Efficacy and Safety of Traditional Chinese Herbal Medicine for Antipsychotic-Related Constipation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**Background:** Constipation is a common but often ignored side effect of antipsychotic treatment, although it is associated with adverse outcomes. The results of the efficacy and safety of traditional Chinese herbal medicine (TCM) in treating constipation are mixed across studies. This is a systematic review and meta-analysis of randomized controlled trials (RCTs) of the efficacy and safety of TCM compared to Western medicine (WM) in treating antipsychotic-related constipation.

**Methods:** Major international electronic (PubMed, EMBASE, Cochrane Library, and Web of Science) and Chinese (Wanfang, WeiPu VIP, SinoMed, and CNKI) databases were searched from their inception to November 29, 2020. Meta-analysis was performed using the random-effects model.

**Results:** Thirty RCTs with 52 arms covering 2,570 patients in the TCM group and 2,511 patients in the WM group were included. Compared with WM, TCM alone was superior regarding the moderate response rate (risk ratio (RR) = 1.165; 95% confidence interval (CI): 1.096–1.238; \( P < 0.001 \)), marked response rate (RR = 1.437; 95% CI: 1.267–1.692; \( P < 0.001 \)), and remission rate (RR = 1.376; 95% CI: 1.180–1.606; \( P < 0.001 \)) for constipation, while it was significantly associated with lower risk of rash (RR = 0.081; 95% CI: 0.019–0.342; \( P = 0.001 \)). For the moderate response rate, meta-regression analyses revealed that publication year (\( \beta = -0.007, P = 0.0007 \)) and Jadad score (\( \beta = 0.067, P < 0.001 \)) significantly moderated the results. For the remission rate, subgroup and meta-regression analyses revealed that the geographical region...
INTRODUCTION

Constipation is a common side effect of antipsychotics with a prevalence rate between 28.1 and 36.3% (1–3) and is associated with a range of severe consequences, such as paralytic ileus, bowel ischemia, sepsis, intestinal perforation, and even pre-mature mortality (4, 5). The occurrence of constipation in psychiatric patients may be associated with a decrease in gastrointestinal hypomotility due to peripheral muscarinic anticholinergic activity (6, 7). For instance, certain antipsychotics, such as clozapine, quetiapine, and olanzapine (8), have strong affinity to muscarinic cholinergic receptors, which could increase peripheral muscarinic anticholinergic activity (9, 10) and may result in constipation.

Commonly used Western medicine (WM) for constipation, including fiber supplements and laxatives, could cause side effects including nausea, vomiting, diarrhea, and even severe adverse events in certain special populations such as those with renal insufficiency (11, 12). Traditional Chinese herbal medicine (TCM) is commonly prescribed in treating and preventing constipation in clinical practice, particularly in Asian countries such as China (13–15), with good evidence found in some high-quality studies (16–20).

To date, findings on the efficacy and safety of TCM for antipsychotic-related constipation compared with WM have been inconsistent. Recent reviews (21, 22) summarized the efficacy of TCM for antipsychotic-related constipation but only included publications in English databases, even though most relevant studies were only published in Chinese language journals. Consequently, only two studies conducted in China were included; one study (23) focused on physical therapy of traditional Chinese Medicine (e.g., acupuncture and Tuina) and the other focused on the use of 250 ml of 10% mannitol with 2 g of Rhubarb-soda plus 0.8 g of Phenolphthalein Tablets (24). This gave us the impetus to conduct this systematic review and meta-analysis of randomized controlled trials (RCTs) of the efficacy and safety TCM and WM in treating antipsychotic-related constipation.

MATERIALS AND METHODS

This meta-analysis was registered in PROSPERO (CRD42020168832) and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria and Outcome Measures

According to the PICOS acronym (25), the inclusion criteria were as follows: Participants (P): patients with constipation caused by antipsychotic medications. Intervention (I): TCM alone. Comparison (C): WM alone or concurrent use of two or more WMs. Outcomes (O): efficacy and safety of TCM. Study design (S): RCTs. Exclusion criteria included (a) severe physical comorbidities and (b) receiving physiotherapy alone or a combination of physiotherapy plus TCM for constipation. Primary outcome included three efficacy measures: moderate response rate, marked response rate, and remission rate. Secondary outcomes included treatment adherence and adverse drug reactions (ADRs), such as nausea, vomiting, and rash.

Search Strategy and Study Selection

Literature search in both international (PubMed, EMBASE, Cochrane Library, and Web of Science) and Chinese (Wanfang, Weipu VIP, SinoMed, and CNKI) databases from inception to October 30, 2019, were independently conducted by two researchers (WWR and JJY), using both subject and free terms of the following search terms: “Constipation [MeSH],” “Medicine, Chinese Traditional [MeSH],” and “Randomized Controlled Trial [MeSH]” (Supplementary Table 2). An updated search to November 29, 2020, was also performed.

The same two researchers (WWR and JJY) independently screened titles and abstracts and then read full texts of relevant publications for eligibility. Any discrepancy was discussed with a third researcher (ZW). In addition, the reference lists of relevant reviews and previous meta-analysis (21, 22) were searched manually for additional studies.

Data Extraction

A pre-designed Excel data collection sheet was used to independently extract relevant data by two researchers (WWR and JJY). The following study and participant characteristics were extracted: the first author, year of publication and survey, sample size, type of medications, mean age of participants, proportion of males, and diagnostic criteria of psychiatric disorders and constipation. Any disagreement was resolved by consensus.

