

## REVIEW

# Bisacodyl: A review of pharmacology and clinical evidence to guide use in clinical practice in patients with constipation

Maura Corsetti<sup>1,2</sup>  | Sabine Landes<sup>3</sup> | Robert Lange<sup>4</sup>

<sup>1</sup>NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust, University of Nottingham, Nottingham, UK

<sup>2</sup>Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, UK

<sup>3</sup>Consumer Health Care, Medical Affairs - Digestive Health, Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany

<sup>4</sup>Consumer Health Care, Global Medical Affairs, Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany

## Correspondence

Maura Corsetti, Nottingham Digestive Diseases Biomedical Research Centre, Queens Medical Centre - E Floor, West Block, Derby Road, Nottingham, NG7 2UH, UK.  
Email: Maura.Corsetti@nottingham.ac.uk

## Funding information

The development of this manuscript was supported by Sanofi.

## Abstract

**Background:** Bisacodyl is a member of the diphenylmethane family and is considered to be a stimulant laxative. It has a dual prokinetic and secretory action and needs to be converted into the active metabolite bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM) in the gut to achieve the desired laxative effect. Bisacodyl acts locally in the large bowel by directly enhancing the motility, reducing transit time, and increasing the water content of the stool. A recent network meta-analysis concluded that bisacodyl showed similar efficacy to prucalopride, lubiprostone, linaclotide, tegaserod, velusetrag, elobixibat, and sodium picosulfate for the primary endpoint of  $\geq 3$  complete spontaneous bowel movements (CSBM)/week and an increase of  $\geq 1$  CSBM/week over baseline. The meta-analysis also found that bisacodyl may be superior to the other laxatives for the secondary endpoint of change from baseline in the number of spontaneous bowel movements per week in patients with chronic constipation. This observation stimulated the authors to review the available literature on bisacodyl, which has been available on the market since the 1950 s.

**Purpose:** The aim of the current review was to provide an overview of the historic background, structure, function, and mechanism of action of bisacodyl. Additionally, we discuss the important features and studies for bisacodyl to understand its peculiar characteristics and guide its use in clinical practice, but also stimulate research on open questions.

## KEYWORDS

Bisacodyl, constipation, laxative, mode of action, secretagogue, sodium picosulfate

## Key Points

- Bisacodyl is a locally acting laxative with unique dual mechanism of action upon gut secretion and motility, and is considered a standard treatment for constipation.
- We provide the first overview of the historic background, pharmacokinetics, and mechanism of action of bisacodyl, including practical guidance for clinicians and explore open questions warranting further research.
- Recent advances in the understanding of colonic motility and the distinct effects of available laxatives on colonic motor patterns suggest that bisacodyl still has unexplored potential.

## 1 | INTRODUCTION

Constipation is one of the most prevalent gastrointestinal conditions presenting to primary care or subspecialty physicians and surgeons globally. In a systematic review and meta-analysis of 41 adult populations in 2011, Ford et al estimated the pooled global prevalence of constipation to be 14%, with a similar prevalence observed in most geographical regions.<sup>1</sup> Constipation represents a significant cost for the healthcare system worldwide.<sup>2-4</sup> Indeed, recent Hospital Episode Statistics data collected between 2017 and 2018 in the UK documented that 71,430 people in England were admitted to hospital with constipation; this is equivalent to 196 people a day, and £162 million was spent by NHS England on treating the condition during this period.<sup>5</sup>

Constipation is characterized by a number of symptoms, such as hard stools, excessive straining, infrequent bowel movements, and/or a feeling of incomplete evacuation.<sup>1,6</sup> It can occur on an occasional/episodic basis, which is often treated by self-medication, or a chronic basis (typically >4 weeks or in accordance with consensus criteria >3 months),<sup>2,6,7</sup> which is likely to be treated by a physician or through specialty care.

Constipation is categorized into idiopathic chronic constipation (CC) and constipation secondary to organic diseases (such as neurological disease) or to certain treatments (such as opioids).<sup>6</sup> The causes of CC are still unclear, but alteration of colonic and anorectal motility have been implicated in the pathophysiology of symptoms.<sup>6,8</sup> Patients are generally classified into three groups, based on assessments of colonic transit and anorectal function: normal transit constipation, slow transit constipation (STC), and pelvic floor dysfunction or defecation disorders.<sup>6,9</sup> The contribution of abnormalities in colonic secretion and absorption to the pathophysiology of constipation is poorly understood. Several drugs which increase colonic secretion are used to manage constipation.<sup>6,10</sup> In the colon, high amplitude propagated contractions (HAPCs) play a relevant role in propulsion,<sup>6</sup> and they occur mostly at awakening and after meals.<sup>11</sup> Studies have shown decreased or absent colonic motor response and lower incidence of HAPCs in patients with STC, compared with healthy volunteers, as investigated by the use of conventional colonic manometry.<sup>8,12-14</sup>

A range of pharmacological treatments for constipation exist and those with demonstrated efficacy compared with placebo include osmotic (polyethylene glycol [PEG]) or stimulant laxatives (bisacodyl and sodium picosulfate), prokinetics (prucalopride), and secretagogues (linaclotide and plecanatide).<sup>6</sup> In a recent systematic review and network meta-analysis, bisacodyl, sodium picosulfate, prucalopride, and velusetrag were shown to be more effective than placebo in a responder analysis comprising  $\geq 3$  complete spontaneous bowel movements (CSBM) per week and an increase over baseline of  $\geq 1$  CSBM per week.<sup>15</sup> Interestingly, the analysis also suggested that bisacodyl may be superior to prucalopride, lubiprostone, linaclotide, tegaserod, velusetrag, elobixibat, and sodium picosulfate for change from baseline in the number of spontaneous bowel movements per week in patients with CC.<sup>15</sup> This observation, in combination with

the fact that bisacodyl is also commonly used as a rescue medication in clinical trials designed to study the efficacy of new constipation compounds,<sup>16-20</sup> suggested to the authors of the present review that a deep understanding of bisacodyl would be useful.

## 2 | HISTORIC BACKGROUND OF BISACODYL

Bisacodyl is a locally acting laxative and has been used to treat constipation and facilitate defecation since the 1950 s.<sup>15,21,22</sup> Bisacodyl is part of the diphenyl methane derivatives group.<sup>23,24</sup> Phenolphthalein, one of the earliest members of this derivatives group, had a weak laxative efficacy and required 30-200 mg daily to elicit a response in adults.<sup>25</sup> Subsequent systematic structure-activity studies of compounds structurally related to phenolphthalein revealed the diphenolic laxative group.<sup>26,27</sup>

### 2.1 | Structure-activity insights

The term diphenolic laxatives are derived from the two free hydroxyl groups in *para* positions on the two benzene rings, which are necessary to provoke a secretagogue and laxative action.<sup>28</sup> Additionally, the secretagogue efficacy depends on the structure of the third aryl group. If a nitrogen is present in the aromatic ring, the distance from the central carbon atom of the methyl group and the dissociation constant of the nitrogen group will affect the secretagogue action.<sup>28</sup>

Bisacodyl and sodium picosulfate are both prodrugs<sup>7</sup> and are converted in the gut into the same active metabolite, bis-(*p*-hydroxyphenyl)-pyridyl-2-methane (BHPM), which causes the desired laxative effect.<sup>29</sup> Conversion of bisacodyl into BHPM is mediated by the action of endogenous deacetylase enzymes on the mucosa of the small intestine and colon, whereas sodium picosulfate is converted to BHPM by the action of colonic bacteria desulfate enzymes (eg, arylsulfate sulfotransferase of *Eubacterium rectale*) (Figure 1).<sup>30</sup> As sodium picosulfate depends on bacterial activity, the use of antibiotics can affect its activity.<sup>29</sup> Similar considerations are valid for senna and cascara, which are also metabolized by colon bacteria.<sup>31</sup>

## 3 | PHARMACOKINETICS

Bisacodyl is administered as a 5-layer enteric-coated tablet (Figure 2) that does not disintegrate until it reaches the lower intestine, thereby reducing the already limited absorption and ensuring it is converted into BHPM in the colon.<sup>7,24</sup> Bisacodyl is available for adults and adolescents (age over 10 years) as an enteric-coated oral dragee/tablet at a dose of 5 mg or as a rectal suppository at a dose of 10 mg,<sup>13,32,33</sup> and for children aged 4-10 years as an oral tablet or rectal suppository at a dose of 5 mg.<sup>32,34</sup> The onset of action occurs between 6 and 12 hours after oral administration, while the suppository can

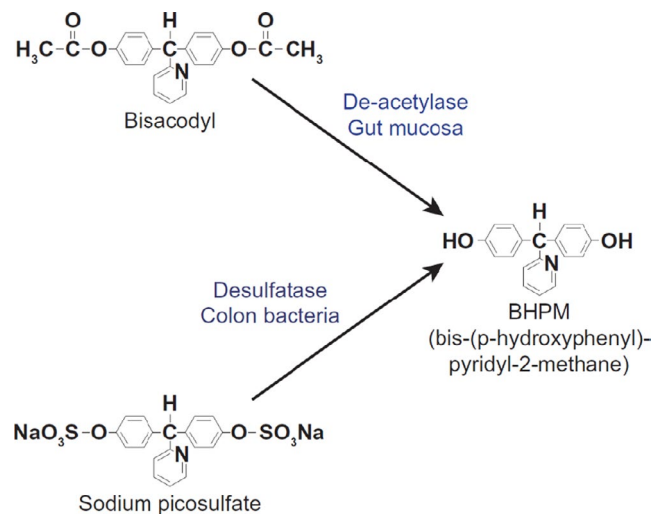


FIGURE 1 Metabolism of bisacodyl and sodium picosulfate into BHPM. BHPM, bis-(p-hydroxyphenyl)-pyridyl-2-methane.

