Habit forming properties of laxatives for chronic constipation: A review [version 2; peer review: 1 not approved]

Previously titled: Expert opinion on the habit forming properties of laxatives in patients with constipation

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Abstract
Constipation is a commonly reported disorder in many patients. Constipation treatment using laxatives on a regular and long term basis can lead to patient dependence, especially among the elderly. However, there is scanty data on the habit-forming potential of laxatives in Indian constipated patients. This review has explored literature evidence and expert opinion on patients’ experience regarding habit-forming attributes of stimulant and osmotic laxatives. Additionally, structured face-to-face discussions were conducted with 2 key opinion leaders to understand their clinical experience on the habit-forming aspects stimulant and osmotic laxatives in patients with constipation. Based on literature evidence, lactulose is not known to lead to any habit-forming behaviors in patients. Furthermore, experts pointed out that dependence on stimulant laxatives is common, but not on osmotic laxatives, and emphasized that milk of magnesia is not habit forming. In conclusion, no habit-forming characteristics or dependence was observed with the use of osmotic laxatives in India. Nevertheless, real-world, studies exploring patient and physician perspectives are warranted to establish the dependence and habit forming attributes of laxatives.

Keywords
Constipation, habit forming laxatives, treatment dependence, stimulant laxatives, osmotic laxatives

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Introduction

Constipation is a common functional gastrointestinal disorder. In India, constipation has become a frequent health problem contradicting the popular belief that constipation may be infrequent due to high fiber vegetarian diet and higher frequency of bowel movement. According to a meta-analysis of 45 community studies, the global prevalence of constipation is 14%. Incidence of constipation is higher among women than men due to slow transit, pelvic floor dysfunction because of hard stool forms, obstetric trauma, and over-reporting. Among subjects aged >35 years, weekly stool frequency was lower in women than in men.

Constipation also impacts the quality of life of patients. Constipation can be physically and cognitively troublesome for many patients, as identified in several population-based studies, and can interfere with daily living and well-being, particularly in older patients. Moreover, constipation can have a substantial impact on healthcare utilization, resulting in greater economic burden. Testing for constipation can cost $6.9 billion, apart from treatment costs, assuming that 2.5 million people are annually evaluated for constipation. Furthermore, constipation has a negative impact on employment, work productivity, and physical ability. Findings from a recent National Health and Wellness Survey indicate that patients with constipation have a significantly greater percentage of missed work time and had impairment in daily activities.

Various factors, such as delayed colonic transit, visceral hypersensitivity, altered central perception, and abnormalities in sensory/motor function, either independently or in combination, are thought to contribute to the pathophysiology of chronic constipation. Primary causes of constipation may be intrinsic impairment of anorectal or colonic function, whereas secondary causes may be related to systemic disease, organic disease, or medications.

Guidelines for constipation management

Management of constipation begins with patient education on changes needed in diet and lifestyle, training on toilet habits, and instruction on defecation dynamics. Figure 1 illustrates the algorithm for management of Rome IV functional disorders of chronic constipation. Clinical guidelines also suggest daily supplementation with 25-30 g of dietary fibers. Intake of dietary fibers was shown to improve stool frequency, but no improvement in stool consistency or painful defecation versus placebo. Bowel (habit) retraining is another form of lifestyle modification wherein patients are advised to defecate only when colonic motor activity is highest i.e. when there is an urge to defecate. The American Gastroenterological Association (AGA) Guidelines suggest gradual increase in fiber intake along with use of an osmotic agent such as milk of magnesia or polyethylene glycol (PEG) to manage constipation. Depending on the stool consistency, the next step in the treatment pathway may include supplementation with a stimulant laxative such as bisacodyl or glycerol suppositories. In a randomized, clinical trial involving patients with constipation, daily therapy with 17 g of PEG for 14 days significantly improved bowel movement frequency when compared with placebo treatment. Traditional therapies such as lactulose and psyllium have shown improvement in symptoms of constipation, but scare evidence is available on the use of other common agents, such as bisacodyl, milk of magnesia, senna, and stool softeners. Furthermore, long-term laxative use has been known to cause cathartic colon.