Quality Assessment and Evidence Level

The two researchers (WWR and JJY) independently assessed study quality using both the Jadad scale (0–5 points) (26) and Cochrane risk of bias tool (27). Studies with a Jadad total score of 3 or higher were considered as “high quality;” otherwise, they were considered as “low quality.” The Grading of Recommendations Assessment, Development, and Evaluation
(GRADE) methodology was used to evaluate evidence level of primary and secondary outcomes (i.e., very low, low, moderate, or high) (28).

**Statistical Analyses**
Due to different sample sizes, types and doses of antipsychotic medications, and demographic characteristics between studies, the random-effects model was used to synthesize outcome data, with risk ratio (RRs) and its 95% confidence intervals (CIs) as the effect size. Heterogeneity was assessed using the Cochran’s $Q$ and $I^2$ statistic. $P$-values of $\geq$50% and $P$-value of $\leq$0.10 indicated great heterogeneity across studies. Publication bias was tested using forest plots, Egger’s regression test, Begg’s rank test, and Duval and Tweedie’s trim-and-fill analysis. The sources of heterogeneity between studies on primary outcomes (e.g., moderate/ marked response and remission rates of constipation) were examined by subgroup analyses for categorical variables [e.g., diagnostic criteria for psychiatry: Chinese Mental Disorder Classification and Diagnosis, Third Edition (CCMD-3) vs. Chinese Mental Disorder Classification and Diagnosis, Second Edition (CCMD-2)/Chinese Mental Disorder Classification and Diagnosis, Second Edition, Revised (CCMD-2-R) vs. International Classification of Diseases, Tenth Edition (ICD-10), geographic region (east vs. middle vs. west), analysis method (intent to treat vs. per-protocol), and inpatient group (Yes vs. Mix)] and meta-regression analyses for continuous variables (e.g., publication year, trial duration, Jadad total score, and overall sample size). Sensitivity analysis was carried out to identify outlying studies. All statistical analyses were performed using Comprehensive Meta Analysis (version 2.0; Biostat), with a significance level of 0.05 (two-sided).

**RESULTS**

**Literature Search and Study Characteristics**
A total of 1,725 articles were initially identified. After screening the titles and abstracts, 133 articles were retrieved for full-text review. Finally, 30 studies with 52 arms (2,570 patients in the TCM group and 2,511 patients in the WM group) were included for meta-analyses (Figure 1).

Included studies were published from 1993 to 2020. All studies were conducted in China: 19 studies were conducted in the eastern region, 8 in the central region, and 3 in the western region of China. Sixteen studies used the CCMD-3; two used the CCMD-2; one used the CCMD-2-R; one used the ICD-10; and ten studies did not report diagnostic criteria. The sample size ranged from 60 to 328, and mean age ranged between 28.08 and 69.85 years. Study duration ranged from 0.42 to 28 days (Table 1).

**Assessment Quality and Outcome Evidence**
The mean Jadad scores of the 30 studies ranged from 0 to 4 with a median of 1; of them, 3 were considered as “high quality” (Table 1). Non-blinded assessment and omission of reported dropout were the major reasons for low quality. For the assessment of Cochrane risk of bias, five RCTs mentioned “randomization” in detail (i.e., low risk), and five RCTs used randomization with incorrect methods (i.e., high risk). In addition, no RCT described allocation concealment; therefore, the biases were unclear. Two RCTs mentioned “blinding” (Supplementary Figure 1). The overall quality of the 13 meta-analyzable outcomes was rated as “moderate” (15.4%, 2/13) and “high” (3.03%, 1/33) according to the GRADE approach (Supplementary Table 1).

**Systematic Review and Meta-Analysis**

**Response Rate**
Traditional Chinese herbal medicine alone had significant advantages in terms of the moderate response rate (RR = 1.165; 95% CI: 1.096–1.238, $P < 0.001$, $I^2 = 77.17$%, Table 2, Supplementary Figure 2 and Supplementary Table 3), marked response rate (RR = 1.437; 95% CI: 1.267–1.692, $P < 0.001$, $I^2 = 81.40$%, Table 2, Supplementary Figure 3 and Supplementary Table 3), and remission rate (RR = 1.376; 95% CI: 1.180–1.606, $P < 0.001$, $I^2 = 78.88$, Table 2, Supplementary Figure 4 and Supplementary Table 3) compared to WM. In contrast, no significant difference was found regarding the onset of response after treatment between TCM alone and WM groups (SMD = −0.142; 95% CI: −0.783–0.499; $P = 0.664$, $I^2 = 91.45$, Table 2).

**Treatment Adherence**
No difference was found between TCM alone and WM groups in both overall adherence, full adherence, and partial adherence rates (all $P$-values $> 0.05$; Table 2).

**Adverse Drug Reactions**
No group differences were found in most of the ADRs (e.g., diarrhea, nausea and vomiting, bloating/abdominal pain, borborygmus, and loose stools) (all $P$-values $> 0.05$; Table 2), while rash was less frequent (RR = 0.081, 95% CI: 0.019–0.342; $P = 0.001$, $I^2 = 0.0$) in the TCM group compared to the WM group (Table 2).

Three RCTs reported relapse or exacerbation rates of constipation after discontinuation and all studies found that those receiving WM had a higher relapse rate than those receiving TCM. Specifically, one RCT found that the TCM group had a significantly lower relapse rate than the WM group at 1, 3, and 6 months after discontinuation (36). Another RCT had a similar finding (TCM: 13.24% vs. WM:36.37%; $X^2 = 8.45$, $P < 0.01$) at 1 month after discontinuation (43). Jiang et al. (45) reported that some participants had relapsed after discontinuation in the WM group, but the result in the TCM group was not reported.