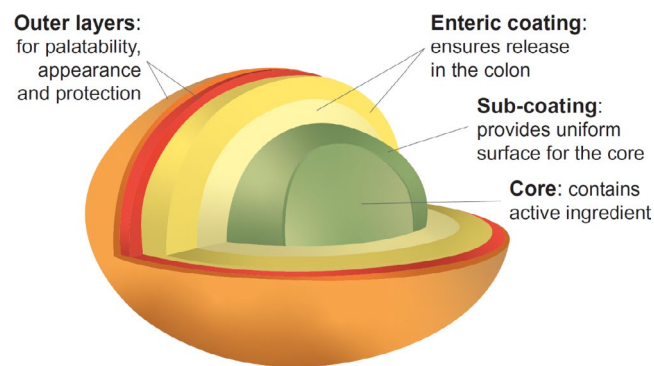


FIGURE 2 Structure of the bisacodyl dragee.

take effect between 15 and 60 minutes following rectal administration.<sup>32,33</sup> Tablets are recommended to be taken at night and the bowel movement typically occurs the following morning, at the time when colonic motor activity is normally highest.<sup>11,32</sup>

After oral and rectal administration, only small amounts of the drug are absorbed and are almost completely conjugated in the intestinal wall and the liver to form the inactive BHPM glucuronide.<sup>32</sup> There is no detectable free BHPM in the plasma, even following multiple once-daily dosing with 2 x 5 mg bisacodyl enteric-coated tablets, although the inactive glucuronidated BHPM is detectable.<sup>7,35</sup> The mean plasma elimination half-life of BHPM has been estimated to be 7.7 hours for bisacodyl tablets.<sup>7</sup> Following the administration of enteric-coated bisacodyl tablets, an average of 51.8% of the dose was recovered in the feces as free BHPM and 10.5% of the dose was recovered in the urine as BHPM glucuronide.<sup>29</sup> In a study by Friedrich et al, 12% of the bisacodyl dose was recovered as total (free +glucuronidated) BHPM in the urine.<sup>7</sup> In the latter study, the authors also investigated excretion of total and free BHPM into human breast milk in two groups of eight healthy lactating women and found that it did not accumulate after multiple administrations of bisacodyl and was not excreted into the breast milk.<sup>7</sup> No data

from controlled human pregnancy studies are available. Long-term post-marketing surveillance has not shown evidence of undesirable or damaging effects during pregnancy. Early studies reported mild side effects<sup>36-38</sup> and other reviews<sup>39-42</sup> deem bisacodyl safe for use during pregnancy. For the suppositories, a prior study demonstrated that in half (n = 6/12) of the healthy volunteers included, no plasma levels of bisacodyl metabolites could be detected and only 3.1% of the dose was excreted in the urine.<sup>35</sup>

Bisacodyl is a locally acting laxative and absorption is not required for the laxative effect. The time to onset depends on the time taken for the prodrug to reach the lower intestine and be converted in the active pharmaceutical ingredient BHPM.<sup>35</sup> There is a lag time before any increase in plasma levels of glucuronidated BHPM is seen. The absence of a temporal relationship between the laxative effects and the plasma levels supports the view that BHPM acts locally.<sup>35</sup>

#### 4 | MECHANISM OF ACTION OF BISACODYL

An overview of the key results from *in vitro* and *in vivo* studies investigating the mechanism of action of bisacodyl is provided in Table 1, with information regarding the animal model used (where applicable).

Animal studies to date have investigated the effect of bisacodyl on motility and water transport. In 1975, Schubert et al investigated the effect of bisacodyl in isolated smooth muscle from the large and small intestine of guinea pigs.<sup>43</sup> Bisacodyl was found to increase the contraction in the isolated muscle, with a dose-dependent response that was greater in the large than in the small intestine.<sup>43</sup> In 1977, Saunders et al investigated the effect of bisacodyl *in vitro* from rat intestinal segments and found it inhibited net water transport, with the degree of inhibition linearly related to the logarithmic intraluminal concentration of bisacodyl.<sup>44</sup> A more recent study in rats investigated the role of aquaporin 3 (AQP3), which is thought to play a role in water transfer in the colon, and found that after oral administration of bisacodyl, expression of prostaglandin E2 increased significantly whereas AQP3 levels decreased by up to 60%.<sup>45</sup> The reduced expression of AQP3 inhibits water transfer from the luminal to vascular side of the colon and leads to a laxative effect, that is thought to be induced by increased secretion of prostaglandin E2. However, although AQP3 is expressed in mucosal epithelial cells in the human colon,<sup>46</sup> the physiological role and the regulation of AQP3 expression in humans are little known.<sup>47</sup> Interestingly, in this manuscript the authors suggested that concomitant administration of nonsteroidal anti-inflammatory drugs could reduce the effect of bisacodyl.<sup>45</sup>

The effects of bisacodyl on colon motility have been confirmed *in vitro* in humans. An early study demonstrated that high concentrations of bisacodyl (10 µg/mL, corresponding to 36 µM/L) enhanced contractility in muscle strips of human large intestine through a tetrodotoxin-insensitive mechanism.<sup>48</sup> In 2000, Voderholzer et al investigated the effect of BHPM on human colon motility in isolated

TABLE 1 Overview of the key studies investigating the mechanism of action of bisacodyl.

Study	Model	Key results
<i>In vitro</i>		
Schubert, et al. <sup>43</sup>	Guinea pig	Bisacodyl (60 µg/mL) initiated dose-dependent contractile responses in isolated guinea pig longitudinal muscle fibers (guinea pig isolated ileum and taenia coli)
Saunders, et al. <sup>44</sup>	Rat	Bisacodyl (0.05–2.0 mg/100 mL) inhibited net water transport from the lumen of the small intestine and colon in rats. Inhibition of net water transport in rat intestine was negatively correlated to the dose of bisacodyl
Saunders, et al. <sup>44</sup>	Human	Bisacodyl (1.0 mg/100 mL) inhibited net water transport from the lumen of the small intestine in humans
Mitznegg, et al. <sup>48</sup>	Human	Maximal contractions in isolated muscle strips of human colon after treatment with bisacodyl (10 µg/mL) were delayed in onset compared with those achieved with acetylcholine (1 µg/mL), histamine (1 µg/mL), and nicotine (0.5 µg/mL)
Voderholzer, et al. <sup>49</sup>	Human	BHPM dose-dependently induced contractions in isolated human colon that were not inhibited by atropine, tetrodotoxin, or Nω-Nitro-L-arginine. In the presence of BHPM, dose-response curves of carbachol and substance P were shifted to the right, showing an inhibitory effect. The inhibitory effect occurred at high concentrations of BHPM
Krueger, et al. <sup>50</sup>	Human	BHPM (0.5–5 µM) increased tone in muscle from the large and small intestine in a concentration-dependent manner with greater effect on large intestine and on longitudinal as compared with circular smooth muscle.
<i>In vivo</i>		
Ikarashi, et al. <sup>45</sup>	Rat <sup>a</sup>	Fecal water content increased significantly from baseline at 2 hours after oral bisacodyl (20 mg/kg) administration. Aquaporin 3 levels in the colon decreased significantly from baseline at 2 hours after bisacodyl administration
Ewe, et al. <sup>57</sup>	Human Healthy volunteers	Following the administration of bisacodyl (5.5–6.6 mg) by intestinal perfusion into the cecum, sodium and water absorption was reversed, with sodium and water entering the intestinal lumen and an increase in potassium secretion.
Ewe <sup>56</sup>	Healthy volunteers	Bisacodyl (10 mg/10 mL ethanol/1L via intestinal perfusion) induced reversible net secretion of water and sodium.
Giorgio, et al. <sup>67</sup>	Human (Pediatric patients)	In colonic segments after intracolonic infusions of bisacodyl (0.2 mg/kg and 0.4 mg/kg), the number of HAPCs was decreased and low-amplitude propagating sequences were more frequent in STC patients than in control subjects
Saunders, et al. <sup>44</sup>	Human (Patients with ileostomies)	Bisacodyl (5 mg) administered orally every 6 hours to five patients with ileostomies increased stoma output by 15%
Gosselink, et al. <sup>55</sup>	Human (Women with obstructed defecation)	Intrarectal bisacodyl (10 mg) significantly increased rectal tone from baseline in women with obstructed defecation and in controls. Tonic response was absent or significantly impaired in patients with prolonged colonic transit time
De Schryver, et al. <sup>13</sup>	Human (Patients with STC and healthy volunteers)	In patients with STC, there was decreased colonic motor response to a meal and to intracolonic bisacodyl (3 mg/10 mL 0.9% saline) versus healthy volunteers. Mean amplitude and frequency of HAPCs were decreased and time to onset of HAPC was prolonged in patients with STC versus healthy volunteers
Herve, et al. <sup>14</sup>	Human (Patients with STC and healthy volunteers)	In patients with severe intractable chronic constipation and decreased numbers of HAPCs, endoluminal bisacodyl (10 mg/10 mL water) induced HAPCs in all groups of patients with constipation and promoted propagated motor activity in the majority of patients compared with versus healthy volunteers
Corsetti, et al. <sup>82</sup>	Human (Patients with STC and healthy volunteers)	Pan-colonic pressurizations (simultaneous pressure increases) and associated relaxations of the anal sphincter represented a new colonic motor pattern appearing to be defective in patients with STC who did not respond to pharmacological treatment with intracolonic bisacodyl
Hamid, et al. <sup>68</sup>	Human (Pediatric patients)	Intrarectal and intracecal bisacodyl (0.2 mg/kg) induced HAPCs which were quantitatively and qualitatively similar to naturally occurring HAPCs in children with functional fecal retention, effect was similar with both modes of administration. Edrophonium did not induce HAPCs.
Manabe, et al. <sup>53</sup>	Healthy volunteers	Administration of oral bisacodyl (5 mg) resulted in accelerated emptying of the ascending colon relative to placebo
Corsetti, et al. <sup>54</sup>	Healthy volunteers	Bisacodyl (10 mg, oral), PEG (13.8 g), and prucalopride (2 mg) showed distinct effects on colonic phasic activity, with bisacodyl inducing increased numbers of HAPCs compared with PEG and prucalopride

