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REVIEW

Understanding and treating refractory constipation

Gabrio Bassotti, Corrado Blandizzi

Gabrio Bassotti, Gastroenterology and Hepatology Section, Department of Medicine, University of Perugia, 06156 Perugia, Italy
Corrado Blandizzi, Division of Pharmacology and Chemotherapy, Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy
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Correspondence to: Gabrio Bassotti, Professor, Gastroenterology and Hepatology Section, Department of Medicine, University of Perugia, Ospedale Santa Maria della Misericordia, Piazzale Menghini 1, 06156 Perugia, Italy. gabassot@tin.it
Telephone: +39-75-5784423 Fax: +39-75-5847570
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Abstract

Chronic constipation is a frequently encountered disorder in clinical practice. Most constipated patients benefit from standard medical approaches. However, current therapies may fail in a proportion of patients. These patients deserve better evaluation and thorough investigations before their labeling as refractory to treatment. Indeed, several cases of apparent refractoriness are actually due to misconceptions about constipation, poor basal evaluation (inability to recognize secondary causes of constipation, use of constipating drugs) or inadequate therapeutic regimens. After a careful re-evaluation that takes into account the above factors, a certain percentage of patients can be defined as being actually resistant to first-line medical treatments. These subjects should firstly undergo specific diagnostic examination to ascertain the subtype of constipation. The subsequent therapeutic approach should be then tailored according to their underlying dysfunction. Slow transit patients could benefit from a more robust medical treatment, based on stimulant laxatives (or their combination with osmotic laxatives, particularly over the short-term), enterokinetics (such as prucalopride) or secretagogues (such as lubiprostone or linaclotide). Patients complaining of obstructed defecation are less likely to show a response to medical treatment and might benefit from biofeedback, when available. When all medical treatments prove to be unsatisfactory, other approaches may be attempted in selected patients (sacral neuromodulation, local injection of botulinum toxin, anterograde continence enemas), although with largely unpredictable outcomes. A further although irreversible step is surgery (subtotal colectomy with ileorectal anastomosis or stapled transanal rectal resection), which may confer some benefit to a few patients with refractoriness to medical treatments.

Key words: Chronic constipation; Laxatives; Medical treatment; Refractory constipation; Surgical treatment

Core tip: The majority of patients affected by chronic constipation can be managed by conventional therapeutic approaches. However, a subset of constipated patients displays a condition of actual refractoriness to standard medical treatment, even after careful clinical re-evaluation. These patients require more in-depth diagnostic evaluations to ascertain the underlying pathophysiological mechanisms, as well as more intensive, targeted and tailored therapeutic approaches, which may rely on the use of newly released drugs (enterokinetics, enteric secretagogues), rehabilitation (biofeedback), invasive measures (sacral neuromodulation, local injection of botulinum toxin, antegrade continence enemas) and surgical procedures (subtotal colectomy with ileorectal anastomosis or stapled transanal rectal resection).

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INTRODUCTION

Chronic constipation is one of the most frequent complaints faced by physicians during their daily activity[1] since a relatively large number of subjects in the general population (ranging from about 9% to more than 20%, depending on the geographical area) is or believe to be affected by constipation[2]. The costs for medical care are high for patients complaining of constipation, from childhood to adulthood[3]. Constipation is highly prevalent among female subjects[4] and it has been demonstrated that women with constipation have significantly higher medical care utilization and expenditures compared with women without constipation[5].

At present, constipated patients can be managed by a variety of medical therapeutic options that yield satisfying results in most cases[6,7]. However, a subset of constipated patients fails to benefit from conventional (and sometimes even intensive) treatments[8]. Although these subjects are often regarded as being resistant to therapy, their refractoriness may not be actual in nature but rather results from several factors related to the patient, the physician, or to their false beliefs and misunderstandings, as discussed in detail below. However, after careful re-evaluation, some patients are found to hold a condition of true refractory constipation, which is often a therapeutic challenge and deserves different and more tailored therapeutic approaches, up to demolitive surgical procedures.

