

Chronic Idiopathic Constipation in Adults: A Review on Current Guidelines and Emerging Treatment Options

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Abstract: Chronic idiopathic constipation (CIC) is a common functional bowel disorder characterized by difficult, infrequent, and/or incomplete defecation. It has a great impact on the quality of life and on health care system and represents a heavy economic burden. The diagnosis is based on symptoms, classified by the Rome IV criteria. The aim of this review was to evaluate the current therapeutic guidelines for adult CIC and highlight new emerging treatments. In detail, European, French, Spanish and Korean guidelines have been identified and compared. Osmotic laxatives, and in particular polyethylene glycol, represent the first-line therapeutic approach. Stimulant laxatives are recommended as a second-line therapy. Pelvic floor rehabilitation is recommended in patients with ano-rectal dyssynergia. In patients who fail to improve with pharmacological therapies sacral nerve stimulation is considered as last chance before surgery. Surgical approach has however limited indications in selected cases. Inertia coli refractory to any approach and obstructed defecation are two subtypes which can benefit from surgery. Among emerging agents, prucalopride, a prokinetic agent, is recommended as a second-line treatment in refractory CIC patients. In addition, the secretagogues linaclotide and plecanatide and the bile acid transported inhibitor elobixibat can be effective in patients not responsive to a second-line therapeutic regimen, although they are not worldwide commercially available.

Keywords: chronic idiopathic constipation, guidelines, osmotic laxatives, pelvic floor rehabilitation, prokinetics, secretagogues

Introduction

Chronic idiopathic constipation (CIC) is a common functional disorder associated with an impaired quality of life (QoL),¹ with a negative impact on social and professional life, and with a heavy economic burden.^{2–5} CIC affects about 10–17% of the world population, with a higher prevalence among females and elderly people,^{6,7} and may cause disabling symptoms.

The most widely used diagnostic criteria to assess CIC are the Rome IV Criteria.⁸ In fact, the diagnosis of constipation in the clinical setting is mainly made on the basis of symptoms alone. Routine extensive diagnostic testing is not recommended for chronic constipation. Objective testing can be suggested to rule out organic disease, in presence of alarm symptoms, or in refractory cases to identify underlying differential diagnoses.⁹

A considerable amount of CIC patients in different countries use conventional laxatives, and their use is related to increasing age, symptom frequency, and

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duration of constipation. In particular, osmotic laxatives represent the first line in the treatment of CIC.^{10–12} On the other hand, the increased prevalence of constipated patients refractory to traditional laxatives led to the development of new emerging therapeutic resources. Several guidelines aimed at improving the diagnostic and therapeutic management of CIC have been published. The purpose of this review was to evaluate the current guidelines on CIC in adults and the emerging therapeutic options of this functional disorder. Several guidelines aimed at improving the therapeutic management of CIC have been published, and will be discussed in this article. Even though consensus documents and positions papers are also available, these are source of conflicting results and cannot be considered as guidelines. Therefore, the present review will focus on the available guidelines and the emerging treatment options for CIC patients.

Methods

Search Strategy

A comprehensive online search of Medline and the Science Citation Index was made using the keywords “colon”, “constipation”, “chronic constipation”, “treatment”, “adults”, “laxatives”, “new modalities”, “guidelines”, in various combinations with the Boolean operators and, or, and not. Only articles related to human studies were included, and manual cross-referencing was performed. Articles published in English between January 1960 and July 2021 were selected, but a search in non-English languages and among journals and books older than 1960 was also performed in our Universities and other libraries.

Comparison of Current Guidelines for Treatment of CIC

A thorough literature review revealed that only four guidelines for CIC have to date been published: the Korean,¹³ the Spanish,¹⁴ the French,¹⁵ and the European.¹⁶ Tables 1–3 show the methods of assessment in these guidelines.