**Subgroup and Meta-Regression Analyses**
For the moderate response rate, subgroup and meta-regression analyses found that diagnostic criteria of psychiatric disorders (CCMD-2/CCMD-2-R vs. CCMD-3 vs. ICD-10), geographical region (east vs. middle vs. west), analysis method (intent to treat vs. per-protocol), inpatient group (Yes vs. Mix), trial duration ($\beta = −0.0002$, $P = 0.128$, $n = 44$ arms), total sample size ($\beta = −0.0002$, $P = 0.473$), and sample size in the TCM group ($\beta = 0.0004$, $P = 0.315$) and WM group ($\beta = 0.0002$, $P = 0.717$) did
not moderate the primary results (all \( P \)-values \( > 0.05 \), Table 3), except for the publication year (\( \beta = -0.007, P = 0.0007 \)) and Jadad score (\( \beta = 0.067, P < 0.001 \)). For the remission rate, subgroup analyses revealed that geographical region (\( P = 0.003 \)) and inpatient group (\( P = 0.035 \)) were significantly associated with the results (Table 3). Meta-regression analyses did not reveal significant moderating effects of the publication year (\( \beta = 0.009, P = 0.110 \)), Jadad score (\( \beta = -0.036, P = 0.624 \)), total sample size (\( \beta = 0.0007, P = 0.337 \)), and sample size in the TCM (\( \beta = 0.001, P = 0.469 \)) and WM groups (\( \beta = 0.002, P = 0.248 \)) on the results, except for the trial duration (\( \beta = 0.009, P = 0.013 \), \( n = 23 \) arms).

**Sensitivity Analysis and Publication Bias**

After excluding one outlying study (37) with two arms in which two WMs were used, the primary results did not significantly change (moderate response rate: RR = 1.156, 95% CI: 1.087–1.230, \( P < 0.001 \), \( I^2 = 77.47\% \); marked response rate: RR = 1.391, 95% CI: 1.229–1.575, \( P < 0.001 \), \( I^2 = 80.96\% \)). In addition, we excluded each study one by one, and no significant changes were found in the moderate response rate, marked response rate, or remission rate (Supplementary Figures 8–10).

Both Egger’s and Begg’s-tests (all \( P \)-values \( > 0.05 \)) and funnel plot did not detect publication bias in most outcomes, but publication bias was found in moderate response rate (Egger’s-test: \( t = 4.248, P < 0.001 \); Begg’s-test: \( Z = 2.793, P = 0.005 \); Table 2 and Supplementary Figure 5), marked response rate (Begg’s-test: \( Z = 4.379, P < 0.001 \); Egger’s-test: \( t = 5.790, P < 0.001 \); Table 2 and Supplementary Figure 6), remission rate (Begg’s-test: \( Z = 3.384, P < 0.001 \); Egger’s-test: \( t = 3.855, P < 0.001 \); Table 2 and Supplementary Figure 7), and rash (Egger’s test, \( P = 0.017 \), Table 2). Duval and Tweedie’s trim-and-fill analysis did not find any missing study, which indicates that no
### TABLE 1 | Characteristics of studies included in this meta-analysis.