The pharmacotherapy of refractory constipation is currently regarded as a challenging area, where the paucity of supportive clinical evidence and the persistence of unmet medical needs demand urgent attention in terms of focused clinical research and consensus by experts. Based on these considerations, the present article intends to review current information on the different approaches to the therapeutic management of refractory constipation, with the primary purpose of fostering the debate on this issue and generating new ideas for future clinical research on the employment of old and new drugs.

GENERAL CONSIDERATIONS

As anticipated above, to date, refractory constipation is suspected when a patient, fulfilling the standard diagnostic criteria for functional constipation[9] and lacking any alarm feature for organic conditions, fails to improve upon intake of a high-fiber diet and laxatives, usually polyethylene glycol (PEG) or other osmotic agents[10], the former being superior to lactulose in improving stool frequency, stool consistency and abdominal pain[11].

When facing a constipated patient complaining of resistance to the above therapeutic approaches, there are several issues which deserve careful consideration before labeling the patient as refractory to standard treatment and going on with further diagnostic evaluations and/or therapeutic interventions.

Reliability of information and patient compliance

This point could appear tautological in nature but, based on clinical experience, a certain number of patients are labeled as being "refractory" to medical treatment merely because of misunderstandings with the prescribing physician (*i.e.*, poor or altogether complete lack of communication, lack of acceptance of chronicity of the condition, unwillingness to use drugs long-term, scarce understanding of dose regimens, *etc.*) or as a result of misconceptions on the actual nature and relevance of constipation[12].

Patient expectations

It frequently happens that patients initially classified as refractory to treatment at a more accurate medical interview disclose that they discontinued drug intake after a very few days of therapy owing to the lack of effect onset. In these cases, it is common to find that these patients had not had explained to them that the basic treatment of constipation (*i.e.*, high-fiber diet, PEG or other osmotic agents) may require several days or weeks prior to achieving the effect onset or full effectiveness.

Poor basal evaluation

Patients with suspected refractoriness to medical treatment should be accurately re-evaluated for secondary forms of constipation, with particular regard for those associated with the use of drugs, a condition which can be unraveled only after repeated enquiries, focusing on specific drug classes. This issue is of particular relevance since some forms of drug-induced constipation (*e.g.*, that secondary to the use of opioid analgesics) can be managed by specific therapeutic approaches[13], whereas other (*e.g.*, that secondary to the use of antidepressants) can influence colonic motility to such a degree of severity[14,15] that they may require discontinuation of the offending drug or a switch to different drugs. Another sensitive and easy to miss condition, requiring a strong patient-physician relationship owing to the peculiarity of the issue, is a previous history (often only disclosed after several interviews) of physical or sexual abuse, found mainly in patients with symptoms of obstructed defecation (OD)[16].

Once ascertained that none of the above conditions can be called into play, the patient usually undergoes further diagnostic evaluations in an attempt to highlight specific pathophysiological mechanisms which might drive focused therapeutic interventions[17]. For this purpose, a further diagnostic step must include the evaluation of intestinal transit time[18], anorectal manometry[19] (complemented by the rectal balloon expulsion test[20]) and defecography[21]. Upper gastrointestinal (which might limit or preclude surgical procedures)[22,23] and colonic manometry (possibly with pharmacological testing in patients regarded as eligible for surgery, see below)[24,25] might also be performed.

These investigations usually allow allocation of con-

stipated patients into two major subgroups, comprising those with slow transit constipation (STC) and those with OD, even although it is not uncommon that some patients display both features at the same time[6].

The hallmark of patients with STC is delayed colonic transit, a condition which can be documented by a delayed distribution of radiopaque markers (or radionuclides) throughout the visceral lumen[26] and is characterized by a severe impairment of colonic motor activity that, in some instances, can be almost absent or progress up to a true picture of colonic inertia[27].

In patients with OD, the main pathophysiological features are basically related to rectoanal dysfunction, including the inability to relax or the paradoxical contraction of the pelvic floor while attempting to defecate[28], the lack of rectal motor activity[29], and an abnormal rectal sensitivity[30], although anatomical abnormalities (particularly rectocele and rectal intussusceptions) can also play a role in this setting[31].

