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[Intervention Review]

Pharmacological treatment for antipsychotic-related constipation

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ABSTRACT

Background

Antipsychotic-related constipation is a common and serious adverse effect, especially for people taking clozapine. Clozapine has been shown to impede gastrointestinal motility, leading to constipation, and has been reported in up to 60% of patients receiving clozapine. In rare cases, complications can be fatal. Appropriate laxatives should be prescribed to treat constipation in people taking antipsychotics, but there is a lack of guidance on the comparative effectiveness and harms of different agents in this population. An understanding of the effectiveness and safety of treatment for antipsychotic-related constipation is important for clinicians and patients alike.

Objectives

To evaluate the effectiveness and safety of pharmacologic treatment (versus placebo or compared against another treatment) for antipsychotic-related constipation (defined as constipated patients of any age, who are treated with antipsychotics, regardless of dose, in which constipation is considered to be an antipsychotic-related side effect).

Search methods

We searched the Cochrane Schizophrenia Group's Trials Register (15 June 2015), which is based on regular searches of MEDLINE, Embase, CINAHL, BIOSIS, AMED, PubMed, PsycINFO, and registries of clinical trials, grey literature, and conference proceedings. There are no language, date, document type, or publication status limitations for inclusion of records in this register. We also handsearched bibliographies and contacted relevant authors for additional information.

Selection criteria

We included all published and unpublished randomised controlled trials (RCTs) investigating the efficacy of pharmacological treatments in patients with antipsychotic-related constipation. Pharmacological treatments included laxatives and other medicines that could reasonably be used to combat constipation in this population (e.g. anticholinergic agents, like bethanecol).

Data collection and analysis

Two review authors independently extracted data from all included studies and assessed trials for risk of bias. A third author reviewed 20% of trials. We analysed dichotomous data using relative risks (RR) and the 95% confidence intervals (CI). We assessed risk of bias for included studies and used GRADE to create a 'Summary of findings' table. We discussed any disagreement, documented decisions, and attempted to contact study authors when necessary.

Main results

We identified two relevant Chinese studies (N = 480) that contributed data to this review. Both studies were over ten years old and poorly reported, lacking descriptions of contemporary CONSORT reporting prerequisites, such as sequence generation, allocation concealment, blinding, participant flow, how the sample size was determined, or how outcomes were measured. The studies also did not report trial registration, pre-specified protocols, consent processes, ethical review, or funding source. We were unsuccessful in making contact with the authors to clarify the missing details. We classified both studies as having an overall high risk of bias.

One study compared glycerol suppository with the traditional Chinese medicine (TCM) approaches of tuina massage and acupuncture. Compared to tuina massage, glycerol laxative was less effective in relieving constipation at both two days after treatment (1 RCT; N = 120; RR 2.88, 95% CI 1.89 to 4.39; very low-quality evidence), and three days (1 RCT; N = 120; RR 4.80, CI 1.96 to 11.74, very low-quality evidence). Favourable results were also seen for acupuncture at two days (1 RCT; N = 120; RR 3.50; 95% CI 2.18 to 5.62; very low-quality evidence), and at three days (1 RCT; N = 120; RR 8.00, 95% CI 2.54 to 25.16; very low-quality evidence).

The other study compared mannitol, an osmotic laxative, with rhubarb soda or phenolphthalein. Mannitol was more effective than rhubarb soda or phenolphthalein in relieving constipation within 24 hours of treatment (1 RCT; N = 240; RR 0.07; 95% CI 0.02 to 0.27, very low-quality evidence).

No data were reported for our other important outcomes: need for rescue medication, bowel obstruction (a complication of antipsychotic-related constipation), quality of life, adverse events, leaving the study early, and economic costs.

Authors' conclusions

We had hoped to find clinically useful evidence appraising the relative merits of the interventions routinely used to manage antipsychotic-related constipation, a common and potentially serious adverse effect of the use of these drugs. The results were disappointing. There were no data comparing the common pharmacological interventions for constipation, such as lactulose, polyethylene glycol, stool softeners, lubricant laxatives, or of novel treatments such as linaclotide. Data available were very poor quality and the trials had a high risk of bias. Data from these biased studies suggested that mannitol, an osmotic laxative, was more effective than rhubarb soda and phenolphthalein in relieving constipation, and a two-week course of glycerol suppositories was less effective than the TCM approaches of tuina massage and acupuncture.

Overall, there is insufficient trial-based evidence to assess the effectiveness and safety of pharmacological interventions for treating antipsychotic-related constipation, due to limited, poor quality data (few studies with high risk of bias and no meta-analyses). The methodological limitations in the included studies were obvious, and any conclusions based on their results should be made with caution. Methodologically rigorous RCTs evaluating interventions for treating antipsychotic-related constipation are needed.

PLAIN LANGUAGE SUMMARY

Drug treatments for constipation caused by antipsychotic medications

Background

Constipation is a common side effect for people taking antipsychotic medications, especially clozapine. It has been shown that clozapine reduces bowel motility, and the consequences of this are sometimes serious. For every thousand patients treated with clozapine, it is thought that 300 to 600 will suffer constipation; at least four will develop serious gastrointestinal complications (such as bowel obstruction), from which at least one will die.

Searching

In June 2015, we searched for trials that compared medicines used to treat antipsychotic-related constipation (such as laxatives) against any other treatment. However, we found little useful information. We identified two relevant studies in the Chinese literature, but none in the Western literature.

Main results

The identified studies were of short duration, very likely to be biased, and provided very low-quality evidence. One study suggested that a glycerol suppository was less effective than acupuncture or tuina massage, and the other suggested that mannitol, an osmotic laxative, was more effective than rhubarb soda or phenolphthalein in treating constipation.

Conclusions

Based on our results, we conclude there is currently no good quality trial-based evidence available that can guide clinicians and patients in the pharmacological treatment of antipsychotic-related constipation.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Glycerol laxative versus tuina massage for antipsychotic-related constipation

Glycerol laxative versus tuina massage

Patient or population: antipsychotic-related constipation
Setting: inpatient
Intervention: glycerol
Comparison: tuina

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Tuina	Risk with Glycerol				
1. Global or clinical change in constipation (a) as defined by the study Still constipated (no defecation) at 2 days	Study population 283 per 1000	816 per 1000 (536 to 1,000)	RR 2.88 (1.89 to 4.39)	120 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1, 2	
Global or clinical change in constipation (a) as defined by the study Still constipated (no defecation) at 3 days	Study population 83 per 1000	400 per 1000 (163 to 978)	RR 4.80 (1.96 to 11.74)	120 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1, 2	
(b) Change in the frequency of defecation	No studies reported these important outcomes					
(c) Change in straining at defecation						
(d) Change in the frequency of lumpy or hard stools						
(e) Change in the frequency of manual manoeuvres to facilitate defecation						
2. Need for rescue medication						
3. Presence of antipsychotic-related constipation complications such as bowel obstruction						
4. Quality of life (changed to any extent)						

5. Adverse events
6. Leaving the study early
7. Economic costs

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Randomisation and allocation concealment methods unclear. Management of incomplete outcome data unclear. Blinding unlikely to have occurred - rated as very serious - downgraded by 2.

² No validated method used for measuring constipation. Unclear how reported defecation was assessed (e.g. stool chart, participant recall from memory). No recording of any of the other ROME constipation symptoms (e.g. straining, stool consistency, manual manoeuvres) - rated as serious - downgraded by 1.

Summary of findings 2. Glycerol laxative versus acupuncture for antipsychotic-related constipation

Glycerol laxative versus acupuncture

Patient or population: antipsychotic-related constipation

Setting: inpatient

Intervention: glycerol laxative

Comparison: acupuncture

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with acupuncture	Risk with glycerol laxative				
1. Global or clinical change in constipation	Study population		RR 3.50 (2.18 to 5.62)	120 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1, 2}	
(a) as defined by the study	233 per 1000	817 per 1000				
Still constipated (no defecation) at 2 days		(509 to 1000)				

Still constipated (no defecation) at 3 days	Study population	RR 8.00 (2.54 to 25.16)	120 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1, 2
	50 per 1000 400 per 1000 (127 to 1000)			
(b) Change in the frequency of defecation	No studies reported these important outcomes			
(c) Change in straining at defecation				
(d) Change in the frequency of lumpy or hard stools				
(e) Change in the frequency of manual manoeuvres to facilitate defecation				
2. Need for rescue medication				
3. Presence of antipsychotic-related constipation complications such as bowel obstruction				
4. Quality of life (changed to any extent)				
5. Adverse events				
6. Leaving the study early				
7. Economic costs				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

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Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Randomisation and allocation concealment methods unclear. Management of incomplete outcome data unclear. Blinding unlikely to have occurred - rated as very serious - downgraded by 2.

2 No validated method used for measuring constipation. Unclear how reported defecation was assessed (e.g. stool chart, participant recall from memory). No recording of any of the other ROME constipation symptoms (e.g. straining, stool consistency, manual manoeuvres) - rated as serious - downgraded by 1.

Summary of findings 3. Mannitol versus phenolphthalein or rhubarb soda for antipsychotic-related constipation

Mannitol versus phenolphthalein or rhubarb soda

Patient or population: antipsychotic-related constipation

Setting: inpatient

Intervention: mannitol

Comparison: phenolphthalein or rhubarb soda

Outcomes	Anticipated absolute effects* (95% CI)		Relative ef- fect (95% CI)	Nº of partici- pants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with phenolph- thalein or rhubarb soda	Risk with Mannitol				
1. Global or clinical change in constipation as defined by the study	Study population		RR 0.07 (0.02 to 0.27)	240 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1, 2	Results from the phenolphthalein and rhubarb soda groups were com- bined by the study authors.
a) Still constipated (no defecation) at 24 hours	250 per 1000	18 per 1000 (5 to 68)				
(b) Change in the frequency of defecation	No studies reported these important outcomes					
(c) Change in straining at defecation						
(d) Change in the frequency of lumpy or hard stools						
(e) Change in the frequency of manual ma- noeuvres to facilitate defecation						
2. Need for rescue medication						
3. Presence of antipsychotic-related con- stipation complications such as bowel ob- struction						
4. Quality of life (changed to any extent)						
5. Adverse events	0 per 1000	0 per 1000	Not estimable	240 (1 RCT)	-	It is highly questionable how well ad- verse effects were monitored and

recorded. The study simply notes "No side-effects were detected in the two groups after treatment".