| No. | First author | Publication year | Survey year | Total sample size | Age (Mean ± SD) | Age range | Male (%) | ACT | Province | Region | Inpatients | Analysis | Diagnostic criteria | Type of disorder | Type of medication | Diagnostic criteria for constipation | Randomization | Blinding | Withdrawal and dropouts | Total score of Jadad | References |
|-----|--------------|-----------------|-------------|------------------|----------------|-----------|----------|-----|----------|--------|------------|---------|-------------------|----------------|-------------------|-------------------------------|-------------|----------|---------------------|---------------------|-----------|
| 1   | Zhao et al.  | 1992–1993       | 190         | 38.6 ± 11.64     | 18–69          | 144 (90)   | 3.2      | E   | Yes      | ITT    | NR        | SCH, AD, and PMD | CH, CL, PE, HA, TF, and others | CL, and others | NR | Lasting 4 days without stool | 72h without stool | 2         | 2           | 0      | 4 | (30) |
| 2   | Ding et al.  | 1996–1998       | 174         | 38.8 ± 11.77     | 17–60          | 144 (90.5) | 3.8      | E   | Yes      | ITT    | NR        | SCH, AD, and PMD | CH, CL, PE, HA, TF, and others | CL, and others | NR | Lasting 4 days without stool | 72h without stool | 1         | 0           | 0      | 1 | (30) |
| 3   | Wang et al.  | 1998–1999       | 181         | 36.19 ± 8.80     | 18–52          | 117 (64.6) | 10.5     | E   | Yes      | ITT    | NR        | SCH               | CL               | NR | Lasting 4 days or more with no stool | NR               | 1         | 0           | 0      | 1 | (31) |
| 4   | Liu et al.   | 2001–2006       | 60          | 38.05 ± 7.89     | NR             | 44 (73.3)  | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CL               | NR | More than 3 days with no stool | NR               | 1         | 0           | 0      | 1 | (30) |
| 5   | Hu et al.    | 2000–2009       | 90          | 67.4 ± 12.6      | 18–87          | 48 (53.3)  | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CL               | NR | More than 3 days with no stool | NR               | 1         | 0           | 0      | 1 | (30) |
| 6   | Li et al.    | 2003–2005       | 261         | 17.6 ± 11.42     | 18–20          | 216 (82.8) | 4.1      | E   | Yes      | ITT    | NR        | SCH, AD, and PMD | CH               | NR | Lasting 4 days without stool | NR               | 1         | 0           | 0      | 1 | (37) |
| 7   | Shang et al. | 2005–2006       | 118         | 32.6 ± 3.2       | 16–56          | 72 (61.4)  | 3.2      | E   | Yes      | ITT    | NR        | SCH, AD, and PMD | CH               | NR | Lasting 4 days without stool | NR               | 1         | 0           | 0      | 1 | (30) |
| 8   | Li et al.    | 2004–2005       | 90          | 41.3 ± 17.3      | 18–72          | 90 (103)   | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH               | NR | Lasting 4 days without stool | NR               | 1         | 0           | 0      | 1 | (30) |
| 9   | Shang et al. | 2006–2007       | 120         | 38.2 ± 15.3      | 18–64          | 87 (72.3)  | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH               | NR | Lasting 4 days without stool | NR               | 1         | 0           | 0      | 1 | (30) |
| 10  | Meng et al.  | 2007–2008       | 115         | 28.8 ± 13.1      | 18–65          | 64 (55.7)  | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH               | NR | Lasting 4 days without stool | NR               | 2         | 0           | 0      | 0 | (42) |
| 11  | Pan et al.   | 2006–2007       | 120         | 39.2 ± 16.6      | 20–72          | 126 (94.3) | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH               | NR | Lasting 4 days without stool | NR               | 2         | 0           | 0      | 0 | (42) |
| 12  | Lin et al.   | 2008–2009       | 134         | 33.63 ± 9.67     | 15–58          | 87 (64.3)  | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH, RI, CL, PE, HA, and others | NR | Lasting 4 days without stool | NR               | 0         | 0           | 0      | 0 | (43) |
| 13  | Xie et al.   | 2009–2010       | 100         | 34.5 ± 15.9      | 17–58          | 72 (56.3)  | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH, RI, CL, PE, HA, and others | NR | Lasting 4 days without stool | NR               | 0         | 0           | 0      | 0 | (44) |
| 14  | Jiang et al. | 2009–2010       | 119         | 28.08 ± 12.06    | 19–52          | 42 (48.3)  | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH, RI, CL, PE, HA, and others | NR | Lasting 4 days without stool | NR               | 0         | 0           | 0      | 1 | (45) |
| 15  | Liu et al.   | 2007–2008       | 305         | 31.97 ± 10.29    | 10–29          | 175 (57.4) | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH, RI, CL, PE, HA, and others | NR | Lasting 4 days without stool | NR               | 1         | 0           | 0      | 1 | (46) |
| 16  | Li et al.    | 2008–2009       | 76          | 39.92 ± 11.00    | NR             | 76 (100.0) | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH, RI, CL, PE, HA, and others | NR | Lasting 4 days without stool | NR               | 1         | 0           | 0      | 1 | (47) |
| 17  | Han et al.   | 2009–2010       | 120         | 49.9 ± 15.93     | 17–70          | 61 (50.8)  | 3.2      | E   | Yes      | ITT    | NR        | SCH               | CH, RI, CL, PE, HA, and others | NR | Lasting 4 days without stool | NR               | 1         | 0           | 0      | 1 | (48) |

(Continued)
| No. | First author     | Publication year | Survey year | Total sample size | Age range | Male (%) | ACT | Province | Region | Inpatients | Analysis | Diagnostic criteria | Type of disorder | Type of medication | Diagnostic criteria for constipation | Randomization | Blinding | Withdrawal and dropouts | Total score of Jadad | References |
|-----|-----------------|-----------------|-------------|------------------|-----------|----------|-----|----------|--------|------------|----------|-------------------|-----------------|-----------------|--------------------------------------|--------------|----------|----------------------|------------------|-----------|
| 27  | Tang            | 2018            | 2015–2017   | 80               | 41.6 ± 11.13 | 20–60    | 47  | (58.8)  | Hubai  | M        | NR       | ITT      | CC-MD-3      | NR              | CL             | Criterion G                                       | 0             | 0        | 0                    | 0                | (55)      |
| 28  | Wang et al.     | 2015–2017       | 2015–2017   | 100              | 38.6 ± 3.2     | 18–60    | NR  | Guangdong | E      | Yes       | PP       | ICD-10   | SCH          | NR              | NR             | Lasting 3 days without stool = Criterion D | 1             | 0        | 1                    | 2                | (54)      |
| 29  | Zhu             | 2017–2018       | 120         | 48.1 ± 4.87     | 25–68    | 76       | 60.3| Yes      | Zhejiang | E        | Yes      | ITT      | CC-MD-3      | SCH            | AD             | Lasting 3 days without stool              | 2             | 0        | 0                    | 2                | (57)      |
| 30  | Wu et al.       | 2018–2019       | 70          | 38.85 ± 2.15    | 22–56    | 41       | (58.6)| Shandong | W      | Yes       | ITT      | CC-MD-3      | SCH          | NR             |                                       |              |          |                      |                  | (58)      |