A condition of apparent refractoriness to drug therapy in these two subgroups of patients may thus be underpinned by different pathophysiological grounds that may deserve different medical and/or non-medical (surgical, behavioral) approaches.

THERAPEUTIC MANAGEMENT OF REFRACTORY PATIENTS: PHARMACOLOGICAL APPROACH

In patients with true unresponsiveness to first-line osmotic laxatives, a combination approach can be used, introducing stimulant laxatives such as bisacodyl and sodium picosulfate. These agents are able to elicit bowel propulsion[32], as well as to exert antiabsorptive and secretory effects on the enteric mucosa, and appear to be quite safe even in the long-term[6]. Initially, these drugs should be employed as rescue agents when patients do not defecate after two-three days while using osmotic agents[33], although patients should be encouraged to persist for longer periods on osmotic laxatives before adding a stimulant agent. Of note, controlled clinical studies on stimulant laxatives have been published only in recent years and they have documented both the effectiveness of these agents and their favorable impact on disease-related quality of life, even in the medium-term[34-36]. Moreover, the supposed damaging actions of stimulant laxatives on enteric neural structures have not been confirmed by means of modern techniques[37]. Nevertheless, data on the long-term use of stimulant laxatives, either alone or in combination with osmotic laxatives, are lacking. Moreover, even laxative combinations may not be sufficient to achieve a satisfactory and steady resolution of constipation. Therefore, pharmacological research in this area has moved towards drugs that might be able to increase or restore the propulsive activity of the large bowel, in both the short- and long-term.

In this context, a promising drug, tegaserod, endowed with enteric prokinetic effects resulting from its partial agonistic activity on 5-HT$_4$ serotonin receptors, was withdrawn from the drug market due to concerns about possible adverse cardiovascular effects[38] and the research in this area shifted towards the development of effective drugs devoid of cardiovascular toxicity. Along this line, prucalopride, a thoroughly studied prokinetic drug with particular regard for its cardiovascular safety, has been recently introduced in Europe for treatment of constipated women not responding to conventional first-line regimens[39]. This compound is a potent and selective 5-HT$_4$ receptor full agonist endowed with enterokinetic properties[40], able to accelerate the gastrointestinal and colonic transit in constipated patients without abnormal rectal evacuatory dysfunction[41], probably as a result of an increase of high-amplitude propulsive contractions[42]. Controlled studies in patients (mostly women) unresponsive to standard medical regimens have shown that this drug (at the dose of 2 mg/d in adults and 1 mg/d in the elderly) can be effective in relieving constipation both in the short- and long-term[43-47], even in patients from non-Western countries[48]. Of note, although in clinical trials prucalopride appeared to be less effective in patients with symptoms of OD[49], a recent study conducted under real-life conditions showed its efficacy even in this setting (with similar percentages to those reported in clinical trials)[50], suggesting that this drug can be regarded as an additional therapeutic tool for refractory patients to provide them with an additional chance to manage their complaints[51]. Moreover, a recent report showing that prucalopride can be as effective as PEG in resolving constipation[52] allows the hypothesis that these two drugs, known to act in different ways and not burdened by serious adverse effects, might be (as already observed empirically in our routine clinical experience) combined advantageously to achieve positive therapeutic results in refractory patients.

With the recent introduction of enteric secretagogues, other therapeutic tools have been made available. The first drug of this class to be approved (currently in USA, but not in Europe) was lubiprostone, a fatty acid structurally related to prostaglandin E$_1$ which acts primarily by activating apical ClC-2 chloride channels in enteric epithelial cells[53]. This compound has been shown to improve constipation (at a dose of 24 μg twice a day)[54-57], even in the long-term[58]. More recently, linaclotide, a guanylate cyclase-C agonist, has been approved in some European countries for treatment of patients with chronic constipation[59]. The activation of guanylate cyclase-C by linaclotide results in an increase in both intracellular and extracellular levels of cyclic guanosine monophosphate, which then stimulates chloride and bicarbonate secretion from enteric epithelial cells into the bowel lumen, leading to an increment of luminal fluids and transit acceleration[59]. This drug (at a dose of 145 μg once daily) has been found to be effective in the short-term for treatment of chronic constipation[60-62], as also stressed in a recent meta-analysis[63]. Since both lubiprostone and linaclotide display different mechanisms of action compared to laxatives or prokinetics, it is likely that their combination with other drugs (for instance, stimulant laxatives

or prucalopride) might help to improve symptoms in patients with refractory constipation. This represents an important medical need which should be addressed by means of specific clinical trials exploring the suitability of drug combinations.

