for the prevention and treatment of OIC. Compared with oral lactulose, the treatment efficiency of the combined group was significantly higher than that of the control group, and the patients also benefited from life treatment. He Baodu <sup>[31]</sup> used “Si Mo Tang” combined with lactulose, using VIP (vasoactive intestinal peptide), MTL (gastrin), GAS (gastrin) and apparent efficiency as evaluation indexes, and compared with oral lactulose, VIP and MTL were significantly higher after treatment, and the treatment efficiency was also higher than that of the lactulose group. Xia Qing <sup>[32]</sup> used the combination of lactulose with “Runguog Tongbei Tang” to improve constipation and relieve the abdominal distension and pain caused by constipation.

#### 3.3.2 Acupuncture Combined with Western Medical Treatment

Qu Chunxia and Ye Yufang <sup>[33]</sup> found that auricular pressure bean combined with lactulose could effectively promote gastrointestinal motility and regulate gastrointestinal hormone secretion. Jiang Zhigui et al <sup>[34]</sup> applied spaced ginger moxibustion combined with oral lactulose, and the significant rate of the treatment group was higher than that of the control group after 15 days (96.7% vs 51.3%). Mao Rongjuan et al <sup>[35]</sup> used lactulose oral solution combined with constipation moxibustion, and although no significant difference was seen in the efficiency rate between the two groups, the incidence of adverse reactions to the laxative-conducting drugs decreased. Zhuo Xiaochun et al <sup>[36]</sup> combined acupuncture with lactulose, which not only improved the constipation symptoms but also enhanced the patients' quality of life. Cai, H. et al <sup>[37]</sup> combined Chinese medicine acupuncture and transcutaneous electrical nerve stimulation therapy, which reduced the patients' fear of acupuncture compared with traditional acupuncture and had a higher apparent efficiency than lactulose. Xu, H. et al <sup>[38]</sup> combined oral probiotics with acupuncture, and patients' quality of life and constipation symptoms improved significantly, and Xu, Y. Yao <sup>[39]</sup> combined thermal moxibustion with lactulose solution, and compared with the control group (oral lactulose), the total clinical efficiency and

apparent efficiency were significantly improved.

### 3.3.3 Traditional Chinese Medicine Combined with Western Medicine

Wang Chuanliang and Xia Liming<sup>[40]</sup> The use of Huang Hao capsule combined with lactulose significantly benefited OIC patients with significant improvement in constipation compared to oral lactulose alone. Feng Guojian<sup>[41]</sup> The treatment group (oral Shou Hao Laxative Capsules + lactulose) and the control group (oral lactulose) were set up and outperformed the control group in terms of significant efficiency as well as recurrence rate of constipation.

### 3.3.4 Herbal Patching Combined with Western Medical Treatment

Shen Nong Yan<sup>[42]</sup> used Chinese herbal acupuncture (Shen Que) combined with neostigmine acupoint injection, and the clinical efficiency (89.58%) was significantly higher than that of the control group. Li Li et al<sup>[43]</sup> used Chinese herbal acupuncture combined with lactulose for the treatment of OIC, and the advantages were obvious in improving constipation and improving patients' quality of life compared with the control group. Dong Guanghui et al<sup>[44]</sup> used mosapride with external laxative application on Shenqui acupoint, and the onset time of medication, improvement of constipation, and quality of life were significantly improved. Wang Xiaoyan et al<sup>[45]</sup> showed significant improvement in constipation with the combined application of acupuncture points and lactulose oral administration, and its painless and noninvasive characteristics also improved patient compliance.

### 3.3.5 Other Combined Chinese and Western Therapies

The combined application of anal lifting exercise and acupuncture by Chao Xia<sup>[46]</sup> not only has the advantage of improving constipation and quality of life, but also is convenient to operate and easily accepted by patients.

## 4. Conclusion

For the treatment of constipation, Chinese medicine and Western medicine have their own characteristics. Chinese medicine starts from a holistic concept and treats with evidence, which improves constipation and also promotes the recovery of gastrointestinal function, thus indirectly improving the patient's constitution. Compared to Western medicine, the drugs are less toxic and cheaper, making them more acceptable to patients. However, there are no uniform standards for TCM treatment, and there is a lack of large sample studies and insufficient basic experiments. Western medicine is a symptomatic treatment for constipation, with rapid results, but long-term use is prone to drug resistance and can even cause serious adverse reactions when used inappropriately. The combined treatment of Chinese and Western medicine, by combining the strengths and weaknesses of the two, can help the body's own positive energy and improve gastrointestinal function, forming a virtuous cycle and improving long-term efficacy, and we hope that the combined treatment of Chinese and Western medicine will open up a new pathway for the clinical treatment of opioid-induced constipation.

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