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Meta-analysis

Use of Prucalopride for Chronic Constipation: A Systematic Review and Meta-analysis of Published Randomized, Controlled Trials

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This article highlights the role of prucalopride in the management of chronic constipation based upon the principles of meta-analysis using data reported in the published randomized, controlled trials. Sixteen randomized, controlled trials on 3943 patients reported the effectiveness of prucalopride in patients with chronic constipation. Prucalopride successfully increased the frequency of spontaneous bowel movements per week in all variable doses of 1 mg (standardized mean difference [SMD], 0.42 [95% CI, 0.18-0.66; $P = 0.006$]), 2 mg (SMD, 0.34 [95% CI, 0.11-0.56; $P = 0.003$]), and 4 mg (SMD, 0.33 [95% CI, 0.22-0.44; $P = 0.00001$]). The risks of adverse events or side effects such as headache, abdominal cramps, excessive flatulence, dizziness, diarrhea, and rash were higher (odds ratio, 1.70 [95% CI, 1.27 to –2.27; $P = 0.0004$]) in prucalopride group. Prucalopride is clinically a beneficial pharmacotherapy for chronic constipation and its routine use may be considered in patients with chronic simple laxative-resistant constipation.
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Key Words
Constipation; Functional bowel disorders; Laxatives; Prucalopride; Secondary constipation

Introduction

Chronic constipation is largely divided into 2 major categories: functional (primary) and secondary. Functional constipation is defined by the Rome III diagnostic criteria[1] and may additionally be sub-divided into the normal transit constipation, slow transit constipation, and defecation disorders.[2] Secondary constipation is caused by conditions and medication use such as diabetes mellitus, hypothyroidism, depression, opioids, anti-depressants, and calcium channel blockers.[3,4] Just like the complexity in the definition of the functional and secondary constipation, the management pathway is also understandably difficult and challenging for both gastrointestinal physicians and gastrointestinal surgeons. Majority of the constipation experts offers several interventions to manage chronic constipation, with initial advice of life style change and failure to

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this approach leads to the use of osmotic laxatives (lactulose), bulk-forming laxatives (ispaghula husk), and stimulant laxatives (senna). In addition, the use of macrogol, bisacodyl or glycerol suppository, sodium phosphate, and arachis oil enema is also a common practice prior to the use of relatively innovative agents.[5-15] Non-pharmacological interventions such as ritualizing bowel habits, biofeedback therapy, behavior therapy, electrical stimulation of pelvic muscles, cognitive therapy, and surgical sub-total colectomy have been reported, mainly from tertiary centers with variable effectiveness, and in the selected group of patients with chronic constipation.[16-19]

Among novel pharmacological agents, cisapride, a pro-motility medicine, which acts as gut prokinetic therapy, was used clinically for the treatment of chronic constipation and studies reported cisapride effectively reduced the need for first and second line laxatives with optimized stool consistency, but failed to demonstrate effect on gut peristalsis in patients with chronic idiopathic constipation.[20] Tegaserod, a selective 5-hydroxytryptamine 4 (5-HT_4) receptor agonist, is reported to be a more successful novel pharmacotherapy agent than placebo in providing relief from the symptoms of chronic constipation, including increased bowel-movement frequency, decreased straining, or hard or lumpy stool in addition to reduced abdominal discomfort/pain, and bloating/distension.[23-25] A systematic review for constipation concluded that tegaserod successfully improved numerous symptoms in patients with chronic constipation.[26] Lubiprostone is a digestive system-targeted bicyclic functional fatty acid that activates chloride channel type-2 in the apical membrane of the gut mucosal epithelium causing increased intestinal water secretion and subsequently enhancing the secretion of chloride leads to an increase in intraluminal fluid in the bowel, which facilitates transit in the intestine and thereby eases stool passage. The efficacy of lubiprostone in the treatment has been reported in many studies, including 2 identical placebo-controlled trials[27-32] but for some reason it failed to attain popularity among gastrointestinal physicians and surgeons, possibly due to side effects.

The fourth novel agent prucalopride, another 5-HT_4 agonist and a unique enterokinetic therapy has also been proven equally effective, and it is the only agent which is recommended by the National Institute For Health Care Excellence (NICE) for chronic constipation in women. This article highlights the role of prucalopride in the management of chronic constipation based upon the principles of meta-analysis using data reported in published randomized, controlled trials as reported by the Cochrane Collaboration.