Other pharmacological options

There is evidence from both controlled and non-controlled clinical trials that colchicine, an old drug still available for the treatment of gout at the dose of 0.6 mg three times per day, can be effective (at least in the short-term) to manage constipated patients, including those refractory to other therapeutic approaches[64-66]. Unfortunately, colchicine has a narrow therapeutic index which is associated with underestimated toxicity and frequent and serious adverse effects[67] that confines its use to extremely selected cases in whom no other options, including surgery (see below), are viable.

The inhibitor of ileal bile acid transporter A3309, after having displayed some benefit in a small pilot clinical study[68], was also shown to be effective in accelerating colonic transit[69] and in treating constipated patients at a daily dose of 10 mg in phase 2 studies[70]. Based on these preliminary experiences, further studies are clearly needed to confirm both the efficacy and safety profile of A3309 in chronic refractory constipation.

An interesting small phase 2 study has suggested that the cholinesterase inhibitor pyridostigmine (60-120 mg three times per day), available in the pharmaceutical market for many years, is able to accelerate colonic transit and improve symptoms in constipated patients with type 2 diabetes mellitus[71]. Since this drug is widely available and (in contrast to newer drugs) relatively inexpensive, further studies are warranted to explore its suitability in idiopathic chronic constipation.

THERAPEUTIC MANAGEMENT OF REFRACTORY PATIENTS: OTHER THERAPEUTIC APPROACHES

In patients with primary defects involving defecatory disorders, particularly OD, currently available medical regimens (although often used as first-line approaches) can be disappointing. Indeed, these patients have been shown to benefit more from behavioral and retraining techniques[72-74], particularly biofeedback[75,76], than drug therapies. Although the efficacy of biofeedback has been advocated for a long time[77], controlled trials have only in recent years shown its efficacy in the treatment of constipation associated with OD[78-83], even in elderly patients[84], although some authors have reported a limited efficacy in the long-term when compared to botulinum toxin[85]. Interestingly, there seems to be no difference among the various available biofeedback techniques in terms of efficacy[86]. However, notwithstanding the good results achieved in the treatment of OD with better therapeutic performances than those of laxatives, biofeedback still appears to have a quite limited role in routine clinical practice, likely because of the scarce appreciation of the benefits achievable with pelvic floor retraining and the limited availability of experienced trainers. Electrogalvanic stimulation, although effective in individual OD patients[87,88], has not been formally studied in controlled trials.

In selected OD patients, local injections of botulinum toxin have been attempted with a certain success, although the evidence remains very scarce and is based on uncontrolled studies[89,90]. Owing to such limitations, this approach cannot be proposed as a standard treatment but should be restricted to patients unresponsive to any other available medical therapy before considering a surgical approach or be employed only for research purposes.

When considering surgical strategies, one should always keep in mind that surgery is usually an irreversible option and that the surgical approach *per se* may introduce or add further damage to an already malfunctioning intestine. Thus, the ideal surgical approach should be aimed at achieving the best results with the minimum of invasiveness. Accordingly, the following paragraphs address the surgical options currently employed for the management of refractory constipated patients.

There is limited experience in adults with antegrade continence enemas (the so-called Malone procedure), which is a relatively invasive surgical procedure proven to be quite successful in children[91] that seems to work in approximately 50% of patients undergoing this procedure[92,93]. The theoretical advantage associated with this technique is that, should the colonic function be recovered, it would be possible to restore the intestinal continuity without a need for resections. However, in current practice this goal can be rarely, if ever, pursued.