Lifestyle, Diet, Exercise

Results are summarized in Table 4. The effect of lifestyle modifications was taken into consideration only by French and European guidelines. The French ones focused on adopting basic behaviours in order to facilitate defecation, such as daily presentation to the toilet, assuming an optimal position for defecation, in a calm and relaxed

environment. However, these suggestions were approved just as an Expert Recommendation. Also, European guidelines reported a positive effect of an overall lifestyle modification. A strong recommendation is unanimously suggested on the latter point, even though based on studies of moderate quality; positive effects were documented not only on constipation but also on general well-being.¹⁷

The French guidelines report as an Expert Recommendation that foods other than fiber (ie, milk, cheese, meat, rice, eggs, etc) has not shown benefits on constipation and that overeating does not show benefits, apart from undernourished patients, ie, anorexic patients. In addition, Korean, Spanish and French guidelines, based on scattered evidence,^{18,19} report that dried plums have a better effectiveness than psyllium in mild and moderate constipation.

The increase of fluid intake alone does not have a positive or negative effect on constipation. An increase in fluid intake has a positive effect only in dehydrated subjects and in people consuming a high fiber diet. French guidelines report a significant effect drinking at least one litre a day of water rich in magnesium.²⁰

Concerning the effect of exercise on constipation, the French and European guidelines did not identify a positive or negative effect, while the Spanish and Korean guidelines reported a positive effect, but with low scientific evidence and with a weak recommendation, because low physical activity is associated with constipation. It is worth noting that studies on the effectiveness of physical exercise in constipated patients provided variable results on intestinal transit time. As a matter of fact, most studies on the effect of diet and lifestyle changes are flawed by methodological biases; therefore, well-designed studies involving larger number of patients are mandatory.

Drugs, Probiotics

These are summarized in Table 5. All guidelines agree that osmotic and bulking laxatives should be used as first-line therapy, due to their effectiveness, low cost and rare adverse reactions, especially for patients with a low-fiber diet. All guidelines agree on the positive effect of a high fiber diet and on the importance of combining it with an increased fluid intake. Korean guidelines assert that this is an optimal initial strategy, due to the low cost and low risk of adverse reactions. However, since some patients may experience worsening symptoms, especially an increase in abdominal pain and bloating, the French and Korean guidelines recommend to slowly increase the amount of

Table 1 Methods Used to Assess Evidence and Recommendation in the Different Guidelines

| | European GL | French GL | Spanish GL | Korean GL |
|---------|--|--|--|---|
| Methods | Level of evidence and strength of recommendation were rated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE, Table 2). All statements were subjected to a Delphi consensus process | Depending on the level of evidence of the studies on which they were based, the recommendations have a degree of variability, listed from A to C according to the scale proposed by the Haute Autorité de Santé (HAS) (Table 3). Variability provides a measure of how accurately any individual score or sample represents the entire population. References cited in the manuscript have contributed towards the development of grade recommendations that rely on all available references on the topic for analysis, on their readability and applicability according to Delphi methodology. In the absence of sufficient scientific data, the recommendations were based on a professional recommendation (Expert Recommendation) | Grading of Recommendations, Assessment, Development and Evaluation (GRADE, Table 2) was used to rate the level of evidence and recommendation. | AGREE II was used to evaluate the quality of the studies for adaptation. Grading of Recommendations, Assessment, Development and Evaluation (GRADE, Table 2) was used to rate the level of evidence (A-high quality evidence, B-moderate quality evidence, C-low quality evidence) and strength of recommendation 1 (strong) or 2 (weak). The results were subjected to a Delphi consensus process. |

Table 2 Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

| Item | Definition |
|------------------------------|---|
| Level of evidence | |
| A. High-quality evidence | Further research is unlikely to change our confidence in the estimate of effect. Consistent evidence from the RCTs without important limitations or exceptionally strong evidence from observational studies. |
| B. Moderate-quality evidence | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies. |
| C. Low-quality evidence | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws, or indirect evidence, or expert's consensus. |
| Strength of recommendation | |
| 1 -Strong recommendation | Recommendation can apply to most patients in most circumstances. |
| 2 -Weak recommendation | The best action may differ depending on circumstances or patient or society values. Other alternatives may be equally reasonable |