Pharmacotherapies

For patients with suspected contributing factors, a course of pharmacological treatment with laxatives before further evaluation may be reasonable. Laxatives aid defecation by decreasing stool consistency (softening) and/or artificially or indirectly promoting colon motility, via one or more number of mechanisms.
per the Indian perspective recommended laxatives as the first line of pharmacotherapy. The mechanism of action, duration of treatment and benefits and side effects of the four major categories of laxatives, namely, bulk-forming, osmotic, lubricant, and stimulant are summarized in Table 1. Consensus provided by the Clinical Practice Guidelines of the Indian Motility and Functional Diseases Association and the Indian Society of Gastroenterology for the management of chronic constipation suggest that initial treatment should include osmotic laxatives with lifestyle modification.

In children, the approach should focus on the nature of the disorder, and the initial therapeutic steps should include toilet training and treatment with laxatives.

In adults, management focuses on ruling out an underlying cause and distinguishing between different subtypes of constipation—normal transit, slow transit or evacuation disorder—all of which have significant therapeutic implications. Management of adult functional constipation involves lifestyle interventions, pelvic floor intervention if there is a rectal evacuation disorder, and pharmacological therapy. Osmotic laxatives are preferred as the first-line therapy

Figure 1. Algorithm for management of chronic constipation. PEG, polyethylene glycol.
Table 1. Laxative compounds commonly used to treat chronic constipation.

<table>
<thead>
<tr>
<th>Class</th>
<th>Key laxative agents</th>
<th>Mechanism of action</th>
<th>Duration of treatment</th>
<th>Adult dosage</th>
<th>Benefits</th>
<th>Possible side effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk-forming</td>
<td>Ispaghula/ Psyllium</td>
<td>Intraluminal water binding and decrease in stool consistency</td>
<td>Up to 4 weeks</td>
<td>20-30 g/day</td>
<td>Improvement in bowel function, increased percentage of normal stools and decreased formation of hard stools</td>
<td>Bloating, flatulence</td>
<td>21,24,25</td>
</tr>
<tr>
<td>Osmotic</td>
<td>Milk of magnesium</td>
<td>Interstitial water binding</td>
<td>8 weeks</td>
<td>30-60 mL/day</td>
<td>Increase in stool frequency and improvement in consistency and straining</td>
<td>Excessive flatulence, abdominal pain and hydroelectrolytic alterations</td>
<td>20–22,26</td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td></td>
<td>1-12 weeks</td>
<td>15-30 mL/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEG</td>
<td></td>
<td>Up to 6 months</td>
<td>17 g/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubricant</td>
<td>Liquid paraffin/ mineral oil</td>
<td>Intraluminal water binding, bulk-forming, and decrease in stool consistency</td>
<td>2-3 months with subsequent tapering</td>
<td>10-30 mL/day</td>
<td>Cheapest and most rapid acting</td>
<td>Anal seepage, lipid pneumonia, interference with absorption of fat-soluble vitamins (A, D, E, and K)</td>
<td>21,26,27</td>
</tr>
<tr>
<td>Stimulant</td>
<td>Bisacodyl</td>
<td>Stimulating action on enteric nerves with decrease in peristaltic contractions; decrease in colic absorption of water and electrolytes</td>
<td>4 weeks</td>
<td>5-15 mg/day</td>
<td>Improvement in constipation-related symptoms, bowel function, and disease-related quality of life.</td>
<td>Electrolyte disturbances, malabsorption, dose dependence, cramping, diarrhea, abuse, development of cathartic colon, and melanosis coli</td>
<td>20–22,28,29</td>
</tr>
<tr>
<td></td>
<td>Sodium picosulfate</td>
<td></td>
<td>4 weeks</td>
<td>5-10 mg/day</td>
<td>Increases the number of (complete) spontaneous bowel movements, and improves symptoms of straining and some aspects of quality of life</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
for constipation in adult patients as well. Two placebo-controlled studies demonstrated that osmotic laxatives are efficacious in increasing stool frequency. If symptoms persist, stimulant laxatives are recommended in clinical guidelines.

While laxatives can be very effective in the acute settings, their long-term use can lead to tolerance and eventually habituation. Both these responses are induced by damage to the colon or an adaptive mechanism that counteracts the laxative effect on motility or secretion. Furthermore, satisfaction with laxatives can be suboptimal because of limited efficacy, non-specific response not targeting the underlying pathophysiology, or association with undesirable side effects.