A more draconian approach, which can be considered in refractory STC patients when pelvic floor dysfunction and relevant upper gastrointestinal motor abnormalities have been excluded[22,94,95], is subtotal colectomy with ileorectal anastomosis[96]. Provided that the above criteria are fulfilled, this technique offers interesting long-term benefits to patients[97]. Conversely, the results are poorer when such criteria are not duly fulfilled[98]. Of course, postoperative complications (*i.e.*, small bowel obstruction, wound infection, anastomotic leakage) may occur as with any surgical intervention, the most frequent being small bowel obstruction[99]. However, most of these complications can be managed in a conservative manner and they usually do not require repeated surgical interventions.

In recent years there has been a renewed interest in treating refractory OD patients by a new surgical approach, designated as stapled transanal rectal resection[100,101], conceived for correcting rectal intussusceptions and large rectoceles (usually at least 5 cm in diameter). Although this procedure may confer benefits to some patients over the short-term period, its efficacy is not superior to that achievable with osmotic laxatives[102], it is burdened by several complications (*e.g.*, pain, bleeding, bowel perforation, fistulas, pelvic sepsis, peritonitis)[103,104] and the results over the long-term period appear to be disappointing even in "ideal" patients[105].

The interesting (although collateral) aspect of surgical procedures is the availability of full-thickness colonic or rectal tissue specimens, which are very useful for pathological investigations[106,107]. Indeed, morphological analyses have the potential of disclosing useful information for understanding the pathophysiological bases of severe constipation[108,109].

Another approach that can be attempted in patients with refractory constipation deals with sacral nerve stimulation (or sacral neuromodulation). This technique is based on the physiological principle that the presence of bioelectrical activity in one neural pathway can modulate a pre-existing activity in another pathway through synaptic interactions. It is carried out by percutaneous placement of an electrode in the third sacral foramen and implantation of a stimulating device under the skin in the buttocks[110]. Although it may be effective in individual patients, the overall efficacy of sacral nerve stimulation is limited and unpredictable[111], with positive results reported in 40%-100% of cases[112]. Therefore, it requires additional well conducted prospective studies to assess its exact role and safety in the management of constipated patients as there is a significant underreporting of the incidence of untoward events associated with this technique[113].

CONCLUSION

To date, the refractoriness of constipation to medical treatments is still a significant issue. Current literature on this topic suggests that a number of pharmacological or non-pharmacological therapeutic options can be offered to patients with true constipation refractory to first-line conventional treatments. However, for the majority of such options, the available supportive evidence is scanty and the clinical outcomes are often not satisfactory. A number of different factors are likely to contribute to these deficiencies, particularly: anecdotal or heterogeneous findings in a limited number of patients; data stemming from randomized clinical trials which may not meet the needs of real clinical life and are usually not suitable for designing tailored interventions based on the pathophysiology of individual patients; and scarcity or lack of information on the possible efficacy and, most importantly, safety of long-term treatments. Besides these arguments, both the literature and daily clinical practice clearly point out that, in a proportion of patients, the refractoriness of their constipation cannot be overcome even with second-line pharmacological interventions and that these subjects become candidates for third-line, more aggressive and/or demolitive, non-pharmacological/surgical therapeutic options which do not ensure favorable outcomes while posing relevant safety issues. Urgent and intensive clinical research efforts are therefore needed to address and resolve these problems. Besides attempts of identifying and developing novel drugs endowed with innovative mechanisms of actions, consistent efforts should be focused on the implementation of improved treatment regimens based on currently available old and new drugs to pursue optimized benefit/risk ratios and long-term maintenance of constipation relief. In this context, attention should be paid to drug combination and/or alternating administration regimens which, while taking advantage of different mechanisms of action, would prevent excessive dose increments of the individual drugs and/or the loss of therapeutic effectiveness on long-term exposure as a possible consequence of tolerance. In particular, based on preliminary evidence and experience in daily clinical practice, combinations of enterokinetics with laxatives (either osmotic or stimulant), enterokinetics with secretagogues, different secretagogues, and even non-pharmacological interventions with enterokinetics or secretagogues might be worthy of validation by clinical research and subsequent consensus agreement by expert panels.

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