Materials and Methods

Electronic medical databases such as the Medline, EMBASE, Cochrane Colorectal Cancer Group Controlled Trial Register, Pain, Palliative and Supportive Care Group Controlled Trial Register, Dementia and Cognitive Improvement Group Controlled Trial Register, Developmental, Psychosocial and Learning Problems Group Controlled Trial Register, Multiple Sclerosis and Rare Diseases of the CNS Group Controlled Trial Register, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library along with the Science Citation Index Expanded were explored until May 2015 to find published randomized, controlled trials. The MeSH terms related to prucalopride and chronic constipation were retrieved from the search engine PubMed, and were used to search the aforementioned electronic databases. Attempts to include additional studies were also made by hand searching of citations of published studies. The statistical analysis of the extracted data was conducted according to the guidelines provided by the Cochrane Collaboration including the use of RevMan 5.3 statistical software, random-effects model analysis, heterogeneity testing by Chi-squared test, heterogeneity quantification by I-squared test, and the use of forest plots for the graphical display of the combined outcomes.[33-39] The combined analysis of continuous variables was expressed as standardized mean difference (SMD) and combined variables were expressed as odds ratio (OR). The primary outcome measure was the incidence of spontaneous bowel movements (SBMs) per week, and the secondary outcome measure was adverse events or side effects of prucalopride use (complications). The reported side effects of prucalopride such as abdominal cramps, abdominal pain, nausea, vomiting, dizziness, diarrhea, rash, headache, constipation, bradycardia, skin disorders, and flatulence were jointly reported in published trials and were analysed in same way in the current article. The critical appraisal tool to score the quality of included trials was adopted from the published guidelines of Jadad et al[40] and Chalmers et al.[41] The short summary of the resulting evidence was presented in a tabulated form by using the tool GradePro,[42] provided by the Cochrane Collaboration. The authors agreed to include all published randomized, controlled trials in patients of any age and gender, diagnosed with chronic constipation of any etiology. The authors excluded studies on animals.

Results

The Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) flow chart to explain the literature search strategy and trial selection is given in Figure 1. Sixteen randomized, controlled trials[43-58] on 3943 patients were retrieved from the search of standard medical electronic databases. The characteristics, salient features and treatment protocols adopted in the included randomized, controlled trials are given in the Table. All trials were adequately randomized using either computer generated sequential pattern or other reliable random pattern methods. These trials varied from phase II[46] to phase III,[51] and were placebo-controlled[43-58] with either single or double blinding. Power calculations, type I and type II errors were adequately covered in the majority of trials. The trial quality indicator Jadad score of included randomized, controlled trials was 4.3 (3.1-5.0). However, the intention-to-treat analysis was lacking in the majority of the trials. The included trials investigated the clinical effectiveness of prucalopride recruiting patients in either 1 arm[47-49,51,58] or 2 arms,[44,45,50,53-57] or even in some cases, 3 arms.[43,46,52] There were diverse inclusion and exclusion criteria in reported randomized, controlled trials and duration of prucalopride use ranged from 1-12 weeks. Although several primary and secondary outcome measures were reported in included trials, in order to get uniform data and uniform combined outcome, this article analysed the frequency of spontaneous bowel movements (SBMs) per week and adverse events including cardiac complications. The combined outcomes following use of 1, 2, and 4 mg doses of prucalopride is given in the following 6 subheadings. The short summary of resulting evidence is given in Figure 2 in tabulated form.

Spontaneous Bowel Movements per Week After Use of 1 mg Prucalopride Versus Placebo

Five included trials (Fig. 3) contributed to the combined calculation of this variable. There was no heterogeneity ($Tau^2 = 0.00$; $Chi^2 = 2.84$, df = 4 [$P = 0.590$]; $I^2 = 0\%$) among the trials. In the random effects model (SMD, 0.42; 95% CI, 0.18-0.66; z = 3.44; $P < 0.0006$), there was a higher risk of reduced SBMs per week in the placebo group and subsequently the frequency of SBMs per week was higher following the use of 1 mg prucalopride to treat chronic constipation.

Adverse Events After Use of 1 mg Prucalopride Versus Placebo

The reported adverse events following the use of prucalopride included abdominal cramps, abdominal pain, nausea, vomiting, dizziness, diarrhea, rash, headache, constipation, skin disorders, and flatulence. Seven included trials (Fig. 4) contributed to the combined calculation of this variable. There was no heterogeneity ($Tau^2 = 0.15$; $Chi^2 = 7.70$, df = 6 [$P = 0.260$]; $I^2 = 22\%$) among the trials. In the random effects model (OR, 2.02; 95% CI, 1.10-3.72;