Table 3 French Guidelines Levels of Evidence

| | |
|---------------------|---|
| Level of evidence A | Data derived from multiple randomized clinical trials or meta-analyses |
| Level of evidence B | Data derived from a single randomized clinical trial or large nonrandomized studies |
| Level of evidence C | Consensus of the expert and/or small studies, retrospective studies and registries |

Table 4 Recommendations and Evidence of Lifestyle Changes, Dietary Suggestions, and Exercise for Chronic Constipation According to the Different Guidelines

| | European GL | French GL | Spanish GL | Korean GL |
|--------------------------|---|---|--|--|
| Lifestyle | Overall lifestyle modifications have a positive effect <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • Agreement: 100% | Behavioural rules (daily presentation to the toilet, optimal position on the toilet, environmental conditions) <ul style="list-style-type: none"> • Positive effect • Expert Recommendation | NA | NA |
| Diet | Increase of fiber intake has positive effect, especially if combined with fluid increase <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak • Agreement 92% | Increase of fiber intake has positive effect. Dried plums have a better efficacy than psyllium in mild to moderate constipation <ul style="list-style-type: none"> • Evidence II, Grade B • Consumption of foods other than fiber: not positive not negative effect • Expert Recommendation • Overeating has positive effect only in undernourished patients • Expert Recommendation | Consuming high fiber foods has a positive effect <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong | Dietary fiber has a positive effect. Evidence: C <ul style="list-style-type: none"> • Recommendation: 2 • Experts' agreement: completely agree: 27.6%; mostly agree: 72.4% • It can be an initial strategy • Evidence: C. • Recommendation: 2. • Experts' agreement: completely agree: 35.7%; mostly agree: 60.7%; partially agree: 3.6% |
| Increase of fluid intake | Positive effects only in dehydrated patients <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Strong • Agreement: 100% | Positive effect in dehydrated patients or in those assuming fiber <ul style="list-style-type: none"> • Expert Recommendation • Positive effect of water rich in magnesium • Level II, Grade B | Positive effect only if associated with fiber supplement <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak | Positive effect in dehydrated patients or when bulking agents are added <ul style="list-style-type: none"> • Evidence: C • Recommendation: 1 • Experts' agreement completely agree: 37.0%; mostly agree: 55.6%; partially agree: 7.4% |
| Exercise | Not positive not negative effect on constipation <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • Agreement: 92% | Not positive not negative effect on constipation <ul style="list-style-type: none"> • Expert Recommendation | Positive effect <ul style="list-style-type: none"> • Evidence: Low • Recommendation weak | Positive effect. <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree: 7.1%; mostly agree: 67.9%; partially agree: 14.3%; mostly disagree: 10.7% |

Abbreviation: NA, not assessed.

dietary fiber. All guidelines agree on their efficacy in CIC patients; the European guidelines report a good evidence on constipation only for soluble fibers, such as psyllium. European, Spanish and Korean ones report psyllium as the preferred one. Spanish guidelines offer methylcellulose as an alternative, even though for semi-synthetics bulking agents the quality of scientific evidence is lower.²¹

French and Korean guidelines start suggesting the use of magnesium as first drug in CIC patients, though it must be carefully evaluated in patients with impaired renal

function, for the risk of hypermagnesemia. The European, French and Spanish guidelines reported that there are many studies about polyethylene glycol (PEG), which effectiveness is higher than lactulose. Korean guidelines in general stated that PEG is more effective than other laxatives in elderly patients, with very few adverse reactions. However, European, Spanish and Korean guidelines report a positive effect of lactulose in chronic constipation and its safety in chronic use. To sum up PEG is the first choice, especially in elderly population, as also