Bulk-forming laxatives act by increasing the volume and softness of feces by absorbing water in the intestine, thereby promoting dilation of the intestinal wall and enhancing propulsive motor function. This group consists of natural or synthetic polysaccharides. These agents demonstrate no systemic effects, and the major concern is obstruction of the esophagus, stomach, small intestine, or colon when ingested without fluid. However, these agents are recommended for long-term use.

Osmotic laxatives act by drawing water into the intestinal lumen because of presence of poorly absorbable substances. The most commonly used osmotic laxatives are ‘milk of magnesia’ (magnesium hydroxide), lactulose, and PEG. Saline laxatives such as citrate salts and magnesium preparations have been shown to release cholecystokinin, which causes accumulation of fluid and electrolytes in the gut lumen and promotes small bowel and perhaps colonic transit. Kinnunen and Salokannel compared the efficacy of magnesium hydroxide and bulk-laxatives in elderly, long-stay patients and found that bowel habits were more frequent and stool consistency was normal in patients receiving magnesium hydroxide versus bulk-forming laxative.

Lubricant laxatives also known as stool softeners, ease defecation due to their surfactant effect. Non-reabsorbable oils and oils that are very difficult to reabsorb such as paraffin, are included in this group. Prolonged use of paraffin may induce malabsorption of fat soluble vitamins, and it is recommended only in special circumstances, such as in some cystic fibrosis patients. Also, lipoid pneumonia may occur if the agent is aspirated, so it should not be used in debilitated patients or just before bedtime.

Stimulant laxatives such as bisacodyl, cascara, senna, and sodium polystyrene sulfonate (SPS) improve intestinal secretions and motility by stimulating the myenteric and the Auerbach plexuses. They also decrease water absorption from the intestinal lumen. These laxatives are mostly used as rescue therapy in the absence of bowel movements for three days. The efficacy of bisacodyl and SPS for the treatment of chronic constipation have been studied in two clinical trials, and in both the studies, the mean number of complete spontaneous bowel movements increased per week as compared to placebo. Bisacodyl has gained popularity as preparation for diagnostic procedures and intermittent use for this purpose is acceptable. Despite its availability for decades, the use of stimulant laxatives is hindered because of its safety, tolerability and lack of sufficient trials supporting its efficacy.

Habitation or tolerance is a common concern with the long-term use of laxatives. Habituation implies a reduction or disappearance of laxative response, while tolerance refers to the need to increase laxative dose to achieve the required result. The habit-forming property of laxatives is most commonly studied in chronic use of stimulant laxatives like anthraquinones, sennoside and bisacodyl. Due to the action on enteric nerves, it is often a matter of concern that there may be irreversible damage to the nerves on long-term use of these laxatives.

Joo et al. investigated the impact of stimulant laxatives on damage and change in the enteric nerves and musculature by observing changes following barium enema given to two groups of subjects, one ingesting stimulant laxatives (Group 1) and the other not (Group 2). Loss of haustral folds was observed in 27.6% of subjects in Group 1 and no subjects in Group 2 (p<0.005). This was particularly observed in patients who regularly used bisacodyl, phenolphthalein, senna, and casamntranol. The authors concluded that chronic use of stimulant laxatives resulted in anatomic changes in the colon, which suggests neuronal injury or damage to colonic musculature.

Reimann et al. have also studied the ultrastructural changes occurring as a consequence of long-term use of laxatives. Colonic biopsies from patients using stimulant laxatives like bisacodyl and anthraquinone derivate demonstrated submucosal nerve damage. There was a significant increase in the axonal area along with a reduction of neurotubules. Since a well-functioning enteric nervous plexus is required for having normal gut motility, it was concluded that such alterations in the nerves may be correlated to the alteration in gut motility in patients with long-term laxative abuse.
However, there is very limited evidence on whether laxatives cause any habituation or tolerance and specifically which classes of laxatives exhibit this effect. Moreover, the amount at which a stimulant laxative is damaging is not yet explored. In the next section of this review, we summarize the evidence available on the habit-forming properties of different laxative classes.

**Habit-forming properties of laxatives**

The ubiquitous availability of laxatives, combined with their relatively low cost, increases their potential for abuse and misuse. Due to the length of time of the abuse maintained, habit forming properties, and daily dose of laxatives, degenerative changes can occur and may lead to serious impairment of coordinated peristalsis of the gut. This impairment may lead to initial functional disorders of intestinal transport mechanism that may develop into acquired hypoganglionosis.