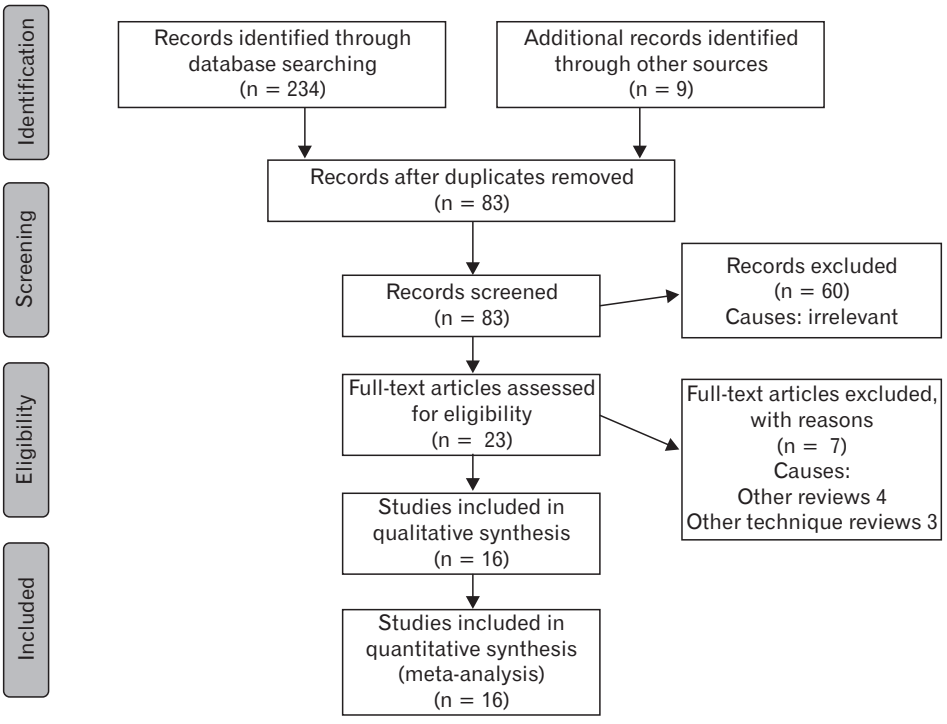

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart to show study selection.

Table. Characteristics of Included Trials

Study	Year	Country	Patients	Comparison Groups	Investigated Variables
Bouras et al[43]	1999	USA	50	0.5 mg vs placebo 1 mg vs placebo 2 mg vs placebo	Colonic transit time
Bouras et al[44]	2001	USA	40	2 mg vs placebo 4 mg vs placebo	Colonic transit time, gastric emptying, small bowel transit time
Camilleri et al[45]	2008	USA, Belgium	620	2 mg vs placebo 4 mg vs placebo	Spontaneous bowel movement per week and HR-QOL measurement and safety
Camilleri et al[46]	2009	USA	89	0.5 mg vs placebo 1 mg vs placebo 2 mg vs placebo	Adverse events, ECG changes, Holter monitor, pharmacokinetics.
Coremans et al[47]	2003	Belgium	55	4 mg vs placebo	Efficacy using VAS, complications, bowel function, transit time
Emmanuel et al[48]	2002	UK	74	1 mg vs placebo	Oro-caecal transit time, visceral sensitivity, HR-QOL and psychological state
Ke et al[49]	2012	Asia-Pacific region	501	2 mg vs placebo	Spontaneous bowel movement per week, safety and adverse events
Krogh et al[50]	2002	Denmark	16	1 mg vs placebo 2 mg vs placebo	Transit time, efficacy, bowel function
Mugie et al[51]	2014	Multicenter	213	2 mg vs placebo	Spontaneous bowel movement per week and HR-QOL measurement
Muller-Nissler et al[52]	2010	Germany	300	1 mg vs placebo 2 mg vs placebo 4 mg vs placebo	Spontaneous bowel movement per week, frequency of bowel movement, safety, tolerability, HR-QOL for constipation
Poen et al[53]	1999	Netherlands	24	1 mg vs placebo 2 mg vs placebo	Total transit time, mean transit time and anorectal physiology studies
Quigley et al[54]	2009	Ireland	641	2 mg vs placebo 4 mg vs placebo	Spontaneous bowel movement per week and HR-QOL measurement and tolerability
Sloots et al[55]	2002	Netherlands	37	1 mg vs placebo 2 mg vs placebo	Anorectal physiological study, bowel diary, transit time and rectal compliance/sensitivity
Sloots et al[56]	2010	Netherlands	196	2 mg vs placebo 4 mg vs placebo	Spontaneous bowel movement per week, safety and adverse events
Tack et al[57]	2009	Belgium	713	2 mg vs placebo 4 mg vs placebo	Spontaneous bowel movement per week and HR-QOL measurement
Yiannakou et al[58]	2015	Multicenter	374	2 mg vs placebo	HR-QOL, constipation severity, spontaneous bowel movements per week

HR-QOL, Health related quality of life; ECG, electrocardiogram; VAS, visual analogue scale.

z = 2.26; P = 0.020), the risk of developing the above mentioned adverse events was higher in the prucalopride group which in fewer cases, lead to the discontinuation of the treatment. A negligible number of patients were non-responders to prucalopride after 2 weeks of therapy and in those cases treatment was discontinued.