6. Leaving the study early	No studies reported these important outcomes
7. Economic costs	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

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¹ Randomisation and allocation concealment methods unclear. Management of incomplete outcome data unclear. Blinding unlikely to have occurred - rated as very serious - downgraded by 2.

² No validated method used for measuring constipation. Unclear how reported defecation was assessed (e.g. stool chart, participant recall from memory). No recording of any of the other ROME constipation symptoms (e.g. straining, stool consistency, manual manoeuvres) - rated as serious - downgraded by 1.

BACKGROUND

Description of the condition

Antipsychotic medications are effective agents in the treatment of schizophrenia and other psychotic disorders, but their adverse effect profiles can be considerable. Constipation due to gastrointestinal hypomotility is one commonly reported and potentially serious adverse effect. Antipsychotics such as clozapine, which have high affinity for muscarinic cholinergic receptors, are the most frequently implicated agents in antipsychotic-related gastrointestinal hypomotility (Nielsen 2012; Talley 2003). For example, in a study using ingested radiopaque markers to measure gastrointestinal motility, colonic transit times were over four times longer in clozapine-treated patients compared with both those on other antipsychotics and with population normative values ($P < 0.0001$). Gastrointestinal hypomotility was demonstrated in 80% of clozapine-treated patients (Every-Palmer 2016).

The earliest manifestation of gastrointestinal hypomotility is usually constipation. Constipation is common with many antipsychotics, and especially so with clozapine (Ozbilen 2009). A recent systematic review found that people taking clozapine had significantly higher rates of constipation compared with those taking other antipsychotics (odds ratio (OR) 3.02, 95% confidence interval (CI) 1.91 to 4.77 (Shirazi 2016)).

For clozapine-treated patients, iatrogenic mortality is higher from constipation or gastrointestinal hypomotility complications than from agranulocytosis (Cohen 2012). For every thousand patients treated with clozapine, it is estimated that 300 to 600 will suffer constipation, and at least four will develop serious gastrointestinal complications (for example bowel obstruction), from which one or more may die (Every-Palmer 2016). Progression from constipation to ileus, intestinal obstruction, bowel ischaemia, megacolon, and death is not uncommon in antipsychotic-treated patients, particularly those on clozapine (Drew 1997; Hibbard 2009; Leung 2008; Nielsen 2012; Palmer 2008; Rousseau 2007; Shammi 1997). The mechanism is usually obstruction caused by an impacted stool bolus (sometimes classified as a pseudo-obstruction), which can increase intraluminal pressure proximal to the impaction, consequently causing ischaemia (Hass 2007), and distension (Boley 1969). This distension may result in perforation, especially if the resultant bowel diameter exceeds 12 cm. Aspiration pneumonia may result from inhalation of faeculent vomitus or as a result of dysphagia (Palmer 2008). However, the underlying pharmacophysiology of these gastrointestinal complications is poorly understood. Primary responsibility is usually attributed to the anticholinergic inhibition of gastrointestinal smooth muscle contraction and peristalsis (Ozbilen 2009; Sirois 2005), but it is likely that antipsychotic medications' antagonism of various serotonin receptor subtypes is contributory (Palmer 2008), because serotonin plays a crucial role in gastrointestinal motility (Crowell 2001).

Antipsychotic-treated patients with serious gastrointestinal hypomotility often under-report symptoms and present late (Palmer 2008). The delayed presentation may arise, at least in part, from patients with psychosis experiencing attenuated pain sensitivity (Dworkin 1994; Fishbain 1982; Rosenthal 1990; Singh 2006), difficulty in communicating discomfort (Bickerstaff 1988), diminished awareness of pain due to the sedative and analgesic effects of psychotropic drugs, such as antidepressants,

neuroleptics, and anticonvulsants (Palmer 2008), or a failure by health professionals to recognise gastrointestinal hypomotility as a potentially life-threatening condition. Consequently, gastrointestinal pathology may be considerably more advanced than the patient's presentation would suggest.

It is important to recognise that while not all patients with objective gastrointestinal hypomotility are aware of constipation symptoms, laxatives may still have a role in improving bowel motility in those without subjective distress (Every-Palmer 2016; Baptista 2015). Prophylactic laxatives for all people starting clozapine are recommended by the Porirua Protocol, to prevent clozapine-related constipation (Every-Palmer 2017).

Description of the intervention

The treatment of chronic constipation generally includes both non-pharmacological and pharmacological interventions. This review will consider pharmacological treatment of constipation in treated antipsychotic patients.

The most commonly used pharmacological intervention for treating constipation is the class of medication commonly referred to as laxatives. The subtypes of conventional laxatives are bulk-forming, emollient, osmotic, and stimulant aperients (see Appendix 1). Other agents that have been researched for their efficacy in treating constipation include: colchicine (Taghavi 2010; Verne 1997; Verne 2003); misoprostol (Roarty 1997; Soffer 1994); cisapride (Vandenplas 1999); lubiprostone (Johanson 2005; Johanson 2005a; Johanson 2007; Johanson 2008); tegaserod (Johanson 2004; Johanson 2004a; Kamm 2005); renzapride (Tack 2006); prucalopride (Camilleri 2008; Camilleri 2009); linaclotide (Andresen 2007; Lembo 2010); and elobixibat (Chey 2011; Wong 2011). In this review, we also included cholinergic agents, such as bethanecol or donepezil, or anticholinesterase inhibitors, such as physostigmine, given the suspected pharmacological mechanism of antipsychotic-related constipation. The usual dose ranges, mechanisms of action and adverse effects are also summarised in Appendix 1.

Some of these medications have significant, serious, or controversial side-effect profiles (e.g. cisapride and tegaserod), and their use has been discontinued, or restricted to certain subgroups of patients. However, these restricted medications have been included within the ambit of this review, given the potential for future relaxation of restrictions, and because their prokinetic properties are of particular interest in treating hypomotility disorders. The potential harms and benefits of all treatments were to be analysed and addressed in the discussion.

The treatment of gastrointestinal hypomotility disorders is an evolving field, and subsequent updates of this review will also consider the evidence for any new treatments.

How the intervention might work

Antipsychotic medications can cause bowel motility problems and reduce bowel transit times, resulting in constipation and more serious sequelae. The goals of constipation management include improving symptoms, restoring normal gastrointestinal function, increasing bowel transit, and facilitating defecation (Bleser 2005).

The mechanisms of actions of the different pharmacological treatments for constipation are summarised in Appendix 1.

Why it is important to do this review

Antipsychotics are widely prescribed throughout the world. They currently comprise the largest class of pharmaceuticals by sales in the United States, and their international market was estimated at \$19.6 billion in 2010 (BCC Research 2010). Until recently, the morbidity and mortality associated with antipsychotic-related constipation has been under-recognised. In a review of 164 English language, randomised controlled trials of clozapine, only 14 of 164 (8.5%) had reported figures on constipation amongst the side-effect data (Meek 2008). Until recently, clinicians have regarded antipsychotic-related constipation as an irksome, but not particularly serious complication of treatment. However, it is now evident that progression from constipation to ileus, intestinal obstruction, bowel ischaemia, megacolon, and death is not uncommon, particularly in patients who have been prescribed clozapine. In Australasia, there have been at least 15 deaths related to clozapine-induced gastrointestinal hypomotility (Palmer 2008). Apart from the life-threatening consequences, constipation has been consistently shown to have a significant impact on the quality of life of those suffering from it (Damon 2004; Dennison 2005; Glia 1997; Wald 2007).

Surprisingly, given the prevalence of chronic constipation and the widespread use of laxatives, reliable evidence-based data regarding their effectiveness are lacking, even in the general population (Brandt 2005; Jones 2002; Ramkumar 2005; Rao 2011). Two systematic reviews comparing medical therapies for chronic idiopathic constipation found good evidence for the efficacy of polyethylene glycol (PEG; Brandt 2005; Ramkumar 2005). However, both of these reviews were restricted to published English language studies indexed in Medline, and both listed drug-induced constipation amongst the exclusion criteria. A Cochrane review similarly endorsed PEG over lactulose for chronic constipation, but also excluded patients with medication-related constipation (Lee-Robichaud 2010). Systematic reviews have considered different aspects of the pharmacological treatment for chronic constipation (Brandt 2005; Evans 2008; Lee-Robichaud 2010; Ramkumar 2005), constipation in adults with central neurological disease (Coggrave 2009), constipation in pregnancy (Jewell 2009; Rungsiaprakarn 2015), and constipation in palliative care (Candy 2015). However, there are no systematic reviews collating and examining the strength of the evidence for the effectiveness and safety of pharmacological treatment in antipsychotic-related constipation.

To date, there is little evidence-based research on the management of constipation in antipsychotic-treated patients. Although guidance exists to minimise antipsychotic medications' adverse haematological (Honigfeld 1998; Lieberman 1989), metabolic (Lambert 2004), and cardiac effects (Berk 2007), these guidelines do not emphasise the need to monitor or treat constipation and its more serious sequelae. Of the few international guidelines that do address antipsychotic-related constipation (Hasan 2012), recommendations are based on a scarce database (Hasan 2016). There is uncertainty about the management of constipation in this group of patients.

OBJECTIVES

To evaluate the effectiveness and safety of pharmacologic treatment (versus placebo, or compared against another treatment) for antipsychotic-related constipation (defined as constipated patients of any age, who are treated with

antipsychotics, regardless of dose, in which constipation is considered to be an antipsychotic-related side effect).

METHODS

Criteria for considering studies for this review

Types of studies

The inclusion criteria were all randomised controlled trials investigating the efficacy of pharmacotherapy for antipsychotic-related constipation.

If a trial was described as double blind and implied randomisation, we had planned to include it in a sensitivity analysis (see [Sensitivity analysis](#)). If participants had been given treatments additional to the pharmacological treatment of constipation, we would only have included data if the adjunct treatment was evenly distributed between groups, and it was only the pharmacological treatment of constipation that was randomised.

We excluded non-randomised studies, quasi-randomised studies (such as allocation by day of the week), case reports, clinical observations (open studies), or studies of laxatives used to treat constipation due to other causes.

We included all eligible studies, regardless of language.

Types of participants

Eligible participants were male or female patients of any age who had developed constipation (diagnosed by any method) while prescribed any antipsychotic medications (any dose) with constipation attributed to a side effect of the antipsychotic.

