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Novel therapies for constipation

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Abstract

Constipation is a common medical problem and when standard laxatives fail it can be difficult to treat. Different aetiologies require tailored therapeutic approaches. Simple constipation may only require dietary manipulation while severe neurological or slow transit constipation may need pharmacologic intervention. Recently new drug therapies have been introduced. PubMed and Ovid were searched for reviews, systematic reviews and meta-analysis published since 2003 using the terms: constipation, prucalopride, linaclotide and lubiprostone. This review summarizes potential novel therapies identified as effective in the management of chronic constipation. Prucalopride is a selective 5-hydroxytryptamine receptor agonist. The prucalopride study was in patients, largely women with idiopathic constipation showed improved spontaneous complete bowel movement (SCBM) at a dose of 2 mg a day with few adverse events reported. Linaclotide is a 14-amino acid peptide guanylate cyclase-C agonist. The linaclotide study was carried out in patients with irritable bowel syndrome, constipation group (IBS-C). There was significant improvement of bowel evacuation and symptom resolution in patients on the active treatment arm. Lubiprostone activates type-2 chloride channels, increasing intestinal fluid secretion. In the trials of this drug, the lubiprostone arms had a greater mean number of SCBM. The novel therapies, prucalopride, lubiprostone, and linaclotide had very different modes of action yet, all three have been shown to be efficacious and safe in the treatment dose for constipation.

Key words: Constipation; Prucalopride; Linaclotide

Core tip: When standard laxatives fail in the management of constipation, licensed medication linaclotide and prucalopride show useful efficacy in clinical trials.

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INTRODUCTION

Constipation is a common complaint reported to General practitioners and Gastroenterologists. A systematic review by Peppas *et al*[1] found that the mean value of constipation rates in Europe is 17.1% and 15.3% in Oceania. Constipation is a symptom complex. A thorough history and physical examination is paramount in the evaluation of a patient presenting with constipation. The physician should seek to understand the patient's perception of their current bowel habit, compared to the past and should include stool frequency, form and the ease of passage of stool[2]. The use of the Bristol Stool Chart may aid the patient in their description of the stool form (Table 1)[2,3].

The presence of alarm features such as unintentional weight loss and rectal bleeding should be excluded during the history taking. The drug history should include the type of laxatives and the dose and duration previously tried. Physical examination should include both an abdominal examination for palpation of any masses or

Table 1 Bristol stool chart

Type	Description
1	Separate hard lumps
2	Sausage shaped but lumpy
3	Like a sausage but with cracks on its surface
4	Like a sausage or snake, smooth and soft
5	Soft blobs with clear cut edges
6	Fluffy pieces with ragged edges, a mushy stool
7	Watery, no solid pieces, entirely liquid

palpable stool and a rectal examination, which may reveal evidence of strictures or fissures.

Various definitions of constipation have been used, ranging from the patients own account of constipation to the formal criteria used in clinical trials. A practical definition would be a reduced frequency or ease of stool passage that is different to the individual's normal pattern. Constipation can be acute and chronic, with chronic constipation defined as duration of greater than three months[2].

The Rome Ⅲ criterion for chronic constipation includes the presence of two or more of six symptoms for at least twelve weeks in the preceding six months (Table 2)[2-4]. Constipation leads to a reduction in quality of life. A recent systematic review by Belsey *et al*[5] has shown that this reduction is predominant in the mental health domain and is equivalent to chronic conditions such as diabetes.

Constipation can be a primarily functional disorder or secondary to medications, and systemic diseases. Constipation can be classified as normal transit, slow transit, or due to obstructed defaecation[6]. A study conducted in Thailand found that 13% of patients had slow transit, 29% had obstructed defaecation, 11% of patients had a mixture of slow transit and obstructed defaecation, with the remaining 47% having normal transit[7].

Obstructed defaecation

Functional outlet obstruction can occur because of dysfunction of the anal sphincter, pelvic floor muscle dyssynergia or structural abnormalities like obstructing rectoceles[6].