Table 5 Recommendations and Evidence of Drugs/Probiotics Suggested for Chronic Constipation According to the Different Guidelines

| | European GL | French GL | Spanish GL | Korean GL |
|---------------------|--|--|--|---|
| Osmotic laxatives | <p>Positive effect, PEG is superior to lactulose.</p> <ul style="list-style-type: none"> • Evidence: Strong • Recommendation: Strong • Agreement: 100% <p>Lactulose is effective</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak • Agreement: 100% | <p>Positive effect as first line therapy</p> <ul style="list-style-type: none"> • Level II, Grade B • Magnesium: Positive effect • Level I, Grade A • PEG is more effective than lactulose • Level I, Grade A | <p>PEG is recommended</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: strong • Lactulose is recommended • Evidence: Low • Recommendation: Strong • PEG is preferred over lactulose • Evidence: Moderate • Recommendation: weak | <p>Magnesium: Positive effect, even if there are few studies</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: I • Experts' agreement: completely agree: 57.1%, mostly agree: 39.3%, partially agree: 3.6% <p>Magnesium: careful attention in patients with impaired renal function for the risk of hypermagnesemia.</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: I • Experts' agreement: completely agree: 44.4%, mostly agree: 51.9%, partially agree: 3.7% <p>Positive effect of nonabsorbable carbohydrates, such as sorbitol and lactulose.</p> <ul style="list-style-type: none"> • Evidence: B • Recommendation: I • Experts' agreement: completely agree: 53.9%, mostly agree: 46.1% <p>Long-term administration of nonabsorbable carbohydrates is allowed because serious adverse reactions are rare.</p> <ul style="list-style-type: none"> • Evidence: A • Recommendation: I • Experts' agreement: completely agree: 39.3%, mostly agree: 60.7% <p>Positive effect also in elderly patients.</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree: 10.7%, mostly agree: 82.2%, partially agree: 7.1% <p>Positive effect of PEG</p> <ul style="list-style-type: none"> • Evidence: A • Recommendation: I • Experts' agreement: completely agree: 73.1%, mostly agree: 26.9% <p>In long-term administration of PEG serious adverse reactions are rare.</p> <ul style="list-style-type: none"> • Evidence: A • Recommendation: I • Experts' agreement: completely agree: 50.0%, mostly agree: 50.0% <p>PEG have positive effect also in elderly patients</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree: 23.1%, mostly agree: 69.2%, partially agree: 7.7% |
| Bulking agents | <p>Positive effect as first line therapy, as psyllium, are preferred to insoluble ones, because of less adverse events</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • Agreement: 100% | <p>Positive effect as first line therapy</p> <ul style="list-style-type: none"> • Level II, Grade B | <p>Positive effect. Psyllium is suggested as a first line treatment</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: weak <p>Methylcellulose is recommended as an alternative</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Strong | <p>Positive effect as first line treatment.</p> <ul style="list-style-type: none"> • Evidence: A • Recommendation: I • Experts' agreement: completely agree: 70.4%, mostly agree: 29.6% <p>Bulking agents can be effective in patients with inadequate fiber intake.</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree: 15.4%, mostly agree: 80.8%, partially agree: 3.8% |
| Lubricant laxatives | <p>NA</p> | <p>Positive effect as second line therapy</p> <ul style="list-style-type: none"> • Level III, Grade C | <p>Positive effect of paraffin oil and docusate sodium</p> <ul style="list-style-type: none"> • Experts recommendation | <p>NA</p> |

(Continued)

Table 5 (Continued).

| | European GL | French GL | Spanish GL | Korean GL |
|---------------------|---|---|---|---|
| Stimulant laxatives | <p>Positive effect. Bisacodyl is well-tolerated</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • Agreement: 100% <p>Sodium picosulfate is efficacious and well tolerated</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • Agreement: 100% <p>Anthraquinones are effective</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak • Agreement: 100% <p>Anthraquinones are well tolerated</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Weak • Agreement: 100% | <p>Positive effect as second line therapy</p> <ul style="list-style-type: none"> • Level II, Grade B <p>They can be proposed if patients have not had stools for several days</p> <ul style="list-style-type: none"> • Level III, Grade C | <p>Positive effect, recommended as rescue therapy</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong <p>Their use is suggested in patients who have not responded to bulking and osmotic laxatives</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: weak | <p>Positive effect as second line therapy.</p> <ul style="list-style-type: none"> • Evidence: B • Recommendation: 2 • Experts' agreements: completely agree: 22.2%, mostly agree: 70.4%, partially agree: 7.4% |
| Local laxatives | <p>Positive effect of rectal suppositories and rectal enemas</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Strong • Agreement: 100% | <p>Positive effect. CO2-releasing suppositories are a first line approach in outlet obstruction constipation and in association with biofeedback</p> <ul style="list-style-type: none"> • Level I, Grade A | <p>Positive effect of cleansing enemas, commercial enemas and/or glycerol or bisacodyl suppositories.</p> <ul style="list-style-type: none"> • Expert recommendation | <p>Positive effect of enemas.</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree: 21.4%, mostly agree: 60.7%, partially agree: 10.7%, mostly disagree: 3.6% and not expressed opinion: 3.6% <p>Enemas should be used carefully because there are no standardized guidelines, and it may cause complications</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree: 42.3%, mostly agree: 38.4%, partially agree: 15.4%, completely disagree: 3.9% |