Types of interventions

1. Any pharmacological treatment of antipsychotic related constipation

Any type of the following medication:

- bulking agents such as psyllium, methylcellulose, calcium polycarbophil, and wheat dextrin;
- faecal softeners, such as mineral oil, docusate;
- stimulant laxatives, such as senna and bisacodyl;
- osmotic agents, such as lactulose, sorbitol, magnesium hydroxide, glycerine, magnesium sulphate, polyethylene glycol;
- alternative agents, such as lubiprostone, misoprostol, colchicine, tegaserod, cisapride, renzapride, prucalopride, linaclotide, elobixibat, orlistat;
- cholinergic agents, such as bethanecol or donepezil, or anticholinesterase inhibitors, such as physostigmine.

2. Any other intervention, placebo or no intervention

Types of outcome measures

Primary outcomes

1. Global or clinical change in constipation as defined by the identified studies, including, but not limited to, the following:

- 1.1 Change in the frequency of defecation;
- 1.2 Change in straining at defecation;
- 1.3 Change in the frequency of lumpy or hard stools;

1.4 Change in the frequency of manual manoeuvres to facilitate defecation.

Secondary outcomes

1. Global state

- 1.1 Significant change in mental or global state (as defined by identified studies);
- 1.2 Average endpoint score on mental or global state scales;
- 1.3 Average change scores on mental or global state scales.

2. Need for rescue medication for constipation

3. Constipation-related outcomes

- 3.1 Gastrointestinal transit time measurement (determined by gastrointestinal motility studies);
- 3.2. Presence of antipsychotic-related constipation complications such as bowel obstruction.

4. Satisfaction with treatment

5. Quality of life

6. Adverse effects

- 6.1 At least one adverse effect;
- 6.2 Specific effects;
- 6.3 Death.

7. Leaving the study early

- 7.1 Due to adverse effects;
- 7.2 Due to non-compliance;
- 7.3 Any reason.

8. Economic Costs

'Summary of findings' table

We used the GRADE approach to interpret findings ([Schünemann 2011](#)), and the GRADE profiler ([GRADEpro GDT](#)) to import data from Review Manager ([Review Manager](#)), to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient-care and decision making. In our protocol, we selected the following main outcomes for the 'Summary of findings' table.

1. Global or clinical change in constipation (as defined by the studies, including, but not limited to, a change in the frequency of: defecation; straining; hard or lumpy stools; or manual manoeuvres to facilitate defecation);
2. Need for rescue medication;
3. Presence of antipsychotic-related constipation complications such as bowel obstruction;
4. Quality of life (changed to any extent);
5. Adverse effects;
6. Leaving the study early (the numbers of participants withdrawing before completion of the study due to non-compliance, adverse effects, or both);
7. Economic costs.

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group's Trials Register

The Information Specialist (formally the Trials Search Co-ordinator) searched the Cochrane Schizophrenia Group's Registry of Trials (5 June 2014 and 15 June 2015), using the following phrase:

constipat:ti,ab,kw of REFERENCE or *constipat*:SCO of STUDY

The Cochrane Schizophrenia Group's Registry of Trials is compiled by systematic searches of major resources (including MEDLINE, Embase, AMED, BIOSIS, CINAHL, PsycINFO, PubMed, and registries of clinical trials), and their monthly updates, hand-searches, grey literature, and conference proceedings (see [Group Module](#)). There are no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We inspected references of all included studies for further relevant studies ([Horsley 2011](#)).

2. Personal contact

We attempted to contact the first author of each included study for information regarding unpublished trials ([Young 2011](#)). Any responses were to be noted in 'Description of Studies' and the 'Characteristics of Included Studies' table.

Data collection and analysis

Selection of studies

Two review authors (SEP and GNH) independently inspected citations from the searches and identified relevant abstracts. A random 20% sample was independently re-inspected by the third author (MC) to ensure reliability. Where uncertainty remained, the full report was acquired for more detailed scrutiny. Full reports of all abstracts meeting the review criteria were obtained and independently inspected by SEP and GNH. Again, a random 20% of reports were re-evaluated by MC in order to ensure reliable selection. Where it was not possible to resolve disagreement by discussion, we attempted to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Two review authors (SEP and GNH) independently extracted data from all included studies. In addition, to ensure reliability, the third author (MC) independently extracted data from a 20% random sample of these studies. Disagreements were discussed, decisions documented, and when necessary, we contacted the authors of studies for clarification. With any remaining problems, MC helped clarify issues, and these final decisions were documented. Data presented only in graphs and figures were extracted where possible, but included only if two review authors independently had the same result. When necessary, we attempted to contact authors through an open-ended request in order to obtain missing information, or for clarification. No included studies were multicentre, but if they had been, we would have attempted to extract data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data onto standard, simple pre-specified forms. If available, we obtained the following information for each of the eligible studies:

- study methods (trial design, duration, sequence generation, allocation sequence concealment, blinding, setting, study eligibility criteria);
- participants (number, age, gender, ethnicity, psychiatric diagnosis, how constipation was defined, dose, type and duration of antipsychotic medication, co-morbidities, drop-outs, or withdrawals);
- pharmacological intervention(s) (type, dose(s), duration, route of administration, integrity of intervention, control used);
- outcome data (outcome measures used, definition of thresholds, change in frequency of defecation, straining, stool consistency, manual manoeuvres to facilitate defecation, global improvement in symptoms, patient satisfaction, need for rescue medication, transit time measurement);
- tolerance and adverse effects.

2.2 Scale-derived data

We would have included continuous data from rating scales only if:

- a) the psychometric properties of the measuring instrument had been described in a peer-reviewed journal ([Marshall 2000](#)); and
- b) the measuring instrument had not been written or modified by one of the trialists for that particular trial.

Ideally, the measuring instrument should have either been (i) a self-report or (ii) completed by an independent rater or relative (not the treatment provider).

2.3 End point versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult to measure conditions. We decided to use primarily end point data, and only use change data if the former were not available. End point and change data were to be combined in the analysis, since, if such data had been available, we would have used mean differences (MD) rather than standardised mean differences (SMD) throughout ([Higgins 2011](#)).

2.4. Skewed data

While no continuous data were eligible for inclusion in this review, for future revisions, recognising that continuous data on clinical outcomes are often not normally distributed, we plan to apply the following standards to all data before inclusion, to avoid the pitfall of applying parametric tests to non-parametric data:

- for example, we will enter data from studies of at least 200 participants in the analysis, regardless of the following rules, because skewed data pose less of a problem in large studies. We will also enter change data when continuous data are presented on a scale that includes a possibility of negative values (such as change data), and it is difficult to tell whether data are skewed

or not. We will present and enter change data into statistical analyses.

For end point data:

- when a scale starts from the finite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation (SD). If this value is less than one, it strongly suggests a skew, and the study will be excluded. If this ratio is higher than one but less than two, there is suggestion of skew. We will enter the study and test whether its inclusion or exclusion would change the results substantially. Finally, if the ratio is larger than two, the study will be included, because skew is less likely ([Altman 1996](#); [Higgins 2011](#));
- if a scale starts from a positive value, the calculation described above will be modified to take the scale starting point into account. In these cases, skew is present if $2 \text{ SD} > (S - S_{\min})$, where S is the mean score and ' $S_{\min}$ ' is the minimum score.

2.5 Common measure

To facilitate comparison between trials, we had intended to convert variables that could be reported in different metrics, such as the number of complete spontaneous bowel motions (mean bowel motions per day, per week or per month), to a common metric (e.g. mean bowel motions per week).

2.6 Conversion of continuous to binary

If relevant, we would have made efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into clinically improved or not clinically improved. If data based on these thresholds had not been available, we would have used the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we entered data so that the area to the left of the line of no effect indicated a favourable outcome for the treatment of constipation. If keeping to this had made it impossible to avoid outcome titles with clumsy double-negatives (e.g. Not improved), we would have reported data so that the left of the line indicated an unfavourable outcome, but this would have been noted in the relevant graphs.

Assessment of risk of bias in included studies

Again, two review authors (SEP and GNH) independently assessed risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality ([Higgins 2011a](#)). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article, such as sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. The third author (MC) assessed the risk of bias for a 20% random sample of these studies.

If the raters disagreed, the final rating was made by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials were provided, we contacted the authors of the studies in order to obtain further information. Non-concurrence in quality assessment was reported, but if disputes arose about which

category a trial was to be allocated, again, we resolved by discussion.

We assessed seven main sources of systematic bias for each included study.

- Randomisation sequence generation (selection bias);
- Concealment of allocation sequence (selection bias);
- Blinding of participants and personnel (performance bias);
- Blinding of outcome assessors (detection bias);
- Level of completeness of outcome data (attrition bias);
- Selective outcome reporting (reporting bias);
- Other bias.

We assessed each domain by determining whether the criteria for that domain had been met (i.e. low risk of bias), whether they had not (i.e. high risk of bias), or whether it was judged 'unclear' because of inadequate reporting.

We did not exclude studies based on a high risk of bias.

Measures of treatment effect

1. Binary data

The outcome measures reported in all four included trials were binary. For these outcomes, where possible, we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RRs are more intuitive than odds ratios (Boissel 1999), and that odds ratios tend to be interpreted as RRs by clinicians (Deeks 2000). The number needed to treat for an additional beneficial outcome and the number needed to treat for an additional harmful outcome with their confidence intervals are intuitively attractive to clinicians, but are problematic, both in the accurate calculation in meta-analyses and interpretation (Hutton 2009). If binary data had been presented in the 'Summary of findings' table(s), we would have calculated illustrative comparative risks.

2. Continuous data

None of the usable data were continuous. For continuous outcomes, we had planned to estimate mean difference (MD) between groups. We prefer not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of considerable similarity had been used, we would have presumed there was a small difference in measurement, and we would have calculated the effect size and transformed it to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Cluster trials were eligible for inclusion, although no such trials were identified. Studies increasingly employ cluster randomisation (such as randomisation by clinician or practice), but analysis and pooling of clustered data pose problems. First, authors often fail to account for intra-class correlation in clustered studies, leading to a unit of analysis error, whereby P values are spuriously low, confidence intervals unduly narrow, and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

If cluster trials had been identified, where clustering was not accounted for in primary studies, we would have presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. If such trials are included in subsequent versions of this review, we will contact first authors of studies to request intra-class correlation coefficients (ICCs) for their clustered data, and will adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect.