Spontaneous Bowel Movements per Week After Use of 2 mg Prucalopride Versus Placebo

Nine included trials (Fig. 5) contributed to the combined calculation of this variable. There was significant heterogeneity (Tau^2 = 0.07; Chi^2 = 36.40, df = 8 [P = 0.0001]; I^2 = 78%) among the trials. In the random effects model (SMD, 0.34; 95% CI, 0.11-0.56; z = 2.94; P = 0.003), there was a higher risk of reduced SBMs per week in the placebo group and subsequently the frequency of SBMs per week was higher following the use of 2 mg prucalopride to treat chronic constipation.

Prucalopride 1 mg versus placebo for chronic constipation

Patient or population: patients with chronic constipation
Settings:
Intervention: prucalopride 1 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Prucalopride 1 mg versus placebo	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Risk of reduced SBM per week Standardized mean difference Follow-up: 1-12 weeks		The mean risk of reduced SBM per week in the intervention groups was 0.42 standard deviations higher (0.18 to 0.66 higher)		277 (5 studies)	⊕⊕⊕⊕ high	SMD 0.42 (0.18 to 0.66)
Complications Odds ratio Follow-up: 1-12 weeks	Study population		OR 2.02 (1.1 to 3.72)	337 (7 studies)	⊕⊕⊕⊕ high	
	512 per 1,000	680 per 1,000 (536 or 796)				
	Moderate					
	500 per 1,000	669 per 1,000 (524 or 788)				

Prucalopride 2 mg versus placebo for chronic constipation

Patient or population: patients with chronic constipation
Settings:
Intervention: prucalopride 2 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Prucalopride 2 mg versus placebo	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Risk of reduced SBM per week Standardized mean difference Follow-up: 1-12 weeks		The mean risk of reduced SBM per week in the intervention groups was 0.34 standard deviations higher (0.11 to 0.56 higher)		1962 (9 studies)	⊕⊕⊕⊕ high	SMD 0.34 (0.11 to 0.56)
Complications Odds ratio Follow-up: 1-12 weeks	Study population		OR 1.76 (1.33 to 2.34)	2812 (13 studies)	⊕⊕⊕⊕ high	
	475 per 1,000	615 per 1,000 (547 or 680)				
	Moderate					

Prucalopride 4 mg versus placebo for chronic constipation

Patient or population: patients with chronic constipation
Settings:
Intervention: prucalopride 4 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Prucalopride 4 mg versus placebo	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Risk of reduced SBM per week Standardized mean difference Follow-up: 1-12 weeks		The mean risk of reduced SBM per week in the intervention groups was 0.33 standard deviations higher (0.22 to 0.44 higher)		1240 (5 studies)	⊕⊕⊕⊕ high	SMD 0.33 (0.22 to 0.44)
Complications	Study population		OR 1.52 (1.13 to 2.05)	1672 (7)		
	637 per 1,000	727 per 1,000 (664 or 782)				
	Moderate					
	556 per 1,000	656 per 1,000 (586 or 720)				

Figure 2. GradePro quality of evidence summary. SBM, spontaneous bowel movement; SMD, standardized mean difference.

Adverse Events After Use of 2 mg Prucalopride Versus Placebo

Thirteen included trials (Fig. 6) contributed to the combined calculation of this variable. There was significant heterogeneity ($Tau^2 = 0.12$; $Chi^2 = 25.44$, df = 12 [$P = 0.010$]; $I^2 = 53\%$) among the trials. In the random effects model (OR, 1.76; 95% CI, 1.33-2.34; z = 3.92; $P < 0.0001$), the risk of developing adverse events was higher in the prucalopride group which in fewer cases, lead to the discontinuation of the treatment. The trend of increased number of patients with adverse events was also noted following the use of 2 mg prucalopride compared to 1 mg. A negligible number of patients were non-responders to prucalopride after 2 weeks of therapy and in those cases treatment was discontinued.