**Order of arms**

| N   | Age (Mean ± SD) | Age range | Male (%) | ACT | Name            | N   | Age (Mean ± SD) | Age range | Male (%) | ACT | Name            |
|-----|-----------------|-----------|----------|-----|-----------------|-----|-----------------|-----------|----------|-----|-----------------|
| 1   | 117 (64.6)      | 18–52     | 60       | NR  | Senna 60        | 89  | 35.54 ± 8.63   | 15–47     | 56       | NR  | Senna 60        |
| 2   | 117 (64.6)      | 18–52     | 60       | NR  | Senna 60        | 89  | 35.54 ± 8.63   | 15–47     | 56       | NR  | Senna 60        |
| 1   | 60              | 38.05 ± 7.89 | 44 (73.3)   | 7    | 30.3 ± 8.2     | 30  | 38.7 ± 7.86    | 15–47     | 56       | NR  | Yu Zhu Shu Tong |
| 1   | 60              | 38.05 ± 7.89 | 44 (73.3)   | 7    | 30.3 ± 8.2     | 30  | 38.7 ± 7.86    | 15–47     | 56       | NR  | Yu Zhu Shu Tong |
| 2   | 60              | 38.05 ± 7.89 | 44 (73.3)   | 7    | 30.3 ± 8.2     | 30  | 38.7 ± 7.86    | 15–47     | 56       | NR  | Yu Zhu Shu Tong |
| 1   | 117             | 25.14     | 66       | NR  | Senna 30        | 30  | 38.7 ± 7.86    | 15–47     | 56       | NR  | Senna 30        |
| 1   | 117             | 25.14     | 66       | NR  | Senna 30        | 30  | 38.7 ± 7.86    | 15–47     | 56       | NR  | Senna 30        |
| 2   | 134             | 25.00     | 66       | NR  | Senna 30        | 30  | 38.7 ± 7.86    | 15–47     | 56       | NR  | Senna 30        |
| 3   | 127             | 25.04     | 76       | NR  | Senna 51        | 51  | 38.7 ± 7.86    | 15–47     | 56       | NR  | Senna 51        |
| 4   | 144             | 25.72     | 76       | NR  | Senna 68        | 68  | 38.7 ± 7.86    | 15–47     | 56       | NR  | Senna 68        |
| 1   | 60              | 38.3 ± 11.7 | 27 (45.0)  | 28   | 30.8 ± 11.1    | 30  | 38.8 ± 11.1    | 14–46.7   | 14 (46.7) | NR  | Qi Rong Run    |

**TCM**

| Order of arms | N   | Age (Mean ± SD) | Age range | Male (%) | ACT | Name        | N   | Age (Mean ± SD) | Age range | Male (%) | ACT | Name        |
|---------------|-----|-----------------|-----------|----------|-----|-------------|-----|-----------------|-----------|----------|-----|-------------|
| 1             | 120 | NR              | NR        | NR       | NR  | NR 1 60    | 60  | NR              | NR        | NR       | NR  | NR 1 60    |
| 2             | 120 | NR              | NR        | NR       | NR  | NR 1 60    | 60  | NR              | NR        | NR       | NR  | NR 1 60    |
| 1             | 95  | NR              | NR        | NR       | NR  | NR 23.38   | 51  | NR              | NR        | NR       | NR  | NR 23.38   |
| 2             | 84  | NR              | NR        | NR       | NR  | NR 22.94   | 51  | NR              | NR        | NR       | NR  | NR 22.94   |
| 3             | 97  | NR              | NR        | NR       | NR  | NR 23.19   | 51  | NR              | NR        | NR       | NR  | NR 23.19   |
| 1             | 181 | 36.19 ± 8.80    | 18–52     | 117      | 4.62 ± 0.60 | 1    | 35.54 ± 8.63 | 15–47    | 56       | 62.9| 4.65 ± 0.66 | Senna 92 |
| 1             | 60  | 38.05 ± 7.89    | NR        | 44       | 73.30| 7    | 30.3 ± 8.2   | 23       | 76       | 76.7| 4.65 ± 0.66 | Yu Zhu Shu Tong 30 |
| 1             | 60  | 38.05 ± 7.89    | NR        | 44       | 73.30| 7    | 30.3 ± 8.2   | 23       | 76       | 76.7| 4.65 ± 0.66 | Yu Zhu Shu Tong 30 |
| 2             | 60  | 38.05 ± 7.89    | NR        | 44       | 73.30| 7    | 30.3 ± 8.2   | 23       | 76       | 76.7| 4.65 ± 0.66 | Yu Zhu Shu Tong 30 |
| 1             | 117 | 25.14           | 66        | NR       | NR  | NR 25.14   | 66  | NR              | NR        | NR       | NR  | NR 25.14   |
| 2             | 134 | 25.00           | 66        | NR       | NR  | NR 25.00   | 66  | NR              | NR        | NR       | NR  | NR 25.00   |
| 3             | 127 | NR              | NR        | NR       | NR  | NR 25.04   | 76  | NR              | NR        | NR       | NR  | NR 25.04   |
| 4             | 144 | NR              | NR        | NR       | NR  | NR 25.72   | 76  | NR              | NR        | NR       | NR  | NR 25.72   |
| 1             | 60  | 38.3 ± 11.7     | 27        | 45.0     | 30.8 ± 11.1 | 30  | 38.8 ± 11.1    | 14–46.7   | 14 (46.7)| NR  | Qi Rong Run Chang oral liquid 30 |