We have sought statistical advice, and have been advised that the binary data presented in a report should be divided by a design effect. This is calculated using the mean number of participants per cluster (m) and the ICC (Design effect = $1 + (m - 1) * ICC$; Donner 2002). If the ICC had not been reported, it would have been assumed to be 0.1 (Ukumunne 1999).

If cluster studies had been appropriately analysed, taking into account ICCs and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials

While none of our eligible studies were cross-over trials, for future revisions, we will only use data of the first phase of cross-over studies. Our concern with cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological, or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase, the participants can differ systematically from their initial state, despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002).

3. Studies with multiple treatment groups

We included trials with multiple treatment groups in the analyses. When the study involved more than two treatment groups, and the additional treatment groups were relevant, they were presented in comparisons. Binary data were added and combined within the two-by-two table. No continuous outcomes were presented, but if this is the case in future studies, we will combine data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where the additional treatment groups were not relevant, we did not use these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss to follow-up, data must lose credibility (Xia 2009). No loss to follow-up was reported in the four eligible studies included in this review, which in itself raises issues of credibility, which are discussed in the *Incomplete outcome data (attrition bias)* section.

For future versions of this review, we have specified that if more than 50% of the data for any particular outcome are unaccounted for, we will not reproduce these data, or use them in analyses. However, if more than 50% are lost from one randomised group of a study, but the total loss is less than 50%, we will address this in the 'Summary of findings' table(s) by downgrading the quality

of the evidence. Finally, we will also downgrade the quality of the evidence if the total loss is between 25% and 50%.

2. Binary

For future reviews, when attrition for a binary outcome is between 0% and 50%, and when these data are not clearly described, we intend to present data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). Those leaving the study early will be all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcomes of death and adverse effects. For these outcomes, the rate of those who stayed in the study - in that particular arm of the trial - will be used for those who did not. We will undertake a sensitivity analysis to test how prone the primary outcomes are to change when data obtained only from people who completed the study to that point are compared to the ITT analysis, using the above assumptions.

3. Continuous

3.1 Attrition

For future revisions, if studies are included where attrition for a continuous outcome is between 0% and 50%, and only data from people who complete the study to that point are reported, we will reproduce these.

3.2 Standard deviations

If standard deviations (SDs) had not been reported, we would have first tried to obtain the missing values from the authors. If not available, and there were missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals available for group means, and either P or Tau² available for differences in mean, we could have calculated them according to the rules described in the *Cochrane Handbook for Systemic Reviews of Interventions*: "When only the SE is reported, SDs are calculated by the formula $SD = SE * \text{square root } (n)$ ". Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systemic Reviews of Interventions* present detailed formulae for estimating SDs from P, Tau², or F values, confidence intervals, ranges, or other statistics (Deeks 2011). If these formulae did not apply, we would have calculated the SDs according to a validated imputation method, which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus lose information. Nevertheless, we would have examined the validity of the imputations in a sensitivity analysis, excluding imputed values.

3.3. Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who leave trials early or are lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently, methods, such as multiple imputation or mixed-effects models for repeated measurements (MMRM), have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem. Therefore, in future, we will not exclude studies based on the statistical approach

used. However, we will preferably use the more sophisticated approaches, e.g. MMRM, or multiple-imputation will be preferred to LOCF, and completer analyses will only be presented if some kind of ITT data are not available at all. Moreover, we will address this issue in the Incomplete outcome data item of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered the included studies without seeing comparison data, to judge clinical heterogeneity. We inspected all studies for clearly outlying people or situations, which we had not predicted would arise.

2. Methodological heterogeneity

We considered all included studies without seeing comparison data, to judge methodological heterogeneity. We inspected studies for clearly outlying methods, which we had not predicted would arise.

3. Statistical heterogeneity

3.1 Visual inspection

If meta-analysis had been possible, we would have visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I² statistic

We had planned to investigate heterogeneity between studies by considering the I² statistic alongside the P value of the Chi² test. The I² provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I² depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from Chi², or a confidence interval for I²). An I² estimate of at least 50% accompanied by a statistically significant Chi² statistic would have been interpreted as evidence of substantial levels of heterogeneity (Deeks 2011). If substantial levels of heterogeneity were found in the primary outcome, we would have explored reasons for heterogeneity (see [Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

1. Protocol versus full study

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10.1 of the *Cochrane Handbook for Systemic Reviews of Interventions* (Sterne 2011). We tried to locate the protocols of the included randomised trials. We had planned to compare outcomes in the protocol and in the published report. The protocols were not available for any of our included studies, and so we compared the outcomes listed in the methods section of the trial report with the results actually reported.

2. Funnel plot

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). Again, these are described in Section 10 of the *Cochrane Handbook for Systemic Reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating publication biases

but are of limited use to detect small-study effects. We had planned to use funnel plots for outcomes if there were 10 or more studies, or where all studies were of similar sizes. When funnel plots were possible, we had planned to seek statistical advice in their interpretation.

Data synthesis

No meta-analysis was possible due to the small number of studies and quality issues. We had planned to combine data in a meta-analysis to provide a pooled effect estimate when study data were of sufficient quality and similarity (in diagnostic criteria, intervention, outcome measure, length of follow-up, and type of analysis). We would have used a fixed-effect model in the first instance. We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We had elected to use fixed-effect model for analyses. However, the reader would have been able to inspect the data using the random-effects model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

If a sufficient number of randomised trials had been identified, we had intended to explore the following potential sources of heterogeneity, using subgroup analyses or meta-regression.

1. Different doses, classes, types of antipsychotics (clozapine versus other antipsychotics; highly anticholinergic antipsychotics versus other antipsychotics; high dose antipsychotics versus low dose antipsychotics).
2. Treatment setting (inpatient or outpatient treatment).
3. Treatment duration (less than or more than two weeks).
4. Intervention - different types, class of laxative used.

2. Investigation of heterogeneity

If inconsistency was high, this would have been reported. First, we would have investigated whether data had been entered correctly. Second, if data were correct, we would have visually inspected the graph, and outlying studies would have been successively removed to see if homogeneity was restored. For this review, we had decided that this should be done with data that contributed no more than 10% of the total weight of the pooled data. If data contributed more than 10%, they would not have been pooled, and issues would have been discussed.

When unanticipated clinical or methodological heterogeneity were obvious, we simply stated hypotheses for future reviews or versions of this review. We did not formally analyse them.

Sensitivity analysis

Had we identified sufficient data, we would have conducted these sensitivity analyses to determine their impact on the primary outcomes.

1. Implication of randomisation

We had planned to include trials that implied randomisation in a sensitivity analysis. We would have included data for primary outcomes in the analyses. If the inclusion of these data did not result in a substantive difference, the study would have remained in the analyses. If inclusion did result in important clinically significant but not necessarily statistically significant differences, we would not have added these data to the results of the better trials, but would have presented such data within a subcategory. All included trials for this review implied randomisation so we did not carry out this sensitivity analysis.

2. Assumptions for lost binary data

We had anticipated that people would be lost to follow-up. If assumptions were needed about people lost to follow-up (see [Dealing with missing data](#)), we would have compared the primary outcomes' findings when we used our assumption(s), and when we only used data from people who had completed the study to that point. If there had been a substantial difference, we would have reported and discussed results, but would have continued with our assumption.

If assumptions were needed about missing SDs (see [Dealing with missing data](#)), we would have compared the primary outcomes' findings when we used our assumption(s), and when we only used data from people who had completed the study to that point. We would have completed the analyses to test how prone the results were to change when completer-only data were compared to the imputed data, using the above assumption. If there had been a substantial difference, we would have reported results and discussed them, but continued with our assumption.

3. Risk of bias

We had planned to analyse the effects of excluding trials that were judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available), allocation concealment, blinding, and outcome reporting. If excluding these trials did not substantially alter the direction or precision of the effect estimates, then data from these trials would have been included in the analysis. However, as we judged all studies to be at high risk of bias, we did not conduct this analysis.

4. Imputed values

If we had identified eligible cluster-randomised trials, we would have assessed the effects of including data from trials in which we had used imputed values for ICC when calculating the design effect.

If substantial differences had been noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we would not have pooled data from the excluded trials with the other trials contributing to the outcome, but would have presented them separately.

5. Fixed and random effects

We had planned to synthesise all data using a fixed-effect model, but we had also planned to synthesise data for the primary outcome using a random-effects model, to evaluate whether this altered the significance of the results.

RESULTS

Description of studies

For substantive descriptions of studies, please see [Characteristics of included studies](#), [Characteristics of studies awaiting classification](#), and [Characteristics of excluded studies](#).

Results of the search

The search was completed on 15 June 2015. The database searches identified 69 potentially relevant papers. One further paper was identified through handsearching reference lists, making a total of 70 studies for screening, 25 of which required translation from Chinese, and one from French. We screened all trials by reviewing their abstracts. We obtained 16 full-text articles. Of these, four studies were eligible for inclusion, but only two could be included in this version ([Fan 2004](#); [Wang 1995](#)); the other two are in [Characteristics of studies awaiting classification](#). We excluded 12 studies. [Figure 1](#) charts the project progress from screening to inclusion.

Figure 1. Study flow diagram.

Included studies

The two studies included a total of 480 participants. Both studies were of parallel design, were undertaken in Chinese hospitals, and reported in Chinese journals. One of the studies required translation from Mandarin (Wang 1995), while the other was published in Mandarin, with an accompanying English translation (Fan 2004).

For detailed characteristics of the included studies see [Characteristics of included studies](#).

Neither study was reported according to CONSORT guidelines.

1. Study design

Both studies were described as randomised controlled trials (RCTs), however, it was unclear whether they were RCTs or quasi-RCTs because the methods of randomisation and sequence generation

were not described. No contact details for the authors (e.g. postal, email address, or telephone number) were provided in the articles, and attempts to contact the authors by writing to them at their host institution to clarify the methodology were unsuccessful.

Study durations were short, with outcomes recorded at 24 hours in one of the studies (Wang 1995), and after two weeks in the other study (Fan 2004).

There was no loss to follow-up reported.

2. Participants

Both studies reported sample sizes of 240. All 480 participants were inpatients suffering from antipsychotic-related constipation, defined in both studies as the absence of defecation for four days preceding the trial. Neither study reported whether the absence of defecation was prospectively or retrospectively measured, or was self-reported or clinician-rated. The type of antipsychotic was specified, but not the dose. Overall, 64% (N = 306) of the participants were taking clozapine. The other antipsychotics were chlorpromazine (N = 146, 20 of whom were also prescribed clozapine), sulpiride (N = 12), perphenazine (N = 30), and haloperidol (N = 6). There were 145 male participants and 335 females; one study only recruited female participants (Wang 1995).