Spontaneous Bowel Movements per Week After Use of 4 mg Prucalopride Versus Placebo

Five included trials (Fig. 7) contributed to the combined calculation of this variable. There was no heterogeneity ($Tau^2 = 0.00$; $Chi^2 = 0.65$, df = 4 [$P = 0.960$]; $I^2 = 0\%$) among the trials. In the random effects model (SMD, 0.33; 95% CI, 0.22-0.44; z = 5.78; $P < 0.00001$), there was a higher risk of reduced SBMs per week in the placebo group and subsequently the frequency of SBMs per week was higher following the use of 4 mg prucalo-

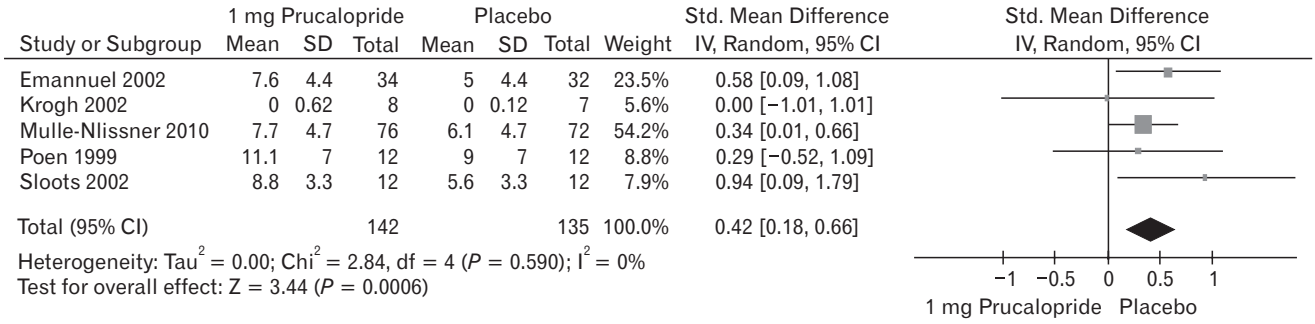

Figure 3. Forest plot for reduced spontaneous bowel movement after 1 mg versus placebo in patients with chronic constipation. Combined outcome is expressed as standardized mean difference.

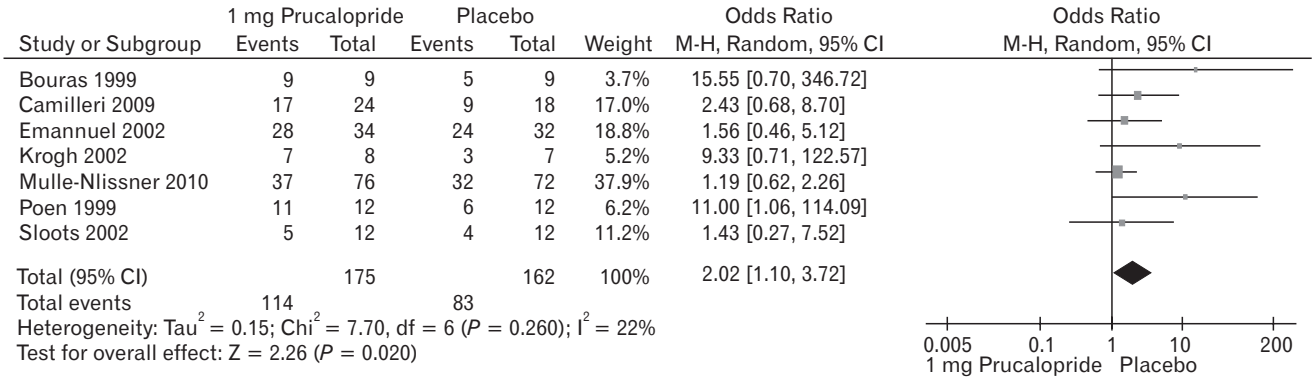

Figure 4. Forest plot for complications after 1 mg versus placebo in patients with chronic constipation. Combined outcome is expressed as odds ratio.