Note: Abbreviation: BHPM, bis-(p-hydroxyphenyl)-pyridyl-2-methane; HAPC, high amplitude propagated contraction; PEG, polyethylene glycol; STC, slow transit constipation.

<sup>a</sup>Rats were euthanized and tissue obtained for testing at various timepoints after administration of bisacodyl.

smooth muscle strips and found that bisacodyl has a stimulatory effect on the human colon, which could be inhibited by calcium channel blockers, and appears not to be present at high concentrations of BHPM.<sup>49</sup> More recent data from an *in vitro* study in humans confirmed the dual effect of bisacodyl on motility and secretion. In a study by Krueger et al, BHPM (administered at a maximum dose of 5  $\mu$ M, estimated to be in accordance with the concentration of BHPM produced following administration of 10 mg of bisacodyl) enhanced colon mucosal secretion, and small bowel and colon muscle tone.<sup>50</sup> The increase in muscle tone was through direct myogenic action involving L-type calcium channels and was larger in longitudinal than circular muscle, and in the large than the small intestine. The effect was sustained for up to 3.5 hours, which was the longest recording period.<sup>50</sup> Two mechanisms were involved in BHPM-induced ion secretion into the lumen: potassium secretion when BHPM acts from the luminal site and nerve-mediated chloride and bicarbonate secretion once BHPM is absorbed.<sup>50</sup> Under these experimental conditions, both pro-secretory actions lasted between 20 and 30 minutes.

Most *in vivo* studies in humans have focused on the effect of bisacodyl on colon motility after direct intraluminal application. This test has been, and continues to be, used in clinical practice to exclude colonic inertia (absence of colon motor response to meal and stimulant drug) in patients with STC refractory to pharmacological treatments.<sup>51,52</sup> In general, these studies showed that intraluminal administration of bisacodyl induced HAPCs both in healthy subjects and in most of the patients with constipation (see Table 1 for key results from relevant *in vivo* studies). Similar findings for the effects of bisacodyl on colonic motility have been observed in pediatric patients (see Table 1 for key results from relevant *in vivo* studies).

Few studies have evaluated the effect of oral administration of bisacodyl on motility in healthy human volunteers. In 2009, Manabe et al evaluated the effect of oral bisacodyl on gut transit in 25 healthy volunteers.<sup>53</sup> The authors found that bisacodyl 5 mg accelerated the emptying of the ascending colon compared with placebo, with a median time of 6.5 hours and 11.0 hours, respectively.<sup>53</sup> More recently, Corsetti et al assessed colonic motility with oral PEG 13.8 g, bisacodyl 10 mg, prucalopride 2 mg, and placebo in 10 healthy volunteers using high-resolution manometry.<sup>54</sup> Administration of PEG resulted in a significant increase in the number of long-distance low-amplitude propagating contractions vs. placebo, whereas bisacodyl significantly increased the number of HAPCs versus PEG, prucalopride, and placebo. Prucalopride increased the amplitude of HAPCs and appeared to increase the number of simultaneous pressure increases.<sup>54</sup> Similarly, there have only been a few mechanistic studies investigating the effect of bisacodyl suppositories. In a study involving women with obstructed defecation, rectal tone was measured before and after administration of a rectal suppository of bisacodyl 10 mg.<sup>55</sup> Rectal tone increased significantly after topical application in both patients with normal colonic transit time and control subjects. In patients with a prolonged colonic transit time, this response was absent or significantly reduced, and in all patients (normal and

prolonged transit time) the rectal sensory perception (evoked urge to defecate) was impaired.<sup>55</sup>

Before the recent *in vitro* study by Krueger et al (the results of which are discussed earlier), the effect of bisacodyl on gut secretion was investigated *in vivo* in humans. In 1987, Ewe studied the effect of intestinal perfusion of bisacodyl (10 mg in 10 mL ethanol and 1 L perfusate) on the transport of intestinal electrolytes, glucose, and water in six healthy volunteers.<sup>56</sup> Bisacodyl induced reversible net secretion of sodium and water, and enhanced potassium secretion.<sup>56</sup> Mean transit time was also reduced, while mean flow rate increased, corresponding to the net change from absorption to secretion of water. The author concluded that the secretory effect of bisacodyl was mainly responsible for the decreased transit times and it was assumed that this effect was mainly caused by enhanced fluid flux into the lumen.<sup>56</sup> These findings on the secretory effects of bisacodyl were supported by earlier findings by Ewe et al, who perfused a colonic segment in five healthy volunteers through a modified 4-luminal perfusion tube.<sup>57</sup> In order to assess the effect of bisacodyl on water and electrolyte transport, volunteers were perfused with standard solution before and after delivery of bisacodyl. At each stage of the experiment, the rectal flow was collected through an anal catheter for analysis of volume and electrolyte concentration. It was demonstrated that, compared with standard solution, perfusion with 5.5-6.6 mg of bisacodyl reversed sodium and water absorption and increased potassium secretion.<sup>57</sup>

## 5 | THERAPEUTIC EFFICACY AND SAFETY DATA FROM CLINICAL TRIALS

Clinical investigations and studies on bisacodyl and sodium picosulfate have been performed since the 1950 s according to standards applicable at the time they were conducted. Since the introduction of good clinical practice, major clinical trials have been performed by Kienzle-Horn et al (2006)<sup>22</sup> and Kamm et al (2011)<sup>21</sup> for bisacodyl, and Mueller-Lissner et al (2010)<sup>58</sup> for sodium picosulfate. Kienzle-Horn (2007)<sup>59</sup> also conducted a comparative study of bisacodyl and sodium picosulfate. An overview of the clinical trials of bisacodyl and sodium picosulfate is provided in Table 2. Large, randomized controlled trials for other stimulant laxatives like senna are missing from the literature. In 2006, Kienzle-Horn et al reported the results of a double-blind, randomized, placebo-controlled study that investigated the effect of bisacodyl 10 mg daily for 3 days on the frequency and consistency of stools in 55 patients with CC.<sup>24</sup> Bisacodyl was associated with a significantly greater mean number of stools per day compared with placebo, as well as an improvement in mean stool consistency score. Treatment was well tolerated, with a similar incidence of adverse events (AEs) between bisacodyl and placebo.<sup>24</sup>

It was not until 2011 that Kamm et al reported the results of the first large randomized, double-blind, placebo-controlled, parallel-group study that determined the efficacy and safety of treatment with bisacodyl in patients with constipation (as defined by the Rome III criteria) over a 4 week period.<sup>21</sup> Patients were randomized 2:1

TABLE 2 Overview of key clinical trials investigating the therapeutic efficacy and safety of bisacodyl and sodium picosulfate in constipation.