3. Interventions

Fan 2004 compared the effect of a glycerol suppository compared with acupuncture alone; tuina massage alone; and combined with acupuncture and tuina massage (Fan 2004). Tuina is a form of Traditional Chinese Medicine (TCM) that aims to 'open the body's defensive (wei) chi and get energy moving in the meridians' (Beal 2000). The specific technique is described in the paper. Acupuncture is another form of TCM that involves penetration of the skin with needles to stimulate certain points on the body (called acupoints). The selected points are described in the paper. The treatments were given every day for 14 days, and then responses to the laxative were recorded over the following three days (days 14 to 17).

Wang 1995 compared a single 250 mL 10% mannitol dose versus two doses of either (a) rhubarb soda or (b) six to eight phenolphthalein tablets. The results from the rhubarb soda and phenolphthalein groups were not presented separately, meaning we could only analyse the data for mannitol versus the combined group. It was not clear how, why, or how many patients were allocated to phenolphthalein (as opposed to rhubarb soda).

4. Outcomes

Our primary outcome of interest was defined broadly as global or clinical change in constipation, as defined by the identified studies including, but not limited to the following: change in the frequency of defecation; change in straining at defecation; change in the frequency of lumpy or hard stools; change in the frequency of manual manoeuvres to facilitate defecation. Neither study used a validated measure (such as the ROME criteria) to diagnose the presence or resolution of constipation. Fan 2004 defined a constipation "cure" as "defecate once within two days with soft stool and free movement of bowels". "Effectiveness" was defined as "defecate once within three days with soft stool and still no free movement of bowels". "Ineffectiveness" was defined as "no symptoms improved after treatment". Wang 1995 defined

defecation within 24 hours as an effective response. It is not clear in either of the studies how response to the laxative was measured, i.e. whether it was self-reported or observed.

Wang 1995 mentioned that no participant reported adverse effects, but these are referred to generically, without any description of whether they screened for adverse effects (and if so, how), or relied on spontaneous complaints.

Neither study reported continuous data, nor presented data on our other pre-defined secondary outcomes including: changes in mental state; need for rescue medication; presence of antipsychotic-related constipation complications, such as bowel obstruction; quality of life; leaving the study early (the numbers of participants withdrawing before completion of the study due to non-compliance, adverse effects, or both); or economic costs.

Excluded studies

We excluded 12 studies after assessing the full-text publications. Reasons for exclusion included the study not being a randomised trial, the population not suffering from antipsychotic-related constipation, or the intervention not constituting a pharmacological treatment for constipation. See [Characteristics of excluded studies](#) table for details.

Most exclusion decisions were straightforward and unanimous, but discussion was required between the authors in order to make a decision on Chukhin 2013. This study compared orlistat, a peripherally acting anti-obesity agent, with placebo in overweight clozapine-treated patients in a placebo-controlled add-on study. The proportion of constipation in each group was compared, using the Bristol Stool Chart as a measurement tool. This study was excluded because the study population selected did not all suffer antipsychotic-related constipation; of the forty participants, only half were identified as constipated at the start of the trial, and separate data were not provided for this cohort.

Ongoing studies

Searches of trial registries did not identify any ongoing trials in this area.

Studies awaiting classification

After extracting data from the four potentially eligible studies, it became evident that two of these studies, both of which compared senna to TCM remedies, could not be included without further clarification from the authors (Liang 2002; Zhang 2004). We had concerns about discrepancies in methodology and data analysis, and serious concerns that the papers were virtually identical, although credited to different authors, raising concerns about authenticity and credibility. To date, we have been unsuccessful in making contact with the authors to clarify these issues. These two studies remain in the [Characteristics of studies awaiting classification](#) section.

Risk of bias in included studies

Both trials under-reported key design features. The majority of information across all the quality domains was at high or unclear risk of bias. Attempts to contact the authors to clarify these areas of bias were unsuccessful. See [Characteristics of included studies](#) for full details of risk of bias judgements for each study. Graphical

representations of the overall risk of bias for included studies are presented in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fan 2004	?	?	-	?	?	?	?
Wang 1995	?	?	-	?	-	?	-

Allocation

Neither study adequately described how random allocation was generated, nor the methods used to conceal random allocation. In both studies, the number of participants were evenly balanced in each group. It is possible that one or both of these studies were in fact not randomised, or were quasi-randomised. A poor researcher understanding of the difference between randomisation and quasi-randomisation in older TCM studies has been demonstrated in other medical fields. In a systematic review considering TCM for ectopic pregnancy, the reviewers communicated by telephone with the original authors of 243 potentially eligible studies that had been described as randomised (Qu 2011). Of these, all 243 were excluded. More than 67% of study authors were shown to have misunderstood the concepts of randomisation and allocation concealment.

Unfortunately we did not receive responses to our letters to study authors requesting further details, so could not clarify whether the studies were randomised or quasi-randomised. We have rated this domain as unclear risk of bias for both studies.

Blinding

No information regarding blinding was provided in either of the studies. Owing to differences in the physical characteristics of the pharmacological treatment and the comparison, blinding was thought highly unlikely to have occurred in the participants and personnel. Assessor blinding was methodologically possible, although was not described in either study.

Incomplete outcome data

Neither study provided any information about losses to follow-up, or whether intention-to-treat or per-protocol analysis was used. Prima facie across both studies, it appears that all 480 recruited participants completed the study with 0% dropouts or exclusions.

For example, in Fan 2004, 240 psychiatric inpatients were recruited, and for 14 days underwent either daily rectal enemas, daily periods of tuina massage, half an hour of acupuncture, or a combination of all three treatments. It seems improbable, given the nature of the population and interventions that there would be no attrition from either discharges, withdrawal of consent due to inability (or unwillingness) to adhere to the intensive experimental regime,

or protocol deviations due to the need for rescue medications or missed treatments. However, on paper, this study has 100% adherence, no dropouts, no missing data, no protocol violations and no adverse events. We are sceptical about this.

We suspect both studies used a per-protocol (as treated) analysis and only reported outcomes on those who completed the study. Exclusions have been found to be poorly reported in studies from the pre-CONSORT era (Moher 2001). The *Cochrane Handbook of Systematic Reviews of Interventions* speculates that an apparent lack of exclusions may be indicative of poor trial conduct rather than the true lack of exclusions (Higgins 2011).

Selective reporting

It is unclear if the studies were at risk of reporting bias because protocols were not available, therefore, we could not compare pre-specified outcomes with those outcomes reported in the published reports.

Other potential sources of bias

Neither study reported their funding source. This is important, given the strong evidence that industry-funded studies produce results that differ from independently-funded studies, with industry-sponsored trials exaggerating treatment effects in favour of the products preferred by their sponsor (Bekelman 2003; Song 2010; Lundh 2012). This may be particularly important in mental health; although industry influence has been pervasive across medicine, psychiatry has been at the epicentre of much of the controversy about funding source bias and conflict of interest (Every-Palmer 2014). We see the lack of transparency regarding funding source as another potential source of bias.

Both included studies were from the People's Republic of China and involved TCM remedies for constipation compared against a pharmacological intervention. It is unclear if this represented a racial or cultural bias when applied to other regions.

Effects of interventions

See: [Summary of findings for the main comparison Glycerol laxative versus tuina massage for antipsychotic-related constipation](#); [Summary of findings 2 Glycerol laxative versus acupuncture for antipsychotic-related constipation](#); [Summary of findings 3 Mannitol versus phenolphthalein or rhubarb soda for antipsychotic-related constipation](#)

1. Comparison 01: Glycerol laxative versus tuina massage

See also [Summary of findings for the main comparison](#).

1.1 Global or clinical change in constipation: change in frequency of defecation

One study, involving 120 participants in these two arms, provided data for this comparison (Fan 2004). Categorical outcomes were reported for global improvement in constipation as defined by the authors, and categorised as a cure, which was defined as defecating once within two days with soft stool and free movement of bowels effectiveness, which was defined as defecating once within three days with soft stool and still no free movement of bowels, or ineffectiveness, which was no symptoms improved after treatment.

Glycerol was shown to be less effective than tuina massage in promoting defecation by two days (1 RCT; N = 120; RR 2.88, 95% CI

1.89 to 4.39), compared with being not cured, and by three days (1 RCT; N = 120; RR 4.80, 95% CI 1.96 to 11.74; [Analysis 1.1](#)).

Efficacy time was also reported as a continuous measure, in hours. We inferred that this was the mean time-to-defecation for the subset of participants in the cure group, but because this was not clearly defined, they were not usable data.

No data were identified for any of the other pre-specified primary outcomes (change in the frequency of defecation, change in straining at defecation, change in the frequency of lumpy or hard stools, change in the frequency of manual manoeuvres to facilitate defecation), or any of the secondary outcomes.

Adverse effect data were not provided.

2. Comparison 02: Glycerol laxative versus acupuncture

See [Summary of findings 2](#).

The same study also provided data for the second comparison (Fan 2004).

2.1 Global or clinical change in constipation: change in frequency of defecation

Glycerol was shown to be less effective than acupuncture in promoting defecation by two days (1 RCT; N = 120; RR 3.50, 95% CI 2.18 to 5.62), and by three days (1 RCT; N = 120; RR 8.00, 95% CI 2.54 to 25.16; [Analysis 2.1](#)).

Adverse effect data were not provided.

3. Comparison 03: Mannitol versus phenolphthalein or rhubarb soda

See [Summary of findings 3](#).

One study, involving 240 women, provided data for this comparison (Wang 1995).

3.1 Global or clinical change in constipation: change in frequency of defecation

Data were identified for global improvement in constipation as defined by the authors, defined in this study as defecation within 24 hours of treatment. No data were identified for any of this review's other pre-specified primary outcomes (change in the frequency of defecation, change in straining at defecation, change in the frequency of lumpy or hard stools, change in the frequency of manual manoeuvres to facilitate defecation).

The risk of remaining constipated within 24 hours of treatment was lower in women who took mannitol compared with those who took rhubarb soda or phenolphthalein (1 RCT; N = 240; RR 0.07, 95% CI 0.02 to 0.27; [Analysis 3.1](#)).

Average time-to-defecation was also reported for a subset of participants, but because it was not clear how many participants comprised this subset, we could not use these data.

