

Ginger Boyle, MD
Spartanburg Family Medicine
Residency Program,
Spartanburg, SC

Anne Mounsey, MD
University of North Carolina,
Chapel Hill

Karen Crowell, MLIS
University of North Carolina,
Chapel Hill

What is the role of prokinetic agents for constipation?

Evidence-based answer

Erythromycin has a limited role in treating pediatric patients (strength of recommendation [SOR]: **B**, limited-quality, patient-oriented evidence). Tegaserod and cisapride are the only prokinetic agents

available for constipated adults (SOR: **A**, consistent, good-quality, patient-oriented evidence for tegaserod; SOR: **B**, for cisapride), but cardiovascular risk restricts prescribing of both medications.

Evidence summary

Prokinetic agents promote transit of intestinal contents by increasing the frequency or strength of small intestine contractions. Available prokinetics include erythromycin and metoclopramide. Metoclopramide has been tested only for upper gastrointestinal mobility. The only randomized controlled trials (RCTs) of erythromycin for constipation have been conducted in children. Cisapride and tegaserod have been withdrawn from general use because of adverse side effects. The **TABLE** summarizes the available data.

Pediatric constipation:

Erythromycin helps; watch dosage

A small RCT of 14 children between 4 and 13 years of age showed that erythromycin improved symptoms of constipation and decreased laxative use (number needed to treat [NNT]=10).¹ Two RCTs in neonates demonstrated that erythromycin shortened intestinal transit time and improved feeding tolerance.^{2,3}

The erythromycin dose used in these studies was lower than the dosage for antibiotic purposes; no adverse effects were reported. However, cardiac arrhythmias

and death have occurred when erythromycin is given to adults and children at the usual antibiotic doses.⁴

Adult constipation:

The options are limited

One RCT of cisapride for constipation showed that it improved symptoms,⁵ whereas another demonstrated no significant difference between cisapride and placebo in constipation-predominant irritable bowel syndrome.⁶ Reports of fatal arrhythmias have prompted restrictions on the use of the drug.

In 2 RCTs of tegaserod for constipation, patients exhibited improved abdominal symptoms and increased spontaneous bowel movements (NNT=6 for 2 mg and 5 for 6 mg in the first study; NNT=11 for 2 mg and 7 for 6 mg in the second study).^{7,8} A pooled analysis of RCTs of tegaserod revealed an increase in cardiovascular events, prompting withdrawal of the drug from the market (number needed to harm=1000).⁹ Tegaserod is available only for emergency and investigational use.

Renzapride, a newer prokinetic similar to cisapride, is under investigation. It

FAST TRACK

Erythromycin has a limited role in treating pediatric patients with constipation.

TABLE

Prokinetics for constipation: What the research tells us

DRUG	DESIGN (N)	DOSE	OUTCOME	NNT
Erythromycin estolate ¹	Crossover children (14)	20 mg/kg/day divided qid	†Constipation and laxative use	10
Cisapride ⁵	RCT adults (69)	5-10 mg tid	ü Spontaneous BM † Abdominal pain	4
Cisapride ⁶	RCT adults (82)	5-10 mg tid	Abdominal pain and constipation, drug=placebo	N/A
Tegaserod ⁷	RCT adults (1348)	2 mg or 6 mg bid	† Constipation ü Spontaneous BM	6 (2 mg) 5 (6 mg)
Tegaserod ⁸	RCT adults (1264)	2 mg or 6 mg bid	† Constipation and abdominal pain	11 (2 mg) 7 (6 mg)
Renzapride ¹¹	Pilot study adults (17)	Escalating dose: 2 mg daily to 2 mg bid	† Abdominal pain and bloating	Not enough information to calculate
Renzapride ¹²	Parallel group adults (48)	1, 2, or 4 mg daily	ü Colonic transit; stool form and ease of passage, drug=placebo	N/A

BM, bowel movement; N/A, not available; NNT, number needed to treat; RCT, randomized controlled trial.

is one tenth the strength of cisapride and carries a lower potential risk of cardiac complications.¹⁰ Two small placebo-controlled trials demonstrated improved abdominal pain and stool consistency, but only 1 showed statistically significant results compared with placebo.^{11,12}

Recommendations

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition states that the benefits of cisapride do not outweigh the risks.¹³ The American College of Gastroenterology's Chronic Constipation Task Force states that tegaserod effectively treats chronic constipation.¹⁴ Neither guideline includes recommendations regarding other prokinetic agents. ■

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Renzapride is a newer prokinetic that is one-tenth the strength of cisapride and has a lower potential risk of cardiac complications.

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