Study	Study design and aim	Number of patients, treatment, and duration	Key study endpoints	Key efficacy results	Key safety results
Bisacodyl					
Kienzle-Horn, et al. <sup>22</sup>	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial	54 participants with an acute episode of constipation and a documented history of constipation 1:1 randomization to oral bisacodyl (10 mg) or placebo once daily 3 consecutive days' treatment	Primary endpoints: Mean of the total number of stools per day over the 3 treatment days Mean stool consistency	Mean stool frequency was significantly greater in the bisacodyl treatment group (1.8/day) vs. placebo (0.95/day) ( $p = 0.0061$ ) Stool consistency significantly improved over the treatment period in the bisacodyl group ( $p < 0.0001$ )	67% of placebo group patients experienced $\geq 1$ AE, vs. 56% of patients in the bisacodyl group Serum electrolyte levels and incidence of AEs were comparable between treatment groups
Kamm et al. <sup>21</sup>	Randomized, double-blind, placebo-controlled, parallel-group trial	368 participants with constipation (Rome III criteria) 2:1 randomization to oral bisacodyl (10 mg/ 2 dragees as starting dose) or matching placebo once daily Reduction in once-daily oral intake to 1 tablet of either bisacodyl or placebo was permitted 4 weeks' treatment	Primary endpoint: Mean number of CSBMs per week during the treatment period Secondary endpoints: Number of CSBMs per week Number of SBMs per week Number of patients who had $\geq 3$ CSBMs per week Change from baseline in scores for degree of straining, stool quality, sensation of incomplete evacuation Patients overall satisfaction with bowel habits and bothersomeness of constipation, abdominal bloating, abdominal discomfort	Adjusted mean ( $\pm$ SE) number of CSBMs over the 4-week treatment period was $5.2 \pm 0.3$ for bisacodyl and $1.9 \pm 0.3$ for placebo ( $p < 0.0001$ ) All secondary endpoints on number of CSBMs/SBMs per week demonstrated significant differences in favor of bisacodyl ( $p < 0.0001$ ) Percentage of patients with $\geq 3$ CSBMs over 4 weeks treatment period was 67.4% and 27.4% in the bisacodyl and placebo groups, respectively ( $p < 0.0001$ ) Straining with defecation, stool consistency, and sensation of incomplete evacuations all decreased more with bisacodyl than with placebo (statistically significant at each week) Overall satisfaction with bowel habit, and bothersomeness with constipation, abdominal bloating, and abdominal discomfort all improved more with bisacodyl than placebo (statistically significant at each week, except for abdominal discomfort at Week 1)	In the placebo group, 37% of patients experienced $\geq 1$ AE, vs. 72% of patients in the bisacodyl group All reported AEs, besides diarrhea and abdominal pain, were observed at a similar frequency in both groups. Diarrhea and abdominal pain were reported by 53.4% (1.7%) and 24.7% (2.5%) of patients in the bisacodyl group (placebo), respectively Percentage of patients with investigator-defined drug-related AEs decreased from 56.9% in Week 1 to 6.5%, 5.4%, and 4.7% in Weeks 2, 3, and 4 Tolerability as assessed by patients was significantly better in the bisacodyl group than in the placebo group while investigators' assessment was significantly in favor of the placebo group

(Continues)

TABLE 2 (Continued)

Study	Study design and aim	Number of patients, treatment, and duration	Key study endpoints	Key efficacy results	Key safety results
SPS					
Mueller-Lissner et al. <sup>58</sup>	Randomized, double-blind, placebo-controlled, parallel-group trial	367 participants with constipation (Rome III criteria) 2:1 randomization to oral SPS drops (10 mg/ 18 drops as starting dose) or matching placebo once daily Reduction in once-daily oral intake to 9 drops of either SPS or placebo was permitted 4 weeks' treatment	Primary endpoint: Mean number of CSBMs per week during the treatment period Secondary endpoints: Number of CSBMs per week Number of SBMs per week Number of patients who had $\geq 3$ CSBMs per week Change from baseline in scores for degree of straining, stool quality, sensation of incomplete evacuation Patients overall satisfaction with bowel habits and bothersomeness of constipation, abdominal bloating, abdominal discomfort	Adjusted mean ( $\pm$ SE) number of CSBMs over the 4-week treatment period was $3.4 \pm 0.2$ for SPS and $1.7 \pm 0.1$ for placebo ( $p < 0.0001$ ) All secondary endpoints on number of CSBMs/SBMs per week demonstrated significant differences in favor of SPS ( $p < 0.0001$ ) Percentage of patients with $\geq 3$ CSBMs over the 4 weeks treatment period was 51.1% and 18.0% in the SPS and placebo groups, respectively ( $p < 0.0001$ ) Straining with defecation, stool consistency, and sensation of incomplete evacuations all decreased more with SPS than with placebo (statistically significant at each week, except for incomplete evacuation for Weeks 1 and 4) Overall satisfaction with bowel habit, and bothersomeness with constipation, abdominal bloating and discomfort improved more with SPS than placebo (statistically significant at each week)	In the placebo group, 19% of patients experienced $\geq 1$ AE, vs. 44% of patients in the SPS group. All reported AEs, besides diarrhea and abdominal pain, were observed at a similar frequency in both groups. Diarrhea and abdominal pain were reported by 31.8% (4.5%) and 5.6% (2.2%) of patients in the SPS group (placebo), respectively The percentage of patients with investigator-defined drug-related AEs decreased from 31.0% in Week 1 to 3.9%, 4.5%, and 1.9% in Weeks 2, 3, and 4 Dose reduction: at the end of treatment, 46% of patients had reduced the daily SPS dose to $< 15$ drops There were no significant changes in laboratory variables during the course of the study Tolerability as assessed by patients was significantly better in the SPS group than in the placebo group, while there was no difference in the investigators' assessment between both treatment groups
Comparison of Bisacodyl and SPS					
Kienzle-Horn, et al. <sup>59</sup>	Open-label, randomized, parallel-group trial	142 participants with chronic constipation 1:1 randomization to oral bisacodyl (5–10 mg) once daily or oral SPS (5–10 mg as drops) once daily 4 weeks' treatment	Primary endpoint: Number and consistency of stools per day Secondary endpoints: Degree of straining at stool Global assessment of efficacy by investigator	A significant improvement versus baseline in stool frequency, consistency, and straining occurred in both groups at Day 14 and Day 28 ( $p < 0.0001$ ). No significant difference between treatment groups was detected at any time point A significant improvement in investigators' global efficacy assessment was also observed for both groups	In the bisacodyl group, 21.4% of patients experienced $\geq 1$ AE, compared with 23% of patients in the SPS group The most commonly reported AEs were flatulence (bisacodyl: 7.1%, SPS: 9.5%), headache (bisacodyl: 8.6%, SPS: 6.8%), and abdominal pain (bisacodyl: 7.1%, SPS: 6.8%) There was a trend for better tolerability in patients receiving bisacodyl treatment based on the number of drug-related AEs: No significant effect on serum electrolytes was observed in either treatment group

Note: Abbreviations: AE, adverse event; CSBM, complete spontaneous bowel movement; SBM, spontaneous bowel movement; SE, standard error; SPS, sodium picosulfate.

to receive either bisacodyl 10 mg once daily ( $n = 247$ ) or matching placebo ( $n = 121$ ). Patients receiving bisacodyl had a significantly increased mean number of CSBMs per week over the treatment period, from 1.1 at baseline for both groups to 5.2 with bisacodyl and 1.9 in the placebo. (Figure 3A).<sup>21</sup> In addition to improvements in objective constipation-related symptoms, such as straining with defecation or stool consistency, patients also reported improvements in other parameters.<sup>21</sup> Overall satisfaction scores for bowel habits, bothersomeness of constipation, and abdominal discomfort and bloating improved with bisacodyl compared with placebo (unpublished data, see Table 2). Over the study period, the most common AEs in patients treated with bisacodyl were diarrhea and abdominal pain, experienced by 53.4% and 24.7% of patients, respectively, compared with 1.7% and 2.5% in the placebo group, respectively. 17.8% of the bisacodyl-treated patients withdrew prematurely because of AEs, compared with only 5.0% of the placebo group. In the bisacodyl group, the percentage of premature withdrawals decreased over time from 10.5% at week 1 to 2.5% at week 4. However, it should be noted that patients started treatment with a bisacodyl dose of 10 mg daily and were allowed to reduce their dose during the treatment period. The percentage of patients with drug-related AEs in the bisacodyl group declined markedly from 57% at Week 1 to 5% at Week 4 (Table 3 and Figure 3B). This reduction in AEs corresponds with the reduction of the bisacodyl dose during the treatment period. Patients reduced their mean weekly dose from 56 mg in Week 1 to 48 mg in Week 2 and 45 mg in Week 4, with 58% of patients in the bisacodyl arm able to reduce their daily dose from 10 mg to 5 mg by the end of the treatment period (Figure 3C).<sup>21</sup> This finding suggests that the starting dose of bisacodyl selected in this study was too high for a considerable proportion of patients and that treatment was well tolerated once a patient identified a suitable dose. Indeed, treatment tolerability assessed by the patient (using a 4-point ordinal verbal rating scale: 1=good, 4=bad) was significantly better in the bisacodyl group compared with placebo.<sup>21</sup>