Slow transit constipation

Patients with slow transit constipation have a reduction in the frequency of high amplitude colonic contractions[6]. Scintigraphic measurements indicate that slow transit is more common in the left colon than in the transverse and ascending colon[8]. A loss of co-ordination between contractile activity in the rectum and sigmoid colon and a reduced rectal sensory threshold has been implicated in slow transit constipation[6-10].

Normal transit constipation

In this subgroup the colonic transit time is normal and there is no evidence of functional outlet obstruction on testing. It is the cohort of patients with constipation predominant irritable bowel syndrome that typically fall into this subgroup[6].

Table 2 Rome Ⅲ criteria

1 Straining at defaecation on at least 1/4 of occasions.
2 Stools that are lumpy/hard on at least 1/4 of occasions.
3 Sensation of incomplete evacuation on at least 1/4 of occasions.
4 Manual manoeuvres to facilitate at least 25% of defalcations.
5 Sensation of anorectal obstruction/blockage at least 25% of defalcations.
6 Fewer than 3 bowel movements a week.

Health professionals have traditionally advised patients presenting with constipation to increase fibre and fluid intake and to exercise. However, the evidence behind this is inconsistent[11]. Current guidelines don't make any firm recommendations to support the use of laxatives in chronic constipation[12-14].

In recent years new pharmacological agents have appeared on the market. This review article serves to address the following novel therapies available for the management of primary constipation: prucalopride, lubiprostone and linaclotide.

PRUCALOPRIDE

Prucalopride is a selective, high affinity 5-hydroxytryptamine receptor agonist, used in patients with severe chronic constipation. There have been 3 pivotal studies of the use of prucalopride in the management of chronic constipation-Camilleri 2008[15], Tack 2009[16] and Quigley 2009[17]. They enrolled both men and women, however over 85% of the evaluated patients were female. This has led to the drug being restricted to women only. This is not to say that it is not effective in men, it merely hasn't been adequately tested in them. The recommended dose of prucalopride is 2 mg as a dose response effect was not obvious been the 2 mg and 4 mg dose tested in the 3 studies. The use of prucalopride is approved for chronic constipation in women in whom laxatives have failed to provide adequate relief[18].

The study by Camilleri *et al*[15] was a multicentre, randomized, placebo-controlled, trial in 620 patients with severe chronic constipation (< 2 spontaneous, complete bowel movements per week). They found that the proportion of patients with 3 or more spontaneous, complete bowel movements per week was 30.9% of those receiving 2 mg of prucalopride and 28.4% of those receiving 4 mg of prucalopride, compared to 12.0% in the placebo group ($P < 0.001$ for both comparisons). The most frequently reported side effects of the drug have been headache, nausea, and diarrhoea[15].

In the 12 wk study by Tack *et al*[16] 713 patients recruited were given either 2 or 4 mg prucalopride daily *vs* placebo. The number of patients achieving > 3 SCBMs/wk was 19.5%; $P < 0.01$ on 2 mg prucalopride and 23.6; $P < 0.001$ on 4 mg prucalopride *vs* 9.6% for placebo[16].

Quigley *et al*[17] also demonstrated a similar efficacy of prucalopride in 641 patients compared to placebo in chronic constipation. In this 12 wk study 641 patients received either 2 or 4 mg of prucalopride *vs* placebo. In the 2 mg prucalopride group 23.9% had > 3 SCBM per week. In the 4 mg group 23.5% had > 3 SCBM per week ($P < 0.01$, in both cases) *vs* 12.1% with placebo[18].

A study from the Asia-Pacific region evaluated the efficacy and safety of the 2 mg dose of prucalopride compared to placebo in patients with chronic constipation. This study found that prucalopride greatly improved bowel function, and patient satisfaction in individuals suffering from chronic constipation over a 12-wk treatment period. It found that prucalopride was safe and was well tolerated by patients[19].