The authors reported that no adverse effects were detected in either group. They provided no description of what adverse effects they monitored, or how they assessed these.

DISCUSSION

Summary of main results

There was an overall paucity of data, with only two studies contributing data to the review. The included studies were judged to be at high risk of bias. We were only able to analyse three comparisons, with one study each.

Fan 2004 found a glycerol suppository to be less effective than the traditional Chinese medicine (TCM) approach of tuina massage for relieving constipation at two days (RR 2.88, 95% CI 1.89 to 4.39), and at three days (RR 4.80, 95% CI 1.96 to 11.74). In the same study, a glycerol suppository was also less effective than acupuncture at two days (RR 3.50, 95% CI 2.18 to 5.62), and at three days (RR 8.00, 95% CI 2.54 to 25.16). In Wang 1995, a single dose of mannitol, an osmotic laxative, was more effective than rhubarb soda or phenolphthalein in relieving constipation within 24 hours of treatment (RR 0.07, 95% CI 0.02 to 0.27).

Insufficient data were provided for any subgroup analyses.

None of the included studies reported information on the secondary outcomes identified (need for rescue medication, transit time measurement, measures of satisfaction or patient preference, measures of quality of life, cost-effectiveness, or the presence of antipsychotic-related gastrointestinal hypomotility complications, such as bowel obstruction).

Overall completeness and applicability of evidence

1. Completeness

Our review findings are limited. The studies were few and study durations were very short. The data on phenolphthalein could not be presented separately, as it had been combined with results from another intervention (rhubarb soda; Wang 1995). Usable data related only to mannitol and glycerol enemas, neither of which are commonly used for managing constipation in contemporary psychiatric care.

There were no data available on the safety and efficacy of commonly used pharmacological interventions, such as bulking agents (e.g. psyllium, methylcellulose, calcium polycarbophil, and wheat dextrin), faecal softeners (e.g. mineral oil, docusate), or commonly used osmotic agents (e.g. lactulose, polyethylene glycol). Neither were there any studies on novel agents, such as lubiprostone, prucalopride, linaclotide, or elobixibat, on cholinergic agents, such as bethanecol or donepezil, or on anticholinesterase inhibitors, such as physostigmine. The pharmacological intervention was so poorly described in the two senna trials we identified, that the data were unusable (Liang 2002; Zhang 2004).

Within the included studies, many important outcomes were not reported. Both of the included studies used idiosyncratic, invalidated, and poorly described methods to measure constipation, for example the passing of a bowel movement over a specified timeframe (e.g. one or two days), as resolution of constipation.

Simply passing a bowel motion does not equate to a cure for constipation. Constipated people still pass stool, although this may be infrequent, uncomfortable, or difficult. Even severe

constipation leading to faecal impaction may still present with overflow diarrhoea. Assessing stool frequency (usually averaged over a period of time), consistency, amount, and ease of passing are critical in assessing constipation. The Rome criteria for constipation have been the benchmark over the last two decades, and an updated version has just been released (Drossman 2016). It has been recommended that the Rome definition should form the basis of any tool used to assess constipation (Panchal 2007). However, the included studies did not use any standardised tools.

Neither study adequately reported any of our pre-specified secondary outcome measures. Adverse event data were very poorly reported. We were able to extract data from one study, stating they did not collect any data on adverse effects (Fan 2004). The other simply stated that "no side effects were detected in the two groups after treatment", without any description of how adverse effects were defined and monitored (Wang 1995). There were no data on any of the other secondary outcome measures.

There were also insufficient data to perform the intended subgroup analyses, for example comparing constipation treatment efficacy by different doses, classes, and types of antipsychotics, in different treatment settings, or for short-term versus long-term treatment.

2. Applicability

Both studies were conducted in China, in psychiatric inpatients. The primary focus was non-pharmacological TCM techniques, with pharmacological treatment as the comparator. Studies were of very short duration. There are difficulties in applying this evidence to psychiatric practice elsewhere.

Quality of the evidence

The included studies had serious methodological flaws, and overall the quality of the evidence was very low.

Neither of the included studies provided information on whether they were following an a priori protocol. Neither had been registered. There was also a lack of information about any ethical review or any informed consent process. Both trials provided very limited information about trial design and methodology. Neither trial reported a pre-trial estimation of sample size, nor methods of randomisation or allocation concealment. Neither appeared to use any form of blinding. The trials were extremely short, with one running for just 24 hours, and one running for 17 days. Given that antipsychotic-related constipation is a chronic condition, longer trials are clearly needed.

The studies presented only limited outcome data, without the raw data sets, and with confusing data presentation with some obvious mistakes and contradictions.

The studies were both at high or unclear risk of bias in all domains. Please see Figure 2 for 'Risk of bias' graph and Figure 3 for 'Risk of bias' summary. Potential bias may have been present in participant selection, treatment administration, and outcome reporting; all results should be interpreted with caution. The very low-quality evidence means there is currently insufficient evidence to adequately assess the effectiveness and safety of pharmacological interventions for antipsychotic-related constipation.

Potential biases in the review process

None of the review authors could read Mandarin, and studies required translation by third parties.

We identified only a few trials, all from the Chinese literature. It is possible other small Chinese trials exist, which may not have been identified.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews assessing the effectiveness and harms of interventions for antipsychotic-related constipation.

One naturalistic study has shown a significant reduction in the colonic transit times of clozapine-treated patients, when treated with docusate and senna, and augmented by polyethylene glycol, in accordance with the Porirua Protocol (Every-Palmer 2017). Another study found the proportion of patients with constipation reduced with orlistat compared to placebo (Chukhin 2013). Neither of these studies were eligible for this review, but they are noted as they do specifically address the treatment of antipsychotic-related constipation.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people taking antipsychotic medication

While there is strong evidence that some antipsychotics, and particularly clozapine, cause a slow gut and constipation, there is little evidence about how to best treat this. This means it is difficult for those taking antipsychotic medication to make decisions about how best to manage this common and troublesome problem. One study in our review showed that glycerol enemas may not work as well as acupuncture or tuina massage, alone, or together; another study showed that mannitol, an osmotic laxative, may be superior than some traditional Chinese remedies in promoting a bowel movement. This evidence was of low quality and didn't cover important outcomes, like patient satisfaction, quality of life, cost, and adverse effects. Nor were there any studies on the most commonly used constipation treatment, like fibre supplements, senna, docusate, lactulose, or macrogol.

While the evidence for treatment of antipsychotic related-constipation is poor, the evidence for the problems that can be caused by this side effect is strong. Clozapine especially, is known to have potentially serious effects on the gastrointestinal system. Any antipsychotic-treated patient (especially if the medication is clozapine) who experiences constipation or other gastrointestinal symptoms should talk to their clinician. While quality antipsychotic-specific evidence on constipation is lacking, there is evidence supporting the use of laxatives for chronic constipation in the general population which may be helpful to guide treatment choices (e.g. Ford 2011). There is also some early evidence emerging on the management of clozapine-induced gastrointestinal hypomotility, which is increasingly being recognised as an important problem. For example, while not eligible for this review, one observational study has shown a significant reduction in the colonic transit time of clozapine-treated patients when treated with docusate and senna and macrogol

according to the Porirua Protocol (Every-Palmer 2017) and another study found the proportion of patients endorsing constipation reduced with orlistat compared to placebo (Chukhin 2013).

Overall pharmacological interventions for antipsychotic-related constipation have not been adequately investigated by clinical trials and this needs to be addressed. People with antipsychotic-related constipation could encourage such research or support it by agreeing to be randomised to well-designed and reported studies.

2. For clinicians

Clinicians in the field of mental health should be aware that despite antipsychotic-related constipation being common, there has been little research on its treatment. The review could not provide any quality information on the treatment of antipsychotic-related constipation. On the basis of a single study, glycerol enema may be less effective than TCM techniques, and on the basis of another single study, mannitol may be more effective than rhubarb soda or phenolphthalein in improving symptoms. The included studies were of poor quality and short duration. There have been no randomised trials that have evaluated patient tolerability, acceptability, or long-term constipation-related adverse outcomes (e.g. bowel obstruction).

In lieu of specific evidence for the pharmacological treatment of antipsychotic-related constipation, treatment needs to be pragmatic and extrapolated from the evidence from other populations and based on clinical judgement. It is disappointing that antipsychotic-related constipation has not received more attention. Clinicians have a responsibility to advocate for research in this area.

3. For policy makers

There were only minimal usable data in this review. Clinical practice guidelines should include the best available evidence. However, currently, there is insufficient evidence from trials on which to base guidelines for the treatment of antipsychotic-related constipation. Currently, no data are available on satisfaction with care or long-term benefits, and we know of no cost-benefit analysis.

Implications for research

1. General

Clinically meaningful randomised studies are needed to help guide clinicians in their management of antipsychotic-related constipation. Randomised trials are needed to compare pharmacological and other interventions for antipsychotic-related constipation. Such trials should focus on the treatment of constipation, with an emphasis on patient tolerability and satisfaction, along with consideration of clinical state outcome measures. Validated measures should be used to measure the primary outcome and adverse effects should be measured.

2. Specific

Antipsychotic-related constipation is not an obscure adverse effect. It is common, and particularly in the case of clozapine, potentially life-threatening. This important topic has not been adequately addressed by researchers. Rigorous and independent randomised trials, measuring standardised and clinically relevant outcomes in a clearly defined population are needed to establish the effectiveness of treatment options. It is recommended that future trials should

be designed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement ([Schulz 2010](#)).

The methods should be very clearly described and replicable. Studies should include a validated method of measuring constipation (for example using the Rome criteria), and some medium- and long-term outcomes including adverse events (specifically abdominal pain, cramping, diarrhoea), serious outcomes (e.g. bowel obstruction, death), discontinuation of treatment, and satisfaction with treatment. Studies should last longer than a month. To help distinguish between different treatments, there is a need to include measures on tolerability, quality of life, participant preference, and costs.

Some suggested design features for future studies are shown in [Table 1](#).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Fan 2004

Methods	Allocation: Unclear. Described by the authors as "Randomly divided in treatment order with numbers" Blinding: Not described. Unlikely to have occurred. Duration: 14 days. Design: A parallel design trial comparing acupuncture, tuina and glycerol suppository for treating antipsychotic-related constipation. Setting: Inpatient. Country: China..
Participants	Diagnosis: CCDMD-3 criteria for schizophrenia (N = 205), affective disorders (N = 30), neurosis (N = 5). Total N = 240. Sex: M = 145, F = 95. Age: 20 to 61 years. History: Antipsychotics included clozapine (N = 166), chlorpromazine (N = 48), sulpiride (N = 12), perphenazine (N = 8), and haloperidol (N = 6).