In 2010, Mueller-Lissner et al reported the results of a randomized, double-blind, placebo-controlled, parallel-group study that investigated the safety and efficacy of sodium picosulfate over 4 weeks in 367 patients with constipation (as defined by the Rome III criteria).<sup>58</sup> Patients were randomized 2:1 to receive either sodium picosulfate drops (10 mg) or matching placebo. The mean number of CSBMs significantly increased from 0.9 to 3.4 in the sodium picosulfate group, compared with an increase from 1.1 to 1.7 in the placebo group.<sup>58</sup> Significant improvements in health-related quality-of-life, as measured by the constipation-related Patient Assessment of Constipation Quality-of-Life questionnaire, were observed in the sodium picosulfate group compared with the placebo group. Symptoms and satisfaction with bowel habit were also improved following sodium picosulfate compared with placebo.<sup>58</sup> The most common AE was diarrhea, reported in 74 (31.8%) patients in the sodium picosulfate group and six (4.5%) patients in the placebo group. Abdominal pain was reported in 13 (5.6%) and three (2.2%) patients in the sodium picosulfate and placebo groups, respectively.<sup>58</sup> In the group of patients

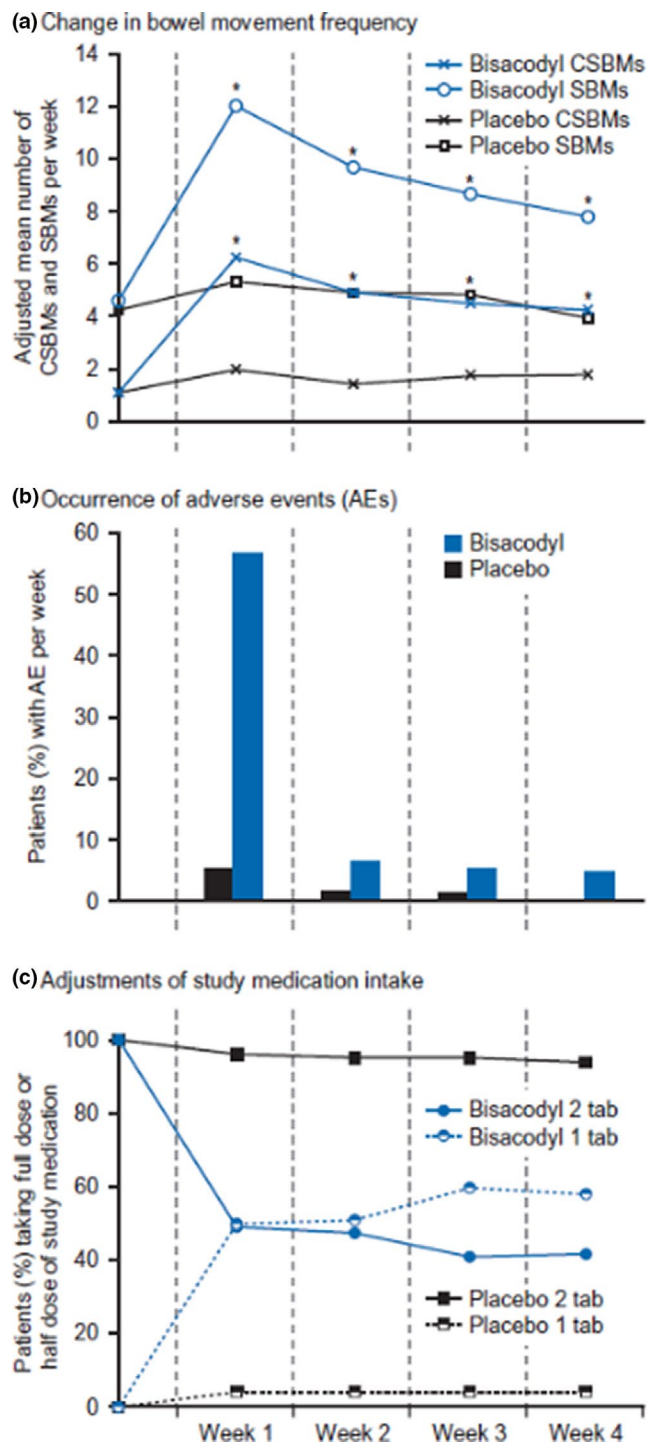


FIGURE 3 Efficacy and safety data per week over the 4 week treatment period. (A) Change in bowel movement frequency, (B) Percentage of patients experiencing AEs, (C) Percentage of patients taking 1 or 2 tablets bisacodyl or placebo. Patients can self-manage their stimulant laxative dose to achieve effective relief of chronic constipation, as demonstrated in two randomized trials. Poster number S1328 presented at Digestive Disease Week 2010, republished with permission from Clinical Gastroenterology and Hepatology and the authors, respectively.<sup>81</sup> AE, adverse event; CSBM, complete spontaneous bowel movement; SBM, spontaneous bowel movement. Data from Kamm et al., 2011<sup>21</sup> and Mueller-Lissner et al., 2018<sup>81</sup>



treated with sodium picosulfate, 5.2% of the patients discontinued the study prematurely, whereas the percentage in the placebo group was 3.8%. In the SPS group, the percentage of premature withdrawals was 0.4% during weeks 1 and 4. The highest percentage of 3.1% premature withdrawals have been reported during week 2. Over the course of the study, the number of drug-related AEs decreased significantly after the first week. Similar to the Kamm et al study with bisacodyl,<sup>21</sup> this reduction in drug-related AEs was in parallel with the individual adjustment of the dose of sodium picosulfate.<sup>58</sup>

Kienzle-Horn et al conducted a randomized, open-label, parallel-group comparison of the safety and efficacy of bisacodyl and sodium picosulfate (both 5–10 mg daily) over a 4-week period in 144 patients with CC.<sup>59</sup> Both treatments were equally effective in treating CC, with significant improvements in symptoms seen in both groups. Neither treatment significantly affected serum electrolytes (Figure 4).<sup>59</sup>

In light of the limited head-to-head randomized controlled trials of treatments for CC, the clinically relevant efficacy and safety findings discussed above have been examined in systematic reviews and meta-analyses by Ford et al,<sup>60</sup> Nelson et al,<sup>15</sup> and Luthra et al.<sup>61</sup> Ford et al noted that the mean number of stools per week was significantly increased for both osmotic and stimulant laxatives compared

with placebo in patients with CC.<sup>60</sup> Nelson et al observed similar efficacy between bisacodyl, prucalopride, lubiprostone, linaclotide, tegaserod, velusetrag, elobixibat, and sodium picosulfate for the primary endpoints of  $\geq 3$  CSBMs/week and an increase from baseline by  $\geq 1$  CSBM/week.<sup>15</sup> However, the authors concluded that bisacodyl may be superior in the secondary endpoint of change from baseline of SBMs per week.<sup>15</sup> Similar conclusions were reached in a recently published network meta-analysis by Luthra et al,<sup>61</sup> in which bisacodyl and sodium picosulfate were ranked first at 4 weeks based on an endpoint of failure to achieve  $\geq 3$  CSBMs per week. The authors also reported that bisacodyl was ranked last in terms of safety for total number of AEs and abdominal pain when assessing the treatment period as a whole.<sup>61</sup> The reduction of AEs over time with bisacodyl occurred in parallel with the reduction of the dosage during the treatment period. While AEs are known to decrease in such studies over time in the absence of dose change, it seems reasonable to suggest that clinicians could consider starting with a lower dosage and increase in case of need.