Prucalopride has not been found to have a significant interaction with the hERG potassium channel which was assumed to have been responsible for the development of adverse cardiovascular effects seen with Cisapride[18,20]. The three pivotal clinical trials of prucalopride did not demonstrate any relevant electrocardiographic changes[15-17]. A recent meta-analysis of seven RCT's of prucalopride found that the number needed to treat (NNT) was 6[21,22].

Lubiprostone

Chloride channels play a vital role in the transport of fluid and maintaining cell volume and pH in cells and tissues, particularly intestinal epithelial cells. The CIC-2 channel when activated promotes the secretion of intestinal fluid. Lubiprostone activates type-2 chloride channels, increasing intestinal fluid secretion. This may facilitate intestinal transit, thereby increasing the passage of stool[23].

In a multicentre 4 wk trial, Johanson et al demonstrated that the use of lubiprostone in chronic constipation produced a bowel motion within 24-48 h of initial dosing and improved frequency of bowel motions with short term treatment. This double-blinded trial recruited 242 patients with constipation. The patients were randomized to receive either 24 mcg oral lubiprostone or placebo twice daily for 4 wk. One hundred and twenty patients received lubiprostone and 122 received placebo. The lubiprostone arm reported a greater mean number of spontaneous bowel movements at week 1 compared with the placebo arm (5.69 *vs* 3.46, $P = 0.0001$), with an increased frequency of spontaneous bowel movements reported at weeks 2, 3 and 4 ($P \leqslant 0.002$). Twenty-four hours after the first dose 56.7% of the lubiprostone group reported a SCBM compared with 36.9% in the placebo group ($P = 0.0024$); within 48 h, 80% and 60.7% of these patients reported a SCBM ($P = 0.0013$), respectively. Nausea (31.7%) and headache (11.7%), were the commonest side effects noted[24].

Barish *et al*[25] showed a similar outcome in their multicentre, double-blinded study. A total of 237 patients with chronic constipation were randomized to 4 wk of 24 mcg oral lubiprostone or placebo twice daily. The lubiprostone arm again had a greater mean number of SCBM at week 1 compared to placebo (5.89 *vs* 3.99, $P = 0.0001$), with a higher proportion having SCBM's in the first 24 h of the initial dose (61.3% *vs* 31.4%, $P < 0.0001$)[25].

Linaclotide

Linaclotide is a 14-amino acid peptide guanylate cyclase-C agonist. It binds to and activates GC-C on the luminal surface of the intestinal epithelium. Activation of GC-C leads to increased cGMP (cyclic guanosine monophosphate) which triggers a signal transduction cascade activating the cystic fibrosis transmembrane conductance regulator. This causes an increase in the secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased luminal fluid secretion and an acceleration of intestinal transit.

A recent 26 wk, randomized, double-blinded trial was done across 102 centres across the United States. The objective of this phase 3 clinical trial was to assess the safety and efficacy of linaclotide at a daily dosage of 290 mcg *vs* placebo to patients with IBS-C. Based on the recommendations for IBS-C trial design and in the FDA guidance for IBS clinical trials, a responder was defined as a patient who reported: (1) An improvement of > 30% from baseline in average daily worst abdominal pain score; and (2) Increase of > 1 complete spontaneous bowel movement from baseline, both in the same week for > 6/12 wk and 3 other primary end points, based on improvements in abdominal pain and CSBMs for 9/12 wk[26,27].

After the initial screening, 804 patients were recruited. 33.7% of the linaclotide arm were FDA end point responders *vs* 13.9% of the placebo arm ($P < 0.0001$). The NNT was 5.1, (95%CI: 3.9-7.1). The pain responder criterion of the FDA end point was met by 48.9% of linaclotide treated patients *vs* 34.5% of placebo-treated patients (NNT = 7.0, 95%CI: 4.7-13.1) and the CSBM responder criterion was met by 47.6% of linaclotide-treated patients, *vs* 22.6% of placebo patients (NNT = 4.0, 95%CI: 3.2-5.4)[26].