Fan 2004 (Continued)

Included: Adult inpatients in a Chinese hospital who had received oral antipsychotic drugs for at least two weeks and who had not defecated for between 2 and 9 days.

Excluded: Participants with physical co-morbidities.

Interventions	<p>1. Glycerin suppository: 40 mL per day. N = 60.</p> <p>2. Acupuncture: one session daily. N = 60.</p> <p>3. Tuina massage: one session daily. N = 60.</p> <p>4. Combined tuina massage and acupuncture. N = 60.</p> <p>40 mL glycerin suppository (N = 60) compared with acupuncture alone (N = 60); tuina massage alone (N = 60); and combined with acupuncture and tuina massage (N = 60). Interventions occurred daily for 14 days.</p>
Outcomes	<p>Global or clinical change in constipation: defecation by 2 days and defecation by 3 days (both compared with not cured).</p> <p>Unable to use</p> <p>Global or clinical change in constipation: time to effectiveness (unclearly defined subset of participants).</p> <p>Adverse effects: no data provided.</p>
Notes	<p>Overall, the study was methodologically poor and methods were poorly described. We had concerns that ethics approval was not reported, and there was no mention of any informed consent process. Attempts were made to contact the authors at the host institution, but no response was received.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Randomisation was implied; sequence generation methods not specified. "All the cases were randomly divided in treatment order with numbers".</p> <p>Comment: We suspect quasi-randomisation (sequential allocation resulting in exactly 60 participants in each of the four groups), but this remains unclear.</p>
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding participants and personnel. Considered unlikely due to the different natures of the treatment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessment, but it is plausible this could have occurred. It is not clear how response to laxatives was assessed and whether it was self-reported or clinician-reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were no comments on missing outcome data. It was unclear if this was because there were no missing data, or because they were not reported.
Selective reporting (reporting bias)	Unclear risk	<p>There was no evidence a pre-specified study protocol was agreed and followed.</p> <p>Outcome data provided only at 14 days – uncertain whether this was chosen a priori or post hoc.</p>

Fan 2004 (Continued)

Alongside the three outcome categories mentioned in the methods sections, time-to-effect was also reported. It appears time may have been only provided for the subset of participants who were deemed cured, but this was unclear.

No adverse event data were provided.

Other bias	Unclear risk	Funding source was not reported.
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Wang 1995

Methods	<p>Allocation: Not clear. Described by the authors as "equally divided into two groups according to their types of psychosis and the drugs they took".</p> <p>Blinding: Not described. Unlikely to have occurred.</p> <p>Duration: 1 day.</p> <p>Parallel design trial comparing mannitol with rhubarb soda or phenolphthalein.</p> <p>Setting: Female psychiatric inpatient unit.</p> <p>Country: China.</p>
Participants	<p>Diagnosis: Reported as 192 schizophrenia, 40 affective psychosis, 2 hysteria (6 unaccounted for).</p> <p>N = 240.</p> <p>Sex: Female.</p> <p>Age: 14 to 56 years.</p> <p>History: Medications included clozapine (N = 120), chlorpromazine (N = 60), perphenazine (N = 22), chlorpromazine and lithium (N = 18), clozapine and chlorpromazine (N = 20).</p> <p>Included: Hospitalised female Chinese psychiatric patients with antipsychotic-related constipation, treated with antipsychotics for at least a week, no bowel movements for at least 4 days.</p> <p>Excluded: Participants with physical co-morbidities.</p>
Interventions	<p>1. Mannitol: one single 10% mannitol oral 250 mL dose twice over the course of one day (N = 120).</p> <p>2. Rhubarb soda twice daily or phenolphthalein 6 to 8 tablets twice over the course of one day (N = 120).</p>
Outcomes	<p>Global or clinical change constipation: change in frequency by 24 hrs.</p> <p>Unable to use</p> <p>Time to defecation (unclear participant numbers).</p> <p>Adverse effects: stated no participant reported adverse effects.</p>
Notes	<p>Statistical analysis was poorly reported, with errors evident. Phenolphthalein and rhubarb soda data were combined. Attempts were made to contact the authors at the host institution, but no response was received.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	While randomisation was mentioned in the abstract, the methods stated participants were "equally divided into two groups according to their types of psychosis and the drugs they took". We suspect quasi or non-randomisation.

Wang 1995 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding participants and personnel. Considered unlikely due to the different natures of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessment. It is not clear how response to laxatives was assessed and whether it was self-reported or clinician-reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Some data were missing but not accounted for (e.g. diagnoses are only reported for 234 participants).
Selective reporting (reporting bias)	Unclear risk	There was no evidence a pre-specified study protocol was agreed and followed. Outcome data provided after only one day – uncertain whether these were chosen a priori or post hoc.
Other bias	High risk	The statistical analysis had errors. A $P > 0.05$ was reported as being significant, the mean and range of times- to-defecation for each intervention contradicted the reported frequencies of defecation within 24 hours. Funding source was not reported.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chukhin 2013	Allocation: Random allocation. Participants: Clozapine-treated patients. Interventions: Orlistat versus placebo. Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria. The prevalence of constipation was compared between the treatment and non-treatment groups.
Ding 1998	Allocation: Random allocation. Participants: Psychiatric inpatients with psychosis. Interventions: Laxatives (senna or glycerol) versus warm salt water, vitamin B, and soap enema. Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria; population of interest was psychiatric inpatients with psychosis.
Li 2002	Allocation: Random allocation. Participants: Chlorpromazine-treated patients with gastric adverse reaction, e.g. dry mouth, bitter taste in mouth, anorexia, nausea, vomiting, constipation. Interventions: Self-made Chinese medicine ‘smoothing-nervous-and-strengthen-spleen syrup’ versus placebo

Study	Reason for exclusion
	Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria; population of interest was antipsychotic-related gastric adverse reactions.
Li 2004	<p>Allocation: Random allocation.</p> <p>Participants: Patients with psychosis and constipation.</p> <p>Interventions: Mannitol versus senna tea.</p> <p>Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria; population of interest was psychosis and constipation, not all participants were prescribed antipsychotics.</p>
Li 2007	<p>Allocation: Random allocation.</p> <p>Participants: Clozapine-treated patients.</p> <p>Interventions: TCM treatment qihuangkongxian versus cyproheptadine.</p> <p>Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria; population of interest was clozapine-treated patients, study investigated the prevalence of hypersalivation and constipation.</p>
Lin 2006	<p>Allocation: Random allocation.</p> <p>Participants: Patients with antipsychotic-related constipation.</p> <p>Interventions: sit ups (30/day) versus no sit ups.</p> <p>Reason for exclusion: Not a pharmacological intervention; investigated sit ups.</p>
Lin 2010	<p>Allocation: Random allocation.</p> <p>Participants: Patients with schizophrenia.</p> <p>Interventions: Diversity of health education versus general health education.</p> <p>Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria; population of interest was patients with schizophrenia. Not a pharmacological intervention; investigated health education.</p>
Lu 2001	<p>Allocation: Random allocation.</p> <p>Participants: Antipsychotic-induced adverse reactions of digestive tract.</p> <p>Interventions: Anshejianpi syrup versus no syrup.</p> <p>Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria; population of interest was antipsychotic induced gastrointestinal side effects, could not identify number of participants with constipation.</p>
Lu 2002	<p>Allocation: Random allocation.</p> <p>Participants: Antipsychotic-induced adverse reactions of digestive tract.</p> <p>Interventions: Anshejianpi syrup versus no syrup.</p> <p>Reason for exclusion: Duplicate paper of Lu 2001. Antipsychotic-related constipation was not an inclusion criteria; population of interest was antipsychotic induced gastrointestinal side effects, could not identify numbers of participants with constipation.</p>
Wang 2004	<p>Allocation: Random allocation.</p> <p>Participants: People with psychosis and constipation.</p>

Study	Reason for exclusion
	Interventions: Laxatives (not specified) versus abdominal massage and health education. Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria; population of interest was people with psychosis and constipation, not all taking antipsychotics. Laxative type not specified.
Wei 2010	Allocation: Random allocation. Participants: People with schizophrenia. Interventions: Daily living skills training versus no daily living skills training. Reason for exclusion: Antipsychotic-related constipation was not an inclusion criteria; population of interest was people with schizophrenia. Intervention was not a pharmacological intervention; investigated daily living skills.
Yue 2002	Allocation: Sequential allocation. Participants: Antipsychotic related constipation. Interventions: Abdominal massage, physical exercise and warm foot baths versus laxatives (not specified). Reason for exclusion: Not a randomised trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Liang 2002](#)

Methods	Parallel design trial comparing a single dose of senna with rhubarb and alcohol paste applied topically to the umbilicus.
Participants	104 Chinese hospitalised psychiatric patients who had not defecated for more than three days, who had been treated with antipsychotics (type and dose not specified) for at least two weeks. All fulfilled CCMD-2-R criteria for psychosis. Included 48 males, 56 females, with a mean age of 38.65 years, range 18 to 66 years.
Interventions	Intervention described as liquid senna in the abstract (but as a single 3 g dose of senna granules, sennoside dose unclear, in the methods section) versus rhubarb and alcohol paste topically applied to umbilicus (TCM shenque point).
Outcomes	Primary outcome reported was defecation within 24 hours. Adverse events were reported as a collective category when the participant reported painful abdomen and diarrhoea.
Notes	Overall methods were poorly described. Randomisation unclear. We had concerns that ethics approval was not reported, and there was no mention of any informed consent process. The dose and preparation of the pharmacological treatment for antipsychotic-related constipation (senna) were not clearly reported, with contradictory descriptions (liquid and granules). About 80% of the text of the paper was identical to Zhang 2004 (but had none of the same authors). Data not usable without further information and clarification. Attempts were made to contact the authors at the host institution, but no response has been received.