(Continued)
| Order of arms | N (Mean ± SD) | Age (Mean ± SD) | Age range | Male (%) | ACT trial duration (days) | TCM | N (Mean ± SD) | Age (Mean ± SD) | Age range | Male (%) | ACT Name |
|---------------|---------------|-----------------|-----------|----------|--------------------------|-----|---------------|-----------------|-----------|----------|---------|
| 1             | 97            | 28.73 ± NR      | 17-57     | 56 (57.7) | NR                       | 5   | 28.5 ± NR     | 18-55          | 29 (55.8) | NR       | Phenolphthalein and Lonicor combination |
| 1             | 60            | NR              | 90 (100)  | NR       | NR                       | 1   | NR            | NR             | NR        | NR       | Phenolphthalein and Glycerine Enema |
| 1             | 118           | 32.6 ± NR       | 16-56     | 72 (10.0) | NR                       | 0.42| 58            | NR             | NR        | NR       | Senna |
| 1             | 328           | 28.47 ± 10.33   | NR        | 229 (99.0) | NR                       | 1   | 165           | NR             | NR        | NR       | Senna |
| 1             | 80            | NR              | NR        | 46 (52.9) | NR                       | 3   | 40            | NR             | NR        | NR       | Phenolphthalein |
| 1             | 87            | 29.10 ± 13.20   | NR        | 28 (52.9) | NR                       | 28  | 28            | 27.97 ± 12.81  | NR        | 18 (64.3) | Phenolphthalein and Rhubarb Combination |
| 1             | 77            | 28.80 ± 12.77   | NR        | 28 (54.6) | NR                       | 28  | 28            | 27.97 ± 12.81  | NR        | 18 (64.3) | Senna |
| 1             | 100           | NR              | NR        | NR       | NR                       | 1   | 50            | NR             | NR        | NR       | Rhubarb |
| 1             | 134           | 33.83 ± NR      | 15-58     | 87 (64.9) | NR                       | 7   | 68            | 34.34 ± NR     | 15-58     | 46 (66.2) | Mass Ren Wan |
| 1             | 64            | NR              | 18-57     | 46 (57.6) | NR                       | 1   | 32            | NR             | 18-57     | 19 (59.4) | Senna |
| 2             | 64            | NR              | 18-59     | 46 (57.6) | NR                       | 1   | 32            | NR             | 18-57     | 19 (59.4) | Senna |
| 1             | 87            | 28.08 ± 12.68   | NR        | 10 (48.3) | NR                       | 10  | 41            | 27.96 ± 12.75  | NR        | 20 (48.8) | Peon and Licorice combination |
| 1             | 305           | 31.97 ± 10.29   | NR        | 175 (57.4) | NR                       | 163 | 163           | 31.59 ± 10.12  | NR        | 97 (59.5) | Rheum Glycyrrhiza decoction |
| 1             | 76            | 39.82 ± 11.00   | NR        | 76 (100)  | NR                       | 28  | 38            | 41.39 ± 10.47  | NR        | (5.39 ± 1.22) d | Ma Ren Ruchang Wana |
| 1             | 80            | 33.15 ± 15.38   | NR        | 39 (48.6) | NR                       | 28  | 40            | 32.6 ± 16.2    | 18-60     | 18 (45.0) | Tongbianling |
| 2             | 39            | NR              | NR        | NR       | NR                       | 21  | 22            | NR             | NR        | NR       | Ma Ren Wan |
| 3             | 44            | NR              | NR        | NR       | NR                       | 21  | 22            | NR             | NR        | NR       | Senna |
| 4             | 48            | NR              | NR        | NR       | NR                       | 21  | 26            | NR             | NR        | NR       | Senna |

(Continued)
| Order of arms | N    | Age (Mean ± SD) | Age range | Male (%) | ACT   | N    | Age (Mean ± SD) | Age range | Male (%) | ACT   | N    | Age (Mean ± SD) | Age range | Male (%) | ACT   |
|--------------|------|----------------|-----------|----------|-------|------|----------------|-----------|----------|-------|------|----------------|-----------|----------|-------|
| 1            | 123  | NR             | NR        | NR       | NR    | 57   | NR             | NR        | NR       | NR    | Senna | 66              | NR        | NR       | NR    | Lactulose |
| 2            | 123  | NR             | NR        | NR       | NR    | 57   | NR             | NR        | NR       | NR    | Senna | 71              | NR        | NR       | NR    | Glycerina Enema |
| 3            | 123  | NR             | NR        | NR       | NR    | 57   | NR             | NR        | NR       | NR    | Senna | 64              | NR        | NR       | NR    | Glycerina Enema |

*Including patients with dropout.