Another 12 wk trial by Rao *et al*[28] recruited 800 patients to a double-blinded, parallel group, placebo controlled trial to placebo *vs* 290 mcg linaclotide once daily, followed by a 4 wk randomized withdrawal period. Thirty three point six percent of the linaclotide-treated patients met the FDA end point compared with 21% of placebo treated patients ($P < 0.0001$) (NNT = 8, 95%CI: 5.4-15.5). Throughout the randomized withdrawal period, patients remaining on linaclotide showed a sustained improvement. The patients that were re-randomized from linaclotide to placebo showed a return of symptoms without any worsening of symptoms relative to baseline[28]. The most common adverse effects were GI-related, of which diarrhoea had the highest incidence[29].

CONCLUSION

Novel therapies such as prucalopride, lubiprostone, and

linaclotide have been shown to be efficacious and safe in the treatment dose for constipation. They have different mechanisms of action influencing and activating colonic motility, secretions and transit time leading to improvement in frequency and consistency of stool and bowel symptoms with greater satisfaction in chronic constipation. Overall, all these new treatment options have been shown to have a good safety profile.

REFERENCES

1 **Peppas G**, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. *BMC Gastroenterol* 2008; **8**: 5 [PMID: 18269746 DOI: 10.1186/1471-230X-8-5]

2 **Gray JR**. What is chronic constipation? Definition and diagnosis. *Can J Gastroenterol* 2011; **25** Suppl B: 7B-10B [PMID: 22114751]

3 **O'Donnell L**, Virjee J, Heaton KW. Detection of pseudodiarrhea by simple clinical assessment of intestinal transit rate. *Br Med J* 1990; **300**: 439-40 [DOI: 10.1136/bmj.300.6722.439]

4 **Longstreth GF**, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491 [PMID: 16678561 DOI: 10.1053/j.gastro.2005.11.061]

5 **Belsey J**, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. *Aliment Pharmacol Ther* 2010; **31**: 938-949 [PMID: 20180788 DOI: 10.1111/j.1365-2036.2010.04273.x]

6 **Paré P**, Bridges R, Champion MC, Ganguli SC, Gray JR, Irvine EJ, Plourde V, Poitras P, Turnbull GK, Moayyedi P, Flook N, Collins SM. Recommendations on chronic constipation (including constipation associated with irritable bowel syndrome) treatment. *Can J Gastroenterol* 2007; **21** Suppl B: 3B-22B [PMID: 17464377]

7 **Gonlachanvit S**, Patcharatrakul T. Causes of idiopathic constipation in Thai patients: associations between the causes and constipation symptoms as defined in the Rome II criteria. *J Med Assoc Thai* 2004; **87** Suppl 2: S22-S28 [PMID: 16083156]

8 **Lundin E**, Karlbom U, Westlin JE, Kairemo K, Jung B, Husin S, Påhlman L, Graf W. Scintigraphic assessment of slow transit constipation with special reference to right- or left-sided colonic delay. *Colorectal Dis* 2004; **6**: 499-505 [PMID: 15521943 DOI: 10.1111/j.1463-1318.2004.00694.x]

9 **Rao SS**, Sadeghi P, Batterson K, Beaty J. Altered periodic rectal motor activity: a mechanism for slow transit constipation. *Neurogastroenterol Motil* 2001; **13**: 591-598 [PMID: 11903920 DOI: 10.1046/j.1365-2982.2001.00292.x]

10 **Penning C**, Steens J, van der Schaar PJ, Kuyvenhoven J, Delemarre JB, Lamers CB, Masclee AA. Motor and sensory function of the rectum in different subtypes of constipation. *Scand J Gastroenterol* 2001; **36**: 32-38 [PMID: 11218237 DOI: 10.1080/00365520150218039]

11 **Leung L**, Riutta T, Kotecha J, Rosser W. Chronic constipation: an evidence-based review. *J Am Board Fam Med* 1999; **24**: 436-451 [PMID: 21737769 DOI: 10.3122/jabfm.2011.04.100272]