Zhang 2004

Methods	Parallel design trial comparing a single dose of senna with aloe and alcohol paste applied topically to the umbilicus.
Participants	96 hospitalised Chinese patients with antipsychotic-related constipation who had not defecated for more than three days, all treated with antipsychotics (type and dose not specified) for at least two weeks, aged 18 to 66 years (mean: 39 years), 56 males, 40 females.
Interventions	Intervention described as liquid senna in the abstract (but as a single 3 g dose of senna granules, sennoside dose unclear, in the methods section) versus aloe and alcohol paste topically applied to umbilicus (TCM shenque point).
Outcomes	Primary outcome reported was defecation within 24 hours. Adverse events were reported as a collective category when the participant reported painful abdomen and diarrhoea.
Notes	Overall methods were poorly described. Randomisation unclear. We had concerns that ethics approval was not reported, and there was no mention of any informed consent process. The dose and preparation of the pharmacological treatment for antipsychotic-related constipation (senna) were not clearly reported, with contradictory descriptions (liquid and granules). About 80% of the text of the paper was identical to Liang 2002 (but had none of the same authors). Data not usable without further information and clarification. Attempts were made to contact the authors at the host institution, but no response has been received.

DATA AND ANALYSES

Comparison 1. Glycerol laxative versus Tuina massage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global or clinical change in constipation: change in frequency of defecation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 no defecation by 2 days	1	120	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [1.89, 4.39]
1.2 no defecation by 3 days	1	120	Risk Ratio (M-H, Fixed, 95% CI)	4.8 [1.96, 11.74]

Analysis 1.1. Comparison 1 Glycerol laxative versus Tuina massage, Outcome 1 Global or clinical change in constipation: change in frequency of defecation.

Study or subgroup	Glycerol n/N	Tuina n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 no defecation by 2 days					
Fan 2004	49/60	17/60		100%	2.88[1.89,4.39]
Subtotal (95% CI)	60	60		100%	2.88[1.89,4.39]
Total events: 49 (Glycerol), 17 (Tuina)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.94(P<0.0001)					
			Favours glycerol	0.05 0.2 1 5 20	Favours tuina

Comparison 2. Glycerol laxative versus acupuncture

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global or clinical change in constipation: change in frequency of defecation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 no defecation by 2 days	1	120	Risk Ratio (M-H, Fixed, 95% CI)	3.5 [2.18, 5.62]
1.2 no defecation by 3 days	1	120	Risk Ratio (M-H, Fixed, 95% CI)	8.0 [2.54, 25.16]

Analysis 2.1. Comparison 2 Glycerol laxative versus acupuncture, Outcome 1 Global or clinical change in constipation: change in frequency of defecation.

Comparison 3. Mannitol versus phenolphthalein or rhubarb soda

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global or clinical change in constipation: change in frequency of defecation	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.02, 0.27]
1.1 no defecation by 24 hours	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.02, 0.27]

Analysis 3.1. Comparison 3 Mannitol versus phenolphthalein or rhubarb soda, Outcome 1 Global or clinical change in constipation: change in frequency of defecation.

ADDITIONAL TABLES

Table 1. Suggested design of future study

Methods	Allocation: centralised, randomised, sequence generation described. Blinding: participants, personnel recruiting and assigning participants, and assessors. Blinding can be tested by asking participants and raters to guess the assigned treatment. Study duration: 12 weeks. Setting: Inpatients and outpatients
Participants	Diagnosis: antipsychotic-related constipation or antipsychotic induced gastrointestinal hypomotility N = sample size obtained through power calculation* Age: any Sex: both
Intervention	Any of the interventions listed in Appendix 1 compared against any other intervention or placebo,

Table 1. Suggested design of future study *(Continued)*

Outcomes	<p>Primary Outcomes</p> <ol style="list-style-type: none"> 1. Global or clinical change in constipation 1.1 Change in the frequency of defecation (e.g. complete spontaneous bowel movements per week) 1.2 Change in straining at defecation 1.3 Change in the frequency of lumpy or hard stools 1.4 Change in the frequency of manual manoeuvres to facilitate defecation <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Global state 2. Need for rescue medication for constipation 3. Objective constipation-related outcomes (e.g. gastrointestinal transit time measurement (determined by gastrointestinal motility studies), Presence of antipsychotic-related constipation complications such as bowel obstruction) 4. Satisfaction with treatment 5. Quality of life 6. Adverse effects 7. Leaving the study early 8. Economic Costs
Notes	* Size of study with sufficient power to detect a approximate 10% difference between the two groups for the primary outcome with 80% certainty.

APPENDICES

Appendix 1. Summary Table: PHARMACOLOGICAL TREATMENT FOR CONSTIPATION

TABLE 1: PHARMACOLOGICAL TREATMENT FOR CONSTIPATION

TREATMENT	USUAL ADULT DOSE	MECHANISM OF ACTION	SIDE EFFECTS
Bulk-forming laxatives			
Psyllium	Up to 1 table-spoon 3 times/day	Increase colonic residue, producing a stretching reflex eventually stimulating colonic peristalsis	Hard to ingest, colonic atony, faecal impaction, obstruction
Methylcellulose	Up to 1 table-spoon 3 times/day		
Calcium polycarbophil	2 to 4 tabs/day		
Wheat dextrin	1 to 6 caplets daily (3 to 18 g fibre)		
Emollients (softeners)			

(Continued)

Docusate sodium	100 mg 2 times/day	Lower the surface tension of the stool, allowing water to enter more easily	Skin rash
Lubricants			
Arachis oil, mineral oil		Coats the surface of the stool and prevents water reabsorption into the GI tract	Depletion of fat soluble vitamins
Osmotic agents			
Polyethylene glycol	8.5 to 34 g in 240 mL liquids	Exerts an osmotic effect on water and electrolytes, which are retained within the GI tract, leading to modification of stool consistency and increased faecal bulk	Nausea, bloating, cramping
Lactulose	15 to 30 mL every other day, or 2 times/day		Abdominal bloating, flatulence, galactosaemia
Sorbitol	120 mL of 25% solution 1 time/day		Abdominal bloating, flatulence
Glycerine	3 g suppository 1 time/day		Rectal irritation, can be distressing
Magnesium citrate	200 mL 1 time/day		Magnesium toxicity (with renal insufficiency)
Magnesium sulphate	15 g 1 time/day		
Stimulant laxatives			
Bisacodyl	10 to 30 mg orally 1 time/day 10 mg suppository 1 time/day	Increase intestinal motility and secretion via fluid and electrolyte accumulation in the distal ileum and colon. Also believed to stimulate sensory nerve ending of the colonic mucosa	Gastric irritation
Senna	2 to 4 tabs/day		Melanosis coli (pigmentation of colonic mucosa)
Other agents			
Lubiprostone	24 mcgs 2 times/day	Bicyclic fatty acid which acts locally on chloride channels, enhancing chloride-rich intestinal fluid secretion	Headache, nausea, diarrhoea, foetal loss reported in animal studies
Misoprotol	200 mcgs 2 times/day	Prostaglandin E analogue	Diarrhoea, abdominal pain, nausea, flatulence, dyspepsia, vomiting, headache, dizziness, foetal loss
Tegaserod	6 mg 2 times/day	Partial 5-HT4 agonist and stimulator of GI motility and secretion. Also decreases visceral sensitivity	Cardiovascular ischaemic events
Colchicine	0.6 to 1mg 1 time/day	Anti-inflammatory alkaloid agent used to treat gout. Known to induce diarrhoea in higher doses (mechanism unknown). Significantly decreases mean colonic transit time	Abdominal discomfort, diarrhoea, nausea, vomiting, myopathy, neuropathy

(Continued)

Cisapride	5 to 10 mg 3 times/day	Prokinetic. 5-HT receptor agonist which reduces GI transit time	Prolongation of QT interval, ventricular arrhythmia, cardiovascular events
Metoclopramide	5 to 10 mg 3 times/day	Prokinetic benzamide. 5-HT ₃ receptor antagonist, 5-HT ₄ agonist. Increases GI peristalsis	Extrapyramidal symptoms (acute dystonic reaction), restlessness, drowsiness, delirium, headache, hypo/hypertension, hyperprolactinaemia
Renzapride	2 mg/day to 2 mg 2 times/day	5-HT ₃ receptor antagonist, 5-HT ₄ agonist. Increases GI peristalsis	Unknown, but early trials demonstrated no significant side effects
Prucalopride	2 mg/day	Dihydrobenzofurancarboxamide derivative with selective high-affinity for 5HT ₄ receptor agonist. Increases GI peristalsis	Headache and abdominal pain
Linaclotide	75-600 mcg/day	Guanylate cyclase C receptor agonist. Activates chloride and bicarbonate secretion in the gut and may reduce visceral hypersensitivity	Diarrhoea
Orlistat	120 mg 3 times/day	GI lipase inhibitor. Unabsorbed fat in GI tract digested by bacteria promoting bacteria	Weight loss, faecal urgency, faecal incontinence, abdominal pain, tooth/gingival disorder
Elobixibat	10 mg/day	Ileal bile acid transporter inhibitor. Induces colonic secretion and accelerates transit	Abdominal cramps and diarrhoea

WHAT'S NEW

Date	Event	Description
24 January 2017	Amended	Minor corrections: spelling of phenolphthalein corrected. Updated reference Every-Palmer 2016b to Every-Plamer 2017.

CONTRIBUTIONS OF AUTHORS

Susanna Every-Palmer wrote the protocol and review

Giles Newton-Howes and Mike Clarke reviewed and amended parts of the protocol and review

Susanna Every-Palmer and Giles Newtown-Howes screened all identified studies and extracted data. Mike Clarke screened and extracted data from 20% of the studies.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- Te Korowai Whariki, Capital and Coast District Health Board, New Zealand.

Institution at which researcher (SEP) is employed

- Wellington School of Medicine, University of Otago, New Zealand.

Institution at which researcher (GNH) is employed

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Elobixibat was added as an eligible pharmacological treatment for antipsychotic-related constipation. We also added cholinergic agents (e.g. bethanecol, donepezil) and acetylcholinesterase inhibitors (e.g. physostigmine) as potentially eligible treatments, recognising that antipsychotic-induced constipation is considered primarily mediated by anticholinergic mechanisms.

INDEX TERMS

Medical Subject Headings (MeSH)

*Rheum; Acupuncture Therapy; Antipsychotic Agents [*adverse effects]; Constipation [chemically induced] [*drug therapy]; Glycerol [*therapeutic use]; Laxatives [*therapeutic use]; Mannitol [*therapeutic use]; Massage [methods]; Phenolphthalein [*therapeutic use]; Randomized Controlled Trials as Topic; Suppositories

MeSH check words

Humans