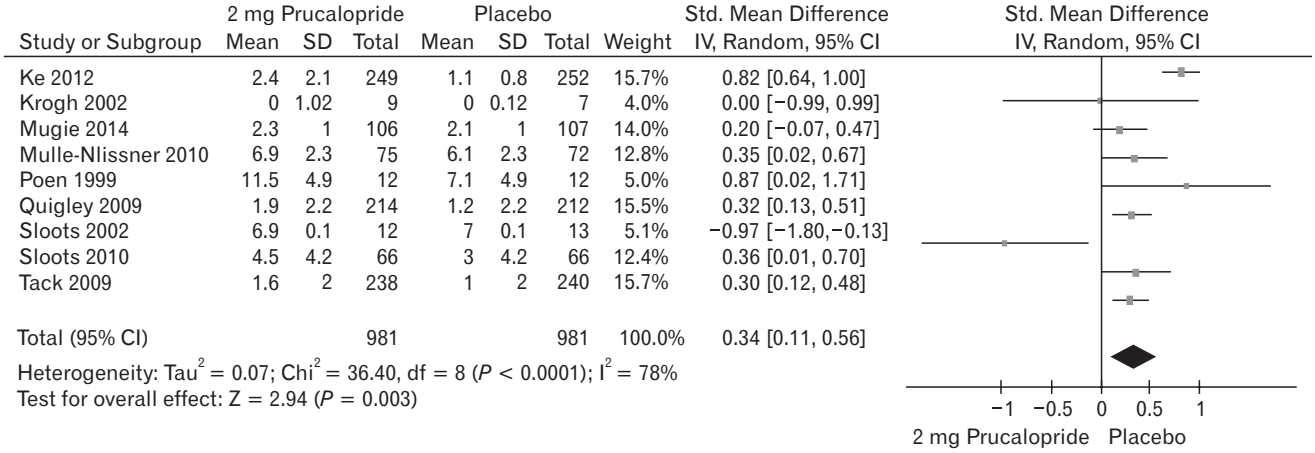

Figure 5. Forest plot for reduced spontaneous bowel movement after 2 mg versus placebo in patients with chronic constipation. Combined outcome is expressed as standardized mean difference.

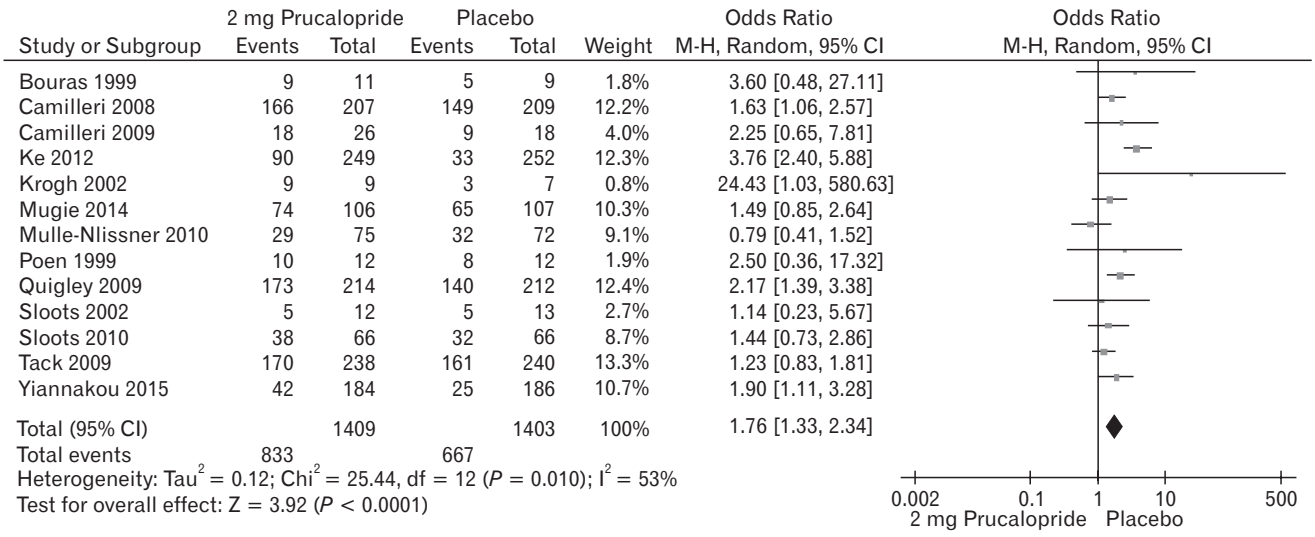

Figure 6. Forest plot for complications after 2 mg versus placebo in patients with chronic constipation. Combined outcome is expressed as odds ratio.

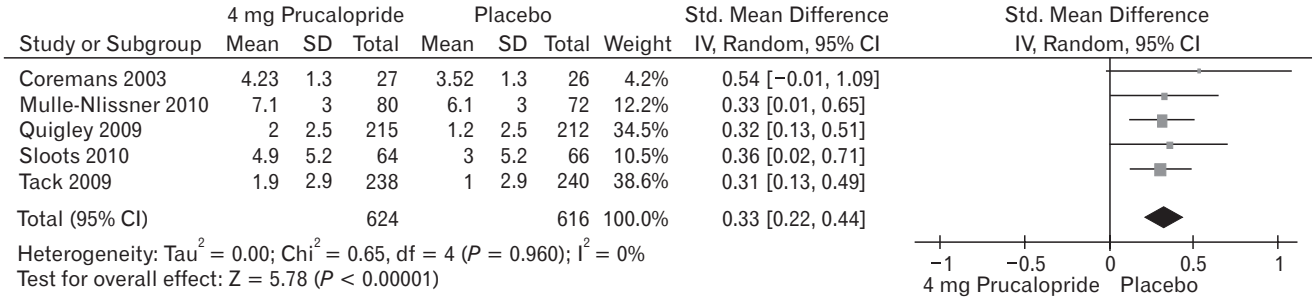

Figure 7. Forest plot for reduced spontaneous bowel movement after 4 mg versus placebo in patients with chronic constipation. Combined outcome is expressed as standardized mean difference.