12 **World Gastroenterology Organisation**. WGO practice guidelines: constipation.2007. Available from: URL: http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/05_constipation.pdf

13 **Locke GR**, Pemberton JH, Phillips SF. AGA technical review on constipation. American Gastroenterological Association. *Gastroenterology* 2000; **119**: 1766-1778 [PMID: 11113099 DOI: 10.1053/gast.2000.20392]

14 **Ramkumar D**, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *Am J Gastroenterol* 2005; **100**: 936-971 [PMID: 15784043]

15 **Camilleri M**, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008; **358**: 2344-2354 [PMID: 18509121 DOI: 10.1056/NEJMoa0800670]

16 **Tack J**, van Outryve M, Beyens G, Kerstens R, Vandeplassche L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut* 2009; **58**: 357-365 [PMID: 18987031 DOI: 10.1136/gut.2008.162404]

17 **Quigley EM**, Vandeplassche L, Kerstens R, Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation--a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2009; **29**: 315-328 [PMID: 19035970 DOI: 10.1111/j.1365-2036.2008.03884.x]

18 **Quigley EM**. Prucalopride: safety, efficacy and potential applications. *Therap Adv Gastroenterol* 2012; **5**: 23-30 [PMID: 22282705 DOI: 10.1177/1756283X11423706]

19 **Ke M**, Zou D, Yuan Y, Li Y, Lin L, Hao J, Hou X, Kim HJ. Prucalopride in the treatment of chronic constipation in patients from the Asia-Pacific region: a randomized, double-blind, placebo-controlled study. *Neurogastroenterol Motil* 2012; **24**: 999-e541 [PMID: 22882724 DOI: 10.1111/j.1365-2982.2012.01983.x]

20 **Potet F**, Bouyssou T, Escande D, Baró I. Gastrointestinal prokinetic drugs have different affinity for the human cardiac human ether-à-gogo K(+) channel. *J Pharmacol Exp Ther* 2001; **299**: 1007-1012 [PMID: 11714889]

21 **Ford AC**, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut* 2011; **60**: 209-218 [PMID: 21205879 DOI: 10.1136/gut.2010.227132]

22 **Liu LW**. Chronic constipation: current treatment options. *Can J Gastroenterol* 2011; **25** Suppl B: 22B-28B [PMID: 22114754]

23 **Johanson JF**, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. *Aliment Pharmacol Ther* 2007; **25**: 1351-1361 [PMID: 17509103]

24 **Johanson JF**, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol* 2008; **103**: 170-177 [PMID: 17916109 DOI: 10.1111/j.1572-0241.2007.01524.x]

25 **Barish CF**, Drossman D, Johanson JF, Ueno R. Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci* 2010; **55**: 1090-1097 [PMID: 20012484 DOI: 10.1007/s10620-009-1068-x]

26 **Chey WD**, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012; **107**: 1702-1712 [PMID: 22986437 DOI: 10.1038/ajg.2012.254]

27 Guidance for industry: irritable bowel syndrome-clinical evaluation of drugs for treatment. Food and Drug Administration 2012. Available from: URL: http://www.fda.gov/downloads/Drugs/GuidanceComp-RegulatoryInformation/Guidances/UCM205269.pdf.2013

28 **Rao S**, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, Shi K, MacDougall JE, Shao JZ, Eng P, Fox SM, Schneier HA, Kurtz CB, Johnston JM. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol* 2012; **107**: 1714-124; quiz p.1725 [PMID: 22986440 DOI: 10.1038/

ajg.2012.255]
29 **Lembo AJ**, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, Shao JZ, Lavins BJ, Currie MG, Fitch DA, Jeglinski BI, Eng P, Fox SM, Johnston JM. Two randomized trials of linaclotide for chronic constipation. N Engl J Med 2011; 365: 527-536 [PMID: 21830967 DOI: 10.1056/NEJMoa1010863]

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