ACT, Average constipation time; h, Hour; d, Day; TCM, Traditional Chinese medicine; WM, Western medicine; CCMD-2, Chinese Mental Disorder Classification and Diagnosis, Second Edition; CCMD-2-R, Chinese Mental Disorder Classification and Diagnosis, Second Edition, Revised; CCMD-3, Chinese Mental Disorder Classification and Diagnosis, Third Edition; ICD-10, International Classification of diseases, Tenth Edition; Criterion A, Patient with abdominal distension, loss of appetite, difficulty in defecation, and no stool discharge for more than 3 days; Criterion B, One of three symptoms (decreasing times of fecal discharge or dry stool or difficult defecation) and a sign cluster (abdomen fullness and discomfort, palpable cord-like mass, dizziness, headache, short urination, dry mouth, bitter mouth, fatigue, irritability, etc.) due to the accumulation of belly stool; Criterion C, Patients with difficult fecal discharge, prolonging defecation time, only defecates once or has a feeling of defecation but cannot defecate in 4–6 days; Criterion D, Rome terion D difficult on Functional Constipation; Criterion E, diagnostic criteria from Thompson et al. 60); Criterion F, Diagnostic criteria for constipation with Yin deficiency syndrome (61); Criterion G, Lasting 3 days with no stool; dry stool; laborious defecation; Criterion H, Constipation severity criteria (level 0: without constipation and defecation once in 1–2 days with soft stool; level 1: defecation one time in 2–3 days after medication and stiff stool into strips with difficulty in defecation; level 2: defecation one time in 3–4 days after medication and stiff stool into granular lump with difficulty in defecation; level 3: defecation one time in more than 5 days after medication, and lumpy stool with difficulty in defecation by yourself, even defecation by external forces); Criterion I, difficulty in defecation, no stool discharge for more than 3 days and change of defecation habits; Criterion J, Guideline for the diagnosis and treatment of chronic constipation (62); ITT, Intention to treat analysis; PP, per-protocol analysis; NR, Not Reported; SD, Standard deviation; SCH, Schizophrenia; AD, Affective disorders; DP, Depression; MD, Mood disorders; SRD, Stress-related disorders; ND, Neurotic disorders; PMD, Psychogenic mental disorders, Ma, Mania, RP, Reactive psychosis; SAP, Schizo-affective psychosis; ALD, Alzheimer’s disease; VD, Vascular dementia; CL, Clozapine; CH, Chlorpromazine; SU, Sulpiride; PE, Perphenazine; RI, Risperidone; HA, Haloperidol; OL, Olanzapine; QE, Quetiapine fumarate; TF, Trifluoperazine; PA, Phenothiazine antipsychotics; CLO, Clozapine; AM, Amitriptyline.
TABLE 2 | Clinical efficacy: moderate response rate (missing studies = 5; new RR = 1.1; 95% CI: 1.030–1.174), marked response rate (missing studies = 10; new RR = 1.219, 95% CI: 1.067–1.392), remission rate (missing studies = 2; new RR = 1.440, 95% CI: 1.231–1.685), time of onset (missing studies = 1; new SMD = −0.028, 95% CI: −0.592–0.536), nausea and vomiting (missing studies = 3; new RR = 1.880, 95% CI: 0.752–4.702), and bloating/abdominal (missing studies = 4; new RR = 1.126, 95% CI: 0.708–1.792).

DISCUSSION

This was the first systematic review and meta-analysis that examined the efficacy and safety of TCM in treating antipsychotic-related constipation. Commonly prescribed TCM included Senna, Apricot Seed and Linum Formula, Ma Ren Wan, etc., while WM included Phenolphthalein, Glycerine Enema, etc. We found that TCM alone was superior to WM in terms of moderate response rate, marked response rate, and remission rate for constipation, while TCM alone was significantly associated with lower risk of rash. Skin rash is a common side effect associated with certain Western drug allergy (63) including antipsychotic drugs (64–66). In this meta-analysis compared to WM, TCM has a lower risk of rash. Traditional Chinese herbal medicine has been widely prescribed in China in treating antipsychotic drug-induced constipation (67), and TCM prescriptions strictly follow relevant treatment guidelines and regulations (68).

Our efficacy findings are similar to the findings of large case-control studies (69). An earlier review found that TCM was more effective than cisapride (RR = 0.24, 95% CI: 0.17–0.34), polyethylene glycol (RR = 0.14, 95% CI: 0.06–0.34), mosapride (RR = 0.33, 95% CI: 0.23–0.46), and phenolphthalein (RR = 0.24, 95% CI: 0.13–0.46) in treating functional constipation (13), which is consistent with the findings of this study and another meta-analysis (70). Traditional Chinese herbal medicine appears more effective for constipation than WM; however, due to the variety of components found across TCM, the mechanisms are still not clear. To date, no basic science research on the efficacy of TCM for constipation has been published.

Subgroup analyses revealed that the remission rate for treating constipation was moderated by geographical regions. When comparing TCM with WM, the RR of TCM vs. WM was 1.219 (95% CI: 1.044–1.423) in the eastern region and 3.713 (95% CI: 1.988–6.902) in the central region, while no difference was found in the western region of China. It should be noted that most studies were conducted in the eastern region, and only two studies with small sample size were conducted in the western region of China; therefore, the results of this subgroup analysis may not be stable. The different dietary habits among populations between regions in China may be partly responsible for the discrepancy. For example, many people in the central region of China (e.g., Hunan, Hubei, and Jianxi provinces) prefer spicy foods, which could increase the risk of constipation (71), while
TABLE 3 | Subgroup analyses of response rate and remission of traditional Chinese medicine compared with Western medicine for constipation.