Additionally, the fear of causing electrolyte imbalance has been disputed in multiple studies which confirmed that the use of bisacodyl does not lead to clinically relevant electrolyte loss.<sup>21,58,59,62,63</sup>

**TABLE 3** Overall summary of adverse events by week for patients with investigator-defined drug-related adverse events in the Kamm et al. 2011 bisacodyl study<sup>21</sup>

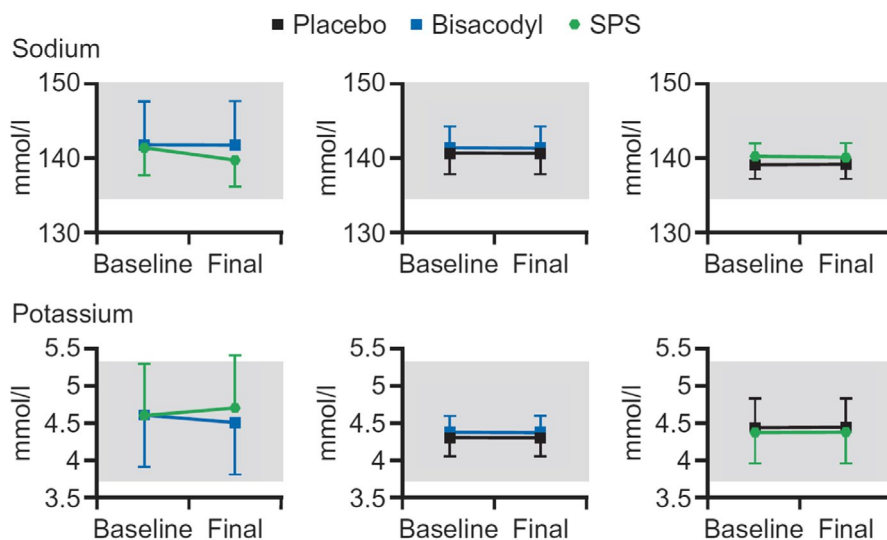
Timepoint	Placebo		Bisacodyl	
	N (%) at risk	N (%) affected	N (%) at risk	N (%) affected
Week 1	117 (100)	6 (5.1)	239 (100)	136 (56.9)
Week 2	114 (100)	2 (1.8)	216 (100)	14 (6.5)
Week 3	111 (100)	1 (0.9)	204 (100)	11 (5.4)
Week 4	105 (100)	0 (0.0)	192 (100)	9 (4.7)

## 6 | WHAT CAN THESE DATA TELL US ABOUT BISACODYL?

### 6.1 | What are the key aspects of bisacodyl pharmacology that clinicians should remember?

Bisacodyl is a prodrug metabolized in the intestinal mucosa and not by bacteria, such as with other stimulant laxatives like picosulfate, senna, and cascara. This suggests that a more consistent effect of bisacodyl is possible, with less influence from factors affecting gut microbiota. Bisacodyl is available as oral (5-layer enteric-coated tablets) and rectal (suppository) formulations, permitting a variable

**FIGURE 4** Serum levels of sodium and potassium at the beginning and end of treatment with bisacodyl, sodium picosulfate, and placebo, respectively, for 4 weeks (mean  $\pm$  SD). SPS, sodium picosulfate; Republished with permission, from Mueller-Lissner, *Open J Gastroenterology*, 2013.



The grey area in each chart represents the physiological range.

immediacy of effect; bowel movement occurs in approximately 6–12 hours following administration with oral tablets and approximately 20 minutes with the suppository (in some cases an effect occurred 45 minutes after administration). The available oral dosing for adults is 5–10 mg once daily. On the basis of randomised controlled trial findings,<sup>21</sup> 5 mg seem to be better tolerated. Therefore, it is sensible to recommend treatment initiation with 5 mg and subsequent dose adjustment on an individualised basis. However, as studies with formal fixed-dose comparison of the 5 and 10 mg dosages are not available, such a comparison may provide additional information on efficacy and tolerability of the two-dose strength.<sup>21</sup> Available dosing in the rectal form is 10 mg for adults, adolescents, and children above 10 years of age,<sup>32,64</sup> and 5 mg for children aged 4–10 years.<sup>34</sup> With both formulations, the active metabolite of bisacodyl has no relevant systemic absorption.<sup>21,29,53,65</sup>

## 6.2 | What are the key aspects of the mechanism of action of bisacodyl?

Bisacodyl has a dual prokinetic and secretory action directly enhancing colon motility, reducing transit time, and increasing the water content of the stool (Figure 5). Colonic motility can present either as phasic contractions (contractions of short duration), or tone (prolonged state of contractions).<sup>66</sup> Local administration *in vitro*<sup>48–50</sup> and rectal administration of suppositories *in vivo*<sup>55</sup> have been shown to increase smooth muscle tone in healthy volunteers and patients with obstructed defecation and normal colonic transit. *In vitro*, this effect on gut tone seems to be more pronounced on the longitudinal than the circular smooth muscle, and in the colon than in the ileum, and persists for up to 3.5 hours.<sup>50</sup>

Intraluminal administration of bisacodyl in the colon and/or in the rectum trigger phasic HAPCs within 60 minutes.<sup>55,67</sup> These contractions start in the proximal colon and propagate distally in both healthy and constipated adults, and in children without colonic inertia.<sup>6</sup> In addition, these HAPCs are similar to those occurring physiologically.<sup>13,14,68,69</sup> It is currently unclear whether the stimulation of these HAPCs *in vivo* in humans is related to the activation of a neuromuscular pathway intrinsic and/or extrinsic to the gut wall, requires the

concomitant presence of gut distension, and/or is determined by the activation of only the longitudinal smooth muscle layer or also circular muscle.<sup>50</sup>

## 6.3 | Can the above information guide the selection of patients who are more likely to respond to bisacodyl?

A better understanding of the effect of bisacodyl on the different motor responses of the gut (ie tone and HAPCs) when administered orally or locally in different formulations would be beneficial in order to clarify whether this can be used in clinical practice in different subgroups of patients. It is possible that patients presenting with defecation disorders and normal colonic transit might benefit from an increase in rectal motility induced by suppositories,<sup>55</sup> while patients with reduced number of HAPCs might benefit more from an oral formulation with a more combined effect on secretion and motility. However, in the absence of ad hoc studies, it is difficult to ascertain whether a specific subgroup of constipation patients would benefit more from oral or local administration.

Recent observations on the different effects on colon motility of some of the currently available constipation treatments (bisacodyl, PEG, and prucalopride) may provide useful information for clinical practice.<sup>54</sup> It is indeed possible that the use of a combination of different medications, which target different colonic motor patterns, could help patients currently not responding to monotherapy. It is also interesting to note that bisacodyl has been used as a rescue medication in many recent clinical trials designed to investigate the efficacy of newer compounds, such as linaclotide and prucalopride.<sup>16,17,19,20</sup> This is unsurprising considering that bisacodyl stimulates HAPCs in healthy individuals, while prucalopride seems to stimulate low-amplitude simultaneous pressure increases and increase the amplitude of HAPCs.

It is interesting to note that some *in vitro* studies suggest that increasing the dose of bisacodyl above the recommended dosage may not increase the colon motor response.<sup>49</sup> This could explain the fact that patients reporting consumption of very high dosages of bisacodyl do not seem to experience stronger stimulation of colon motility.

## 6.4 | Can bisacodyl be considered safe for long-term use?

The current evidence for the efficacy and safety of bisacodyl compared with placebo has been obtained over a period of up to 4 weeks.<sup>21</sup> However, clinical experience, guidelines, and review articles suggest that there are no concerns with using these laxatives over a longer period of time.<sup>9,70–72</sup> In this case, use of these medications with a frequency of two to three times a week may be considered, as the aim should be to have at least two to three bowel movements per week according to the definition of normal bowel habits.<sup>6,73</sup> However, some clinicians are still concerned about

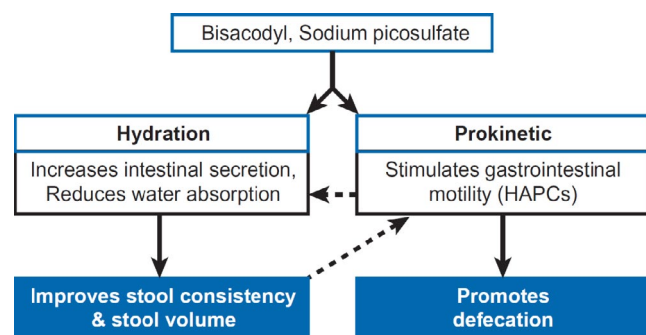


FIGURE 5 Overview of mechanism of laxative action of bisacodyl and sodium picosulfate.

the perception that prolonged use of stimulant laxatives can cause dependency or damage to the gut. It should be noted that these concerns are based on historical anecdotal evidence and unwarranted fears. While some individuals are known to abuse laxatives,<sup>74</sup> the active metabolite from the stimulant laxatives bisacodyl and sodium picosulfate is not absorbed and does not pass through the blood-brain barrier and so there is no pharmacological basis for dependency. Furthermore, the misconception that long-term use of these laxatives could damage the enteric nervous system is based on studies from 1960 to 1970, which have not been confirmed by subsequent studies.<sup>75-79</sup> Similarly, there are no concerns that these laxatives can increase the risk of colorectal cancer as a result of anthranoid derivative associated colonic melanosis. This has been confirmed by prospective studies.<sup>75-79</sup> Available evidence does not indicate that stimulant laxatives at recommended doses are harmful to the colon during long-term use.