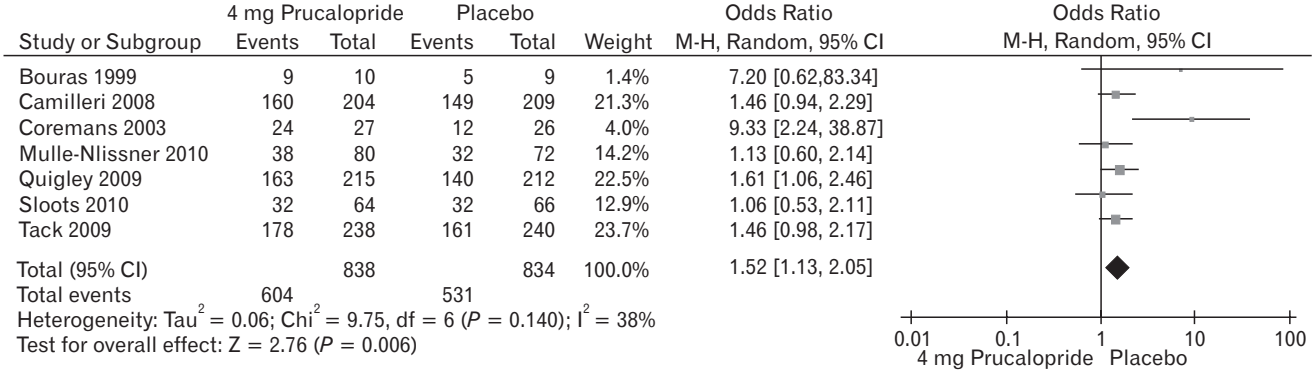

Figure 8. Forest plot for complications after 4 mg versus placebo in patients with chronic constipation. Combined outcome is expressed as odds ratio.

pride to treat chronic constipation. The SBM profile represented as SMD of 1, 2, and 4 mg doses of prucalopride in patients with chronic constipation were 0.42, 0.34, and 0.33 respectively indicating proportional effectiveness of higher doses of prucalopride.

Adverse Events After Use of 4 mg Prucalopride Versus Placebo

Seven included trials (Fig. 8) contributed to the combined calculation of this variable. There was significant heterogeneity ($Tau^2 = 0.06$; $Chi^2 = 9.75$; df = 6 [$P = 0.14$]; $I^2 = 38\%$) among the trials. In the random effects model (OR, 1.52; 95% CI, 1.13-2.05; $z = 2.76$; $P = 0.006$), the risk of developing adverse events was higher in the prucalopride group which in fewer cases lead to the discontinuation of the treatment. The trend of increased number of patients with adverse events was also noted following the use of 4 mg prucalopride compared to 1 mg and 2 mg. A negligible number of patients were non-responders to prucalopride after 2 weeks of therapy, and in those cases treatment was discontinued. The adverse events profile represented as OR of 1, 2, and 4 mg doses of prucalopride in patients with chronic constipation were 2.02, 1.76, and 1.52, respectively indicating proportional effectiveness of prucalopride without causing increased side effects.

Discussion

To the best of our knowledge the results of this largest ever meta-analysis on 16 high-quality randomized, controlled trials published in peer review journals on 3943 patients demonstrate that prucalopride is an effective pharmacotherapy in the management of chronic constipation with acceptable, transient, and negligible side effects.

The findings of the current study are pertinent to only that group of patients which have failed basic laxative therapy (lactulose, ispaghula husk, and senna), life style modifications and stronger laxatives therapy (macrogol, bisacodyl or glycerol suppository, sodium phosphate, and arachis oil enema), and therefore, conclusion cannot be generalized to all types of constipation and on group of patients where early treatment is not optimally tested. However, there are several systematic reviews and meta-analyses evaluating the role of prucalopride[59-68] in the management of chronic constipation and their findings are consistent with the findings of the current study. Although the scope of the current article is the evaluation of clinical effectiveness and adverse events related to prucalopride only, previously reported systematic reviews[59-68] have reported its safety, efficacy, pharmacokinetics, and tolerability providing supporting evidence to our conclusions. As reported by Tack et al[69] "Prucalopride is an important addition to the therapeutic abilities for treating chronic constipation, especially in females poorly responding to laxatives. The safety profile of the drug, to date, is favorable. There is also the possibility that prucalopride might be of benefit to other disorders of gastrointestinal motility with a number of studies currently in progress, which are evaluating alternative applications".