As prolonged treatment of constipation may be required, a laxative must be carefully chosen. It should have a gentle effect, with no systemic activity, no side effects like cramping or salt depletion, and no contraindications, and it must be neither habit forming nor toxic.43

Bulk-forming laxatives increase the fecal mass by stimulating peristalsis. Bulk-forming laxatives are more appropriate for those patients with small hard stools, but are not suitable for patients that require an immediate relief from constipation as they take time to increase the fecal mass. These laxatives are mainly prescribed for patients with uncomplicated constipation, that have normal intestinal motility and where it is impractical to increase dietary intake of fiber any further.44

Osmotic laxatives such as PEG and milk of magnesia draw water into the stool resulting in more frequent and softer stools, which makes it easy to pass bowel movements.45 Osmotic laxatives like lactulose demonstrate their action by increasing osmotic pressure, volume, and peristalsis and decreasing colonic transit time.46 Moreover, osmotic laxative preparations like lactulose have demonstrated a persistent carry over effect. Return to normal bowel function is easier with lactulose, and habituation is less likely to occur with its use.47 Most studies have reported the common side effects that occur with use of osmotic laxatives; however, habit forming property has not been reported as one of the side effects. However, there is limited data reported in literature about the non-habit forming characteristics of osmotic laxatives.

Lubricant laxatives act by reducing the absorption of water and softening the stool, thus allowing easier passage of stools when given orally or rectally.26 Liquid paraffin is popular for treating constipation primarily because of its ease of titration and tolerability.28 Long-term use of lubricant laxatives reduces absorption of fat-soluble vitamins can potentially result in substantial deficiencies.49 Furthermore, the risk of developing colorectal cancer as a result of chronic use of laxatives should also be considered.50 The prevalence of constipation among the elderly is as high as 50%, which can increase to 74% in nursing home residents using daily laxatives.51–53 In these patients, laxatives treatments often precipitate loose stools and incontinence that can result in diarrhea of unknown etiology. There is no clinical evidence, however, that can confirm the habit forming attribute of lubricant laxatives.

Regular use of stimulant laxatives can cause dependency and cathartic colon albeit there is no direct evidence to support this claim.54 Prolonged use of stimulant laxatives leaves users prone to drug dependence, malabsorption, and electrolyte imbalance, and can damage the enteric nervous system, weakening colonic strength and even giving rise to melanosis coli. Moreover, long-term use of stimulant laxatives can damage the myenteric plexus, reducing responsiveness of the colon to intestinal contents and weakening colonic motor function. It is even possible to lose the ability to defecate spontaneously, a condition known as “laxative colon.” Though powerful and fast-acting, stimulant laxatives are not currently recommended for long-term use by elderly patients due to the adverse reactions, and only short-term or intermittent use is advised. Slow transit constipation should be treated with bulk-forming or osmotic laxatives.27 Cathartic colon though observed in some chronic users of stimulant laxatives, it is unclear whether this effect is related to their prolonged use.28

Although correction of faulty bowel habits and a change in dietary regimen is helpful in many cases of constipation, some patients cannot easily adapt to prescribed regimens or in some patients, no desired effect is obtained. In such patients, effective bowel regulation without the use of drastic laxatives is necessary. There is limited data reported in the literature about the habit forming characteristics of lubricant laxatives.

**Expert opinion on constipation and habit forming attributes of laxatives**

As limited literature exists on dependence and habituation associated with laxative use, we garnered real-world experience on the prevalence of constipation, its treatment, and habit-forming attributes of various classes of laxatives.
We observed that acute constipation is common in Indian clinical practice with an average duration of <three months. The treatment approach includes exercise, patient education on scheduled toileting and bowler retraining, and pharmacotherapy with osmotic laxatives, stool softeners or bulk-forming agents for a duration of 2-8 weeks depending on patient profile. Amongst the various laxative classes, dependence was observed to be rare in acute conditions, but it is observed with stimulant laxatives upon chronic use.