## 7 | CONCLUSIONS AND FUTURE PERSPECTIVES

Bisacodyl is a prodrug with a unique dual mechanism of action on gut secretion and motility. The present analysis has reconfirmed that it is well tolerated and effective in the treatment of constipation, and the present review of the literature suggests that the treatment should be started with the lowest dose of 5 mg. Recent advances in the understanding of colonic motility in health and the distinct effects of available drugs for constipation on different colonic motor patterns suggest that bisacodyl still has unexplored potential. Indeed, it would be interesting to understand whether the different response to the oral and rectal administration of the effect of bisacodyl could be used to improve the current treatment of patients presenting with impairment in proximal colon propulsion, compared with those with distal impairment. Furthermore, it would be interesting to investigate whether bisacodyl could be combined with other drugs, such as prucalopride, to treat patients not responding to monotherapy. The results of studies in human samples clearly demonstrate that local administration of bisacodyl in vitro activates ion secretion both in the ileum and the colon, with an effect lasting between 20 and 30 minutes.<sup>50</sup> However, the relative role of secretion and motility in modulating the final laxative effect of bisacodyl in vivo when taken orally remains to be elucidated. Ongoing magnetic resonance imaging studies may clarify this relevant aspect.

Besides the well-known effect on initiating bowel movements, there are potentially further implications from the stimulation of large bowel motility with bisacodyl. Intestinal permeability and fecal flora have been assessed in patients with functional constipation to determine the impact of disturbances in bowel function.<sup>80</sup> Concentrations of *Bifidobacterium* and *Lactobacillus* were significantly lower and potentially pathogenic bacteria and/or fungi were increased in constipated patients. Normalization of evacuatory function with bisacodyl treatment was accompanied by a decrease in counts of potentially pathogenic microorganisms (*E. coli*, fungi)

and increase in counts of obligate microflora (*Bifidobacterium*, *Bacteroides*, *Streptococcus fecalis*).<sup>80</sup> This is also an area that would warrant future research.

## ACKNOWLEDGEMENTS

The authors would like to acknowledge Claire Lydon of iMed Comms, an Ashfield Company, part of UDG Healthcare plc, for medical writing support that was funded by Sanofi in accordance with Good Publication Practice (GPP3) guidelines (<http://www.ismpp.org/gpp3>).

## CONFLICT OF INTEREST

MC is a consultant for Allergan, Kiowa Kyrin, and Arena. SL and RL are employees of Sanofi-Aventis.

## ORCID

Maura Corsetti  <https://orcid.org/0000-0003-2957-4684>

## REFERENCES

1. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:1582-1591; quiz 1581, 1592.
2. Constipation WA. Advances in diagnosis and treatment. *JAMA*. 2016;315:185-191.
3. Albu A, Farcas A, David L, Dumitrascu DL. The economic burden of constipation therapy. *Med Pharm Rep*. 2019;92:261-264.
4. Bruce Wirta S, Hodgkins P, Joseph A. Economic burden associated with chronic constipation in Sweden: a retrospective cohort study. *Clinicoecon Outcomes Res*. 2014;12:369-379.
5. Disney B. Bowel Interest Group, Cost of Constipation Report. 2019 [cited July 2019. Second Edition: [Available from: <https://www.coloplast.co.uk/Global/UK/Continence/Cost%20of%20Constipation%202019.pdf>].
6. Camilleri M, Ford AC, Mawe GM, et al. Chronic constipation. *Nat Rev Dis Primers*. 2017;3:17095.
7. Friedrich C, Richter E, Trommeshauser D, et al. Absence of excretion of the active moiety of bisacodyl and sodium picosulfate into human breast milk: an open-label, parallel-group, multiple-dose study in healthy lactating women. *Drug Metab Pharmacokinet*. 2011;26:458-464.
8. Ferrara A, Pemberton JH, Grotz RL, Hanson RB. Prolonged ambulatory recording of anorectal motility in patients with slow-transit constipation. *Am J Surg*. 1994;167:73-79.
9. Bharucha AE, Lacy BE. Mechanisms, Evaluation, and Management of Chronic Constipation. *Gastroenterology*. 2020;158:1232.e3-1249.e3.
10. Barrett KE. Endogenous and exogenous control of gastrointestinal epithelial function: building on the legacy of Bayliss and Starling. *J Physiol*. 2017;595:423-432.
11. Hoogerwerf WA. Role of clock genes in gastrointestinal motility. *Am J Physiol-Gastrointest Liver Physiol*. 2010;299:G549-555.
12. Bazzocchi G, Ellis J, Villanueva-Meyer J, et al. Postprandial colonic transit and motor activity in chronic constipation. *Gastroenterology*. 1990;98:686-693.
13. De Schryver AM, Samsom M, Smout AI. Effects of a meal and bisacodyl on colonic motility in healthy volunteers and patients with slow-transit constipation. *Dig Dis Sci*. 2003;48:1206-1212.
14. Herve S, Savoye G, Behbahani A, Leroi AM, Denis P, Ducrotte P. Results of 24-h manometric recording of colonic motor

- activity with endoluminal instillation of bisacodyl in patients with severe chronic slow transit constipation. *Neurogastroenterol Motil.* 2004;16:397-402.
15. Nelson AD, Camilleri M, Chirapongsathorn S, et al. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis. *Gut.* 2017;66:1611-1622.
  16. Lembo AJ, Kurtz CB, MacDougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology.* 2010;138:e881.
  17. Lacy BE, Schey R, Shiff SJ, et al. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized controlled trial. *PLoS One.* 2015;10:e0134349.
  18. Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial. *Am J Gastroenterol.* 2017;112:763-774.
  19. Yiannakou Y, Piessevaux H, Bouchoucha M, et al. A randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy, safety, and tolerability of prucalopride in men with chronic constipation. *Am J Gastroenterol.* 2015;110:741-748.
  20. Ke MeiYun, Tack J, Quigley EMM, et al. Effect of prucalopride in the treatment of chronic constipation in Asian and Non-Asian women: a pooled analysis of 4 randomized, placebo-controlled Studies. *J Neurogastroenterol Motil.* 2014;20:458-468.
  21. Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. *Clin Gastroenterol Hepatol.* 2011;9:577-583.
  22. Kienzle-Horn S, Vix JM, Schuijt C, Peil H, Jordan CC, Kamm MA. Efficacy and safety of bisacodyl in the acute treatment of constipation: a double-blind, randomized, placebo-controlled study. *Aliment Pharmacol Ther.* 2006;23:1479-1488.
  23. Farack UM, Nell G. Mechanism of action of diphenolic laxatives: the role of adenylate cyclase and mucosal permeability. *Digestion.* 1984;30:191-194.
  24. Stiens SA, Luttrell W, Binard JE. Polyethylene glycol versus vegetable oil based bisacodyl suppositories to initiate side-lying bowel care: a clinical trial in persons with spinal cord injury. *Spinal Cord.* 1998;36:777.
  25. Cancer I.A.f.R.o. Some antiviral and antineoplastic drugs, and other pharmaceutical agents. *IARC Monogr Eval Carcinog Risks Hum.* 2000;76:345-486.
  26. Schmidt L. Pharmacology and toxicology of a new class of compounds with laxative effect. *Arzneimittelforschung.* 1953;3:19-23.
  27. Beubler E, Juan H. PGE-mediated laxative effect of diphenolic laxatives. *Naunyn Schmiedebergs Arch Pharmacol.* 1978;305:241-246.
  28. Nell G, Rummel W. Action mechanisms of secretagogue drugs. *Pharmacology of Intestinal Permeation.* 1984;11:461-508.
  29. Jauch R, Hankwitz R, Beschke K, Pelzer H. Bis-(p-hydroxyphenyl)-pyridyl-2-methane: the common laxative principle of Bisacodyl and sodium picosulfate. *Arzneimittelforschung.* 1975;25:1796-1800.
  30. Kim DH. Gut microbiota-mediated drug-antibiotic interactions. *Drug Metab Dispos.* 2015;43:1581-1589.
  31. Portalatin M, Winstead N. Medical management of constipation. *Clin Colon Rectal Surg.* 2012;25:12-19.
  32. Summary of Product Characteristics, Bisacodyl tablets 5 mg. EMC.
  33. Summary of Product Characteristics, Bisacodyl suppositories 10 mg EMC.
  34. Summary of Product Characteristics, Bisacodyl suppositories 5 mg EMC.
  35. Roth W, & Beschke K. Pharmacokinetics and laxative effect of bisacodyl following administration of various dosage forms. *Arzneimittelforschung.* 1988;38:570-574.
  36. Baydoun AB. Bisacodyl suppositories: a practical means of securing bowel evacuation during labor. *Am J Obstet Gynecol.* 1963;85:905-907.
  37. Fogel IB. The enema-is it necessary? Comparison of bisacodyl rectal suppository with the soapsuds enema in the parturient in 1,159 cases. *Am J Obstet Gynecol.* 1962;84:825-831.
  38. Smith JJ, Schwartz ED. Evaluation of a new contact laxative, bisacodyl (dulcolax), in obstetrics and gynecology. *West J Surg Obstet Gynecol.* 1964;72:177-180.
  39. Bonapace ES Jr, Fisher RS. Constipation and diarrhea in pregnancy. *Gastroenterol Clin North Am.* 1998;27:197-211.
  40. MacDougall MK, LeGrand SB, Walsh D. Symptom control in the pregnant cancer patient. *Semin Oncol.* 2000;27:704-711.
  41. Wald A. Constipation, diarrhea, and symptomatic hemorrhoids during pregnancy. *Gastroenterol Clin North Am.* 2003;32:vii.
  42. Dathe K, Schaefer C. The use of medication in pregnancy. *Dtsch Arztebl Int.* 2019;116:783-790.
  43. Schubert E, Strunz U, Mitznegg P, Domschke S, Domschke W, Demling L. The mode of action of bisacodyl on the smooth muscle of the small and the large intestine of the guinea pig. *Arzneimittelforschung.* 1975;25:1053-1056.
  44. Saunders DR, Sillery J, Rachmilewitz D, Rubin CE, Tytgat GN. Effect of bisacodyl on the structure and function of rodent and human intestine. *Gastroenterology.* 1977;72:849-856.
  45. Ikarashi N, Baba K, Ushiki T, et al. The laxative effect of bisacodyl is attributable to decreased aquaporin-3 expression in the colon induced by increased PGE2 secretion from macrophages. *Am J Physiol Gastrointest Liver Physiol.* 2011;301:G887-895.
  46. Silberstein C, Kierbel A, Amodeo G, et al. Functional characterization and localization of AQP3 in the human colon. *Braz J Med Biol Res.* 1999;32:1303-1313.
  47. Ikarashi N, Kon R, Sugiyama K. Aquaporins in the colon as a new therapeutic target in diarrhea and constipation. *Int J Mol Sci.* 2016;17:1172.
  48. Mitznegg P, Schubert E, Domschke W, et al. Mode of action of bisacodyl (dulcolax) on isolated muscles of human colon (author's transl). *Klin Wochenschr.* 1975;53:493-495.
  49. Voderholzer WA, Morena M-A, Schindlbeck NE. The influence of bisacodyl on human colon motility in vitro. *Gastroenterology.* 2000;118:A838.
  50. Krueger D, Demir IE, Ceyhan GO, Zeller F, Schemann M. bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM)-the active metabolite of the laxatives bisacodyl and sodium picosulfate-enhances contractility and secretion in human intestine in vitro. *Neurogastroenterol Motil.* 2018;30:e13311.
  51. Bassotti G, Roberto GD, Sediari L, Morelli A. Toward a definition of colonic inertia. *World J Gastroenterol.* 2004;10:2465-2467.
  52. Wilkinson-Smith V, Bharucha AE, Emmanuel A, Knowles C, Yiannakou Y, Corsetti M. When all seems lost: management of refractory constipation-Surgery, rectal irrigation, percutaneous endoscopic colostomy, and more. *Neurogastroenterol Motil.* 2018;30:e13352.
  53. Manabe N, Cremonini F, Camilleri M, Sandborn WJ, Burton DD. Effects of bisacodyl on ascending colon emptying and overall colonic transit in healthy volunteers. *Aliment Pharmacol Ther.* 2009;30:930-936.
  54. Corsetti M, Thys A, Harris A, et al. High-resolution manometry reveals different effect of polyethylene glycol, bisacodyl and prucalopride on colonic motility in healthy subjects: an acute, open label, randomised, crossover, reader blinded study with potential clinical implications. *Neurogastroenterol Motil.* 2020;e14040.
  55. Gosselink MJ, Hop WC, Schouten WR. Rectal tone in response to bisacodyl in women with obstructed defecation. *Int J Colorectal Dis.* 2000;15:297-302.
  56. Ewe K. Effect of bisacodyl on intestinal electrolyte and water net transport and transit. Perfusion studies in men. *Digestion.* 1987;37:247-253.