| Subgroups               | Categories (number of studies) | Sample size | RR | 95% Confidence interval (%) | I² (%) | P within subgroup | P across subgroups |
|-------------------------|--------------------------------|-------------|----|-----------------------------|--------|------------------|-------------------|
| **Moderate response rate** |                               |             |    |                             |        |                  |                   |
| Diagnostic criteria     | CCMD-2/2-R (9)                 | 918         | 1.214 | (0.978, 1.509)              | 70.0   | 0.001            | 0.470             |
|                         | CCMD-3 (27)                    | 2,301       | 1.084 | (1.012, 1.162)              | 75.1   | <0.001           |                   |
|                         | ICD-10 (1)                     | 96          | 1.176 | (0.989, 1.397)              | 0.0    | 1.000            |                   |
| Analysis                | ITT (47)                       | 4,595       | 1.169 | (1.097, 1.246)              | 78.0   | <0.001           | 0.475             |
|                         | PP (2)                         | 194         | 1.112 | (0.983, 1.257)              | 0.0    | 0.368            |                   |
| Region                  | East (38)                      | 3,873       | 1.136 | (1.067, 1.208)              | 71.9   | <0.001           | 0.118             |
|                         | Middle (9)                     | 786         | 1.465 | (1.157, 1.856)              | 89.4   | <0.001           |                   |
|                         | West (2)                       | 130         | 1.120 | (0.946, 1.326)              | 12.7   | 0.284            |                   |
| Inpatient               | Yes (47)                       | 4,575       | 1.172 | (1.097, 1.251)              | 77.9   | <0.001           | 0.064             |
|                         | Mx (1)                         | 134         | 1.066 | (0.989, 1.149)              | 0.0    | 1.000            |                   |
| Publication year*       | ≤2,008 (25)                    | 2,788       | 1.152 | (1.062, 1.251)              | 78.3   | <0.001           | 0.627             |
|                         | >2,008 (24)                    | 2,293       | 1.189 | (1.079, 1.310)              | 76.9   | <0.001           |                   |
| **Remission rate**      |                               |             |    |                             |        |                  |                   |
| Diagnostic criteria     | CCMD-2 (7)                     | 798         | 1.168 | (0.883, 1.544)              | 74.2   | 0.001            | 0.818             |
|                         | CCMD-3 (19)                    | 1,536       | 1.212 | (1.039, 1.414)              | 67.0   | <0.001           |                   |
| Analysis                | ITT (30)                       | 3,124       | 1.386 | (1.185, 1.622)              | 79.6   | <0.001           | 0.487             |
|                         | PP (1)                         | 98          | 1.083 | (0.550, 2.133)              | 0.0    | 1.000            |                   |
| Region                  | East (24)                      | 2,672       | 1.219 | (1.044, 1.423)              | 71.9   | <0.001           | 0.003             |
|                         | Middle (5)                     | 383         | 3.713 | (1.988, 6.902)              | 68.6   | 0.013            |                   |
|                         | West (2)                       | 167         | 1.191 | (0.903, 1.767)              | 74.1   | 0.049            |                   |
| Inpatient               | Yes (28)                       | 2,854       | 1.425 | (1.185, 1.713)              | 80.2   | <0.001           | 0.035             |
|                         | Mx (2)                         | 231         | 1.078 | (0.898, 1.294)              | 42.7   | 0.186            |                   |
| Publication year*       | ≤2,011 (16)                    | 2,049       | 1.310 | (1.074, 1.598)              | 77.7   | <0.001           | 0.478             |
|                         | >2,011 (15)                    | 1,173       | 1.475 | (1.137, 1.914)              | 81.0   | <0.001           |                   |

*Based on the median splitting method.

Bold values: *P* < 0.05. CCMD-2, Chinese Mental Disorder Classification and Diagnosis, Second Edition; CCMD-2-R, Chinese Mental Disorder Classification and Diagnosis, Second Edition, Revised; CCMD-3, Chinese Mental Disorder Classification and Diagnosis, Third Edition; ICD-10, International Classification of diseases, Tenth Edition; ITT, Intention to treat analysis; PP, per-protocol analysis.

those in the eastern region prefer bland foods. The advantage of TCM in terms of remission rate was more obvious in the inpatient group compared to the mixed inpatient and outpatient group, which may be related to better treatment adherence among inpatients (72, 73) or due to a small number of studies on mixed patient sample (n = 2). As expected, meta-regression analysis found that a longer trial duration (*β* = 0.009, *P* = 0.013) was associated with a higher remission rate of constipation, probably because the delivery of TCM is more stable in longer studies. Meta-regression demonstrated that the moderate response rate was negatively related to the publication year (*β* = −0.007, *P* = 0.0007). We speculate that first-generation antipsychotics (FGAs) were widely used in the past, which often led to severe constipation (1). In the past decade, however, FGAs have been gradually replaced by second-generation antipsychotics (SGAs). In contrast, SGAs are less likely to cause severe constipation (74, 75). Unexpectedly, compared to those with only mild constipation, patients with severe constipation were often more likely to respond to TCM. We speculate that the doses of TCM and types of constipation may moderate this association although relevant data were insufficient to clarify this finding, which needs to be confirmed in future studies. The association of the higher response rate with higher-quality studies might be due to the fact that response is more likely to be identified in higher-quality studies, e.g., those with well-trained researchers and sensitive assessment tools.

The strengths of this systematic review and meta-analysis included the inclusion of both international and Chinese databases, large number of included studies, large sample size, and use of sophisticated analyses (e.g., subgroup, meta-regression, and sensitivity analyses). Some methodological limitations should be noted. First, all studies were conducted in China, which may limit the generalizability of the findings to other parts of the world. Additionally, the included studies were not large-scale RCTs. Second, the active ingredients of TCM and their optimal doses for constipation were not analyzed due to insufficient data. Unlike WM, due to the varied ingredients in most TCM, no dosages were provided as they were only administered as tablets and/or capsules in clinical practice. Also, due to different components and forms of TCM between...
included RCTs, head-to-head comparisons of TCM could not be conducted in this meta-analysis. Third, some factors related to constipation, such as lifestyle, outdoor activities and physical exercise status of participants, types and doses of antipsychotic medications, and major physical conditions, were not reported in most of the included studies. Finally, the efficacy and side effects between different TCMs were not compared due to the small number of studies in each subgroup.

In conclusion, this meta-analysis found that the efficacy of TCM on antipsychotic-related constipation was greater compared to WM, but certain side effects of TCM, such as rash, were less frequent. Hence, TCM appears to be an effective and safe treatment for antipsychotic-related constipation in clinical practice. However, these findings will need to be confirmed in future high-quality studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

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AUTHOR CONTRIBUTIONS

W-WR, Y-TX, and WZ: study design. W-WR, J-JY, HQ, and SS: data collection, analysis, and interpretation. W-WR, HQ, and Y-TX: drafting of the manuscript. LZ, GU, and CN: critical revision of the manuscript. All authors: approval of the final version for publication.

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SUPPLEMENTARY MATERIAL

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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