Consistent with literature, we did not observe laxative abuse or habit-forming attributes with osmotic laxatives. Among the osmotic laxatives, we believe that milk of magnesia is not habit forming in acute conditions because it does not cause bowel contraction, given that it elicits its mechanism of action via osmosis i.e. increasing water content in the intestines thereby facilitating peristalsis. This increased water content liquefies the stools for easy defecation. Thus, degeneration of ganglia plexus, which is the primary pathophysiology associated with dependence and abuse, is not likely with milk of magnesia, thereby explaining the absence of habituation with this laxative. However, we recommend that caution should be exercised when recommending milk of magnesia in patients with renal failure and in cases where long-term treatment may be warranted, considering the potential for hypomagnesemia, hypophosphatemia, and secondary hypocalcemia.

Liquid paraffin as a lubricant laxative and stool softener in acute constipation is not habit forming because it does not cause the bowel to contract or spasm and provides a smooth surface for easy passage of stools. Unlike other laxatives, neither milk of magnesia, nor liquid paraffin causes flatulence or bloating and can be beneficial in patients with fissures and hemorrhoids. In patients suffering from bloating or ascites, milk of magnesia can act as a stool lubricant on account of its osmotic effect. Moreover, liquid paraffin is not associated with abdominal cramps, diarrhea, or electrolyte disturbances. Considering the fast onset of action of milk of magnesia (0.5-six hours) and the relatively long duration of action of liquid paraffin (eight-ten hours), we believe that a combination of these laxatives can provide fast and sustained action, thereby making it a treatment of choice in clinical practice.

Conclusion
In summary, habit-forming properties are observed in patients with constipation upon use of stimulant laxatives, but not with osmotic laxatives such as milk of magnesia or lubricant laxatives such as liquid paraffin. A combination of milk of magnesia and liquid paraffin may be beneficial in patients with constipation due to the fast and sustained action, absence of habit-forming attributes on account of their respective mechanisms of action, and absence of side effects such as bloating and flatulence. Nevertheless, real world, prospective studies evaluating patient and physician perspectives about dependence and habit-forming properties of various laxative agents are warranted.

Data availability
Not applicable as this is a review article

Author contributions
Both authors conceptualized the review and provided critical feedback on the manuscript draft and revisions to shape the manuscript. Both authors have also approved the final version for submission

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References


I am still concerned by unsupported statements in this paper as exemplified by the highlighted section in this paragraph:

"Regular use of stimulant laxatives can cause dependency and cathartic colon albeit there is no direct evidence to support this claim. Prolonged use of stimulant laxatives leaves users prone to drug dependence, malabsorption, and electrolyte imbalance, and can damage the enteric nervous system, weakening colonic strength and even giving rise to melanosis coli. Moreover, long-term use of stimulant laxatives can damage the myenteric plexus, reducing responsiveness of the colon to intestinal contents and weakening colonic motor function. It is even possible to lose the ability to defecate spontaneously, a condition known as “laxative colon.” (These statements which seem to contradict the opening and closing sentences of this paragraph MUST be supported by direct evidence.) Though powerful and fast-acting, stimulant laxatives are not currently recommended for long-term use by elderly patients due to the adverse reactions, and only short-term or intermittent use is advised. Slow transit constipation should be treated with bulk-forming or osmotic laxatives. Cathartic colon though observed in some chronic users of stimulant laxatives, it is unclear whether this effect is related to their prolonged use.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: GI motility, FGIDs, microbiome.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.
Eamonn M. M. Quigley
Fondren IBD Program, Lynda K. and David M. Underwood Center for Digestive Disorders, Division of Gastroenterology and Hepatology, Houston Methodist Hospital and Weill Cornell Medical College, Houston, TX, USA

This is an important topic - patients often voice concerns that they will become "addicted" to treatments for constipation. However, this review has number of problems:

1. Far too much of the review is taken up with background information on constipation, in general. The focus should be on the issue of dependence.

2. I would contend that there is no good evidence that laxative injure colonic nerve or muscle - the authors mention this but do not provide evidence to support it. Usually statements like this are based on the study by Barbara Smith from decades ago which has been widely debunked.

3. Little or no evidence is provided to support the conclusions regarding whether some laxatives induce dependence or not. These statements must be rigorously supported.

4. I really do not see the role of two expert opinions here. If they are a part of the writing process why not just include as authors and leave it as that. We are now in the era of evidence-based and not eminence-based medicine.

Is the topic of the review discussed comprehensively in the context of the current literature?
No

Are all factual statements correct and adequately supported by citations?
No

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
No

Competing Interests: No competing interests were disclosed.
Reviewer Expertise: GI motility, FGIDs, microbiome.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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