This study reports a total of 3943 participants from 16 randomized, controlled trials undergoing prucalopride therapy for chronic constipation. The risk of bias in the included trials was low when scored against the standard quality guidelines, and therefore, the quality of the resulting evidence may be considered adequate. However, the potential limitations of this study and evidence include different inclusion and exclusion criteria, combined analysis of phase II and phase III trials, variable primary and secondary outcomes, variable duration of prucalopride therapy and variable duration of follow-up among included randomized, controlled trials.

The reported procedure of statistical examination, included study value scoring and overall worthiness of resulting evidence was evaluated according to the recommendations of the Cochrane Collaboration. The reasons of being reduced possibility of biased can be categorized as cited in the included studies are the existence of blinding, allocation concealment. The reporting of acceptable randomization procedure and optimal employment of the power calculations in studies resulted in the provision of satisfactory power to create stronger evidence in favor of current article. The aforementioned methodological limitations should be acknowledged while accepting the conclusions of this study.

The findings of the current meta-analysis on 16 randomized, controlled trials are in accordance with the conclusions of previously published reviews.[59-67] However, this study provides up to date, comprehensive and cumulative evidence on the use of prucalopride that meaningfully reduce symptoms related to chronic constipation. One review[59] reported the combined analysis of 3 trials, 4 reviews[62,64,65,67] reported the combined analysis of 4 trials each, 2 reviews[64,66] reported systematic review of the trials evaluating four 5-HT_4 agonist agents, whereas 3 reviews[60,61,68] were evidence reviews.

The most commonly reported adverse events following prucalopride therapy for chronic constipation are headache (25-30% prucalopride versus 12-17% placebo), nausea (12-24% versus 8-14%), abdominal pain or cramps (16-23% versus 11-19%), and diarrhea (12-19% versus 3-5%).[45,46,54,57,63,65] The majority of these adverse events were experienced by the study group within the first 24 hours of the commencement of prucalopride therapy and were short

lived.[54] When reported, the incidence of serious adverse events was statistically similar for placebo and prucalopride groups.[45,46,54,57,63,65] Like other 5-HT_4 agonists such as cisapride, there were concerns about the risk of cardiac side effects after the use of prucalopride because prucalopride has not been found to interact with either the human *ether-à-go-go*-related gene (hERG) potassium channel (responsible for cisapride-induced arrhythmias) or 5-HT_{1B} receptors (mechanism behind tegaserod induced side effects), both assumed to be responsible for the bradycardia and cardiovascular adverse events.[45,46,51,56,57,59,63,69] In a similar study evaluating the cardiovascular safety profile of prucalopride in a relatively high-risk population of old-age care home patients with 80% having a prior history of cardiovascular disease, no significant hemodynamic or electrocardiographic changes were reported. Explicitly, there was no increased incidence of prolongation of the QT interval or bradycardia in the prucalopride group compared to placebo.[45,46]

Prucalopride seems to be effective for the management of chronic constipation resistant to conventional laxatives. However, generalizing the outcomes of the current study to every type of patient will be unrealistic. After careful exclusion of secondary causes of constipation, prucalopride may be prescribed to the majority of the patients presenting with chronic constipation. Further studies on a particular group of patients such as normal transit constipation and slow transit constipation are mandatory to define which group of the patients may benefit more from the prucalopride therapy. In addition, in patients with psychiatric and psychological disorders while on multiple antidepressants or anti-psychotics, the role of prucalopride needs further evaluation due to its potential to activate 5-HT_4 receptors. Patients with pelvis floor disorders and obstructive defecation syndrome following pelvic floor exercises or surgical intervention may still need assistance in bowel evacuation. The question still remains to be answered is whether prucalopride can still be used in these groups of patients if conventional laxatives fail to provide symptomatic relief. There are several published studies on the pharmacokinetics of prucalopride but trials in the elderly population are scarce where the incidence of chronic constipation is prevalent, and they usually have associated cardiac, renal, liver, and lung co-morbidities. The safety, tolerability, and clinical effectiveness in the elderly population need further evaluation prior to the routine use of prucalopride therapy for conventional laxative-resistant chronic constipation.

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Conflicts of interest: None.

Author contributions: Muhammad S Sajid, Madhu Hebbar, Mirza K Baig, Andy Li, and Zinu Philiposere equally involved and equally contributed into the study design, study conduction, and drafting the manuscript.

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