57. Ewe K, Holker B. The effect of a diphenolic laxative (Bisacodyl) on water- and electrolyte transport in the human colon (author's transl). *Klin Wochenschr.* 1974;52:827-833.
58. Mueller-Lissner S, Kamm MA, Wald A, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. *Am J Gastroenterol.* 2010;105:897-903.
59. Kienzle-Horn S, Vix JM, Schuijt C, Peil H, Jordan CC, Kamm MA. Comparison of bisacodyl and sodium picosulphate in the treatment of chronic constipation. *Curr Med Res Opin.* 2007;23:691-699.
60. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut.* 2011;60:209-218.
61. Luthra P, Camilleri M, Burr NE, Quigley EMM, Black CJ, Ford AC. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol.* 2019;4:P831-844.
62. Muller-Lissner S. Pharmacokinetic and pharmacodynamic considerations for the current chronic constipation treatments. *Expert Opin Drug Metab Toxicol.* 2013;9:391-401.
63. Müller-Lissner S. Diphenyl methane laxatives do not induce electrolyte imbalance. *Open J Gastroenterol.* 2013;3:272-275.
64. Summary of Product Characteristics, Dulcolax suppositories 10 mg EMC.
65. Flig E, Hermann TW, Zabel M. Is bisacodyl absorbed at all from suppositories in man? *Int J Pharm.* 2000;196:11-20.
66. Boeckxstaens G, Camilleri M, Sifrim D, et al. Fundamentals of neurogastroenterology: physiology/motility - sensation. *Gastroenterology.* 2016;150:1292-1304.
67. Giorgio V, Borrelli O, Smith VV, et al. High-resolution colonic manometry accurately predicts colonic neuromuscular pathological phenotype in pediatric slow transit constipation. *Neurogastroenterol Motil.* 2013;25:70-79.
68. Hamid SA, Di Lorenzo C, Reddy SN, Flores AF, Hyman PE. Bisacodyl and high-amplitude-propagating colonic contractions in children. *J Pediatr Gastroenterol Nutr.* 1998;27:398-402.
69. Hardcastle JD, Mann CV. Study of large bowel peristalsis. *Gut.* 1968;9:512-520.
70. Andresen V, Enck P, Frieling T, et al. S2k guideline for chronic constipation: definition, pathophysiology, diagnosis and therapy. *Z Gastroenterol.* 2013;51:651-672.
71. Bove A, Bellini M, Battaglia E, et al. Consensus statement AIGO/SICCR diagnosis and treatment of chronic constipation and obstructed defecation (part II: treatment). *World J Gastroenterol.* 2012;18:4994-5013.
72. Ruidisch MH, Hutt H-J, König E. Long-term laxative treatment with bisacodyl - Efficacy and tolerability in patients with spinal cord injuries. *Ärztliche Forschung.* 1994;41:3-8.
73. Simren M, Palsson OS, Whitehead WE. Update on rome IV criteria for colorectal disorders: implications for clinical practice. *Curr Gastroenterol Rep.* 2017;19:15.
74. Elran-Barak R, Goldschmidt AB, Crow SJ, et al. Is laxative misuse associated with binge eating? Examination of laxative misuse among individuals seeking treatment for eating disorders. *Int J Eat Disord.* 2017;50:1114-1118.
75. Brenner DM. Stimulant laxatives for the treatment of chronic constipation: is it time to change the paradigm? *Gastroenterology.* 2012;142:402-404.
76. Muller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. *Am J Gastroenterol.* 2005;100:232-242.
77. Dufour P, Gendre P. Ultrastructure of mouse intestinal mucosa and changes observed after long term anthraquinone administration. *Gut.* 1984;25:1358-1363.
78. Kiernan JA, Heinicke EA. Senosides do not kill myenteric neurons in the colon of the rat or mouse. *Neuroscience.* 1989;30:837-842.
79. Bharucha AE, Pemberton JH, Locke GR III. American gastroenterological association technical review on constipation. *Gastroenterology.* 2013;144:218-238.
80. Khalif IL, Quigley EMM, Konovitch EA, Maximova ID. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. *Dig Liver Dis.* 2005;37:838-849.
81. Mueller-Lissner S, Kamm MA, Wald A, et al. S1328 Patients can self-manage their stimulant laxative dose to achieve effective relief of chronic constipation, as demonstrated in two randomized trials. *Gastroenterology.* 2018;138:S-230.
82. Corsetti M, Pagliaro G, Demedts I, et al. Pan-Colonic pressurizations associated with relaxation of the anal sphincter in health and disease: a new colonic motor pattern identified using high-resolution manometry. *Am J Gastroenterol.* 2017;112:479-489.

**How to cite this article:** Corsetti M, Landes S, Lange R. Bisacodyl: A review of pharmacology and clinical evidence to guide use in clinical practice in patients with constipation. *Neurogastroenterology & Motility.* 2021;00:e14123. <https://doi.org/10.1111/nmo.14123>