| | | | | |
|---|---|--|---|--|
| <p>Prokinetics</p> | <p>Positive effect, as second line treatment of prucalopride</p> <ul style="list-style-type: none"> • Evidence: High • Recommendation: Strong • Agreement: 100% <p>Acetylcholinesterase inhibitors (dostigmine, neostigmina) exert prokinetics effect on gut, but they are currently not used in constipation therapy</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Weak • Agreement: 100% <p>Peripherally Acting μ-Opioid Receptor Agonists (PAMORA) are effective in the management of opioid induced chronic constipation</p> <ul style="list-style-type: none"> • Evidence: High • Recommendation: Strong • Agreement: 100% <p>PAMORA may potentially be effective, also in constipation not caused by opioids</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak • Agreement: 100% | <p>Positive effect. Prucalopride (2mg/day) is indicated as second line both in women and also men</p> <ul style="list-style-type: none"> • Level I, Grade A | <p>Positive effect. Prucalopride is a treatment option in women</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: weak | <p>Positive effect of Prucalopride (2mg/day)</p> <ul style="list-style-type: none"> • Evidence: A • Recommendation: I • Experts' agreement: completely agree: 57.7%, mostly agree: 42.3% |
| <p>Secretagogues</p> | <p>Positive effect as second line treatment. Linaclotide is effective and safe in the chronic constipation and IBS-C. Lubiprostone is also effective, but has limited availability in Europe</p> <ul style="list-style-type: none"> • Evidence: High • Recommendation: Strong • Agreement: 92% | <p>Not available in France when guidelines had been published</p> <ul style="list-style-type: none"> • No practical recommendations | <p>When guidelines had been published Lubiprostone was not marketed in Spain and Linaclotide was approved in Spain only for the treatment of irritable bowel syndrome with constipation (IBS-C)</p> | <p>Positive effect of Lubiprostone</p> <ul style="list-style-type: none"> • Evidence: A • Recommendation: not applicable • Experts' agreement: completely agree: 29.2%, mostly agree: 58.3%, partially agree: 4.2% and not expressed opinion: 8.3% <p>Linaclotide, may be effective in patients refractory to conventional laxatives.</p> <ul style="list-style-type: none"> • Evidence: B • Recommendation: not applicable • Experts' agreement: completely agree: 71.4%, partially agree: 14.3%, and not expressed opinion: 7.1% |
| <p>Modulation of microbiota (microbiota transfer or probiotics)</p> | <p>Insufficient evidence to recommend fecal microbiota transfer or probiotics for routine treatment of functional constipation, (even if some positive effects were described)</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak • Agreement: 100% | <p>Not positive not negative effect of probiotics, not recommended</p> <p>Expert: Recommendation</p> | <p>NA</p> | <p>Positive effect of probiotics in conjunction with other drugs.</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree (14.8%), mostly agree (63.0%), partially agree (18.5%), mostly disagree (3.7%) |

Abbreviation: NA, not assessed.

suggested by other authors.²² Osmotic laxatives are also recommended by French and Korean guidelines in addition to a moderate increase of dietary fiber in order to avoid abdominal bloating and pain.

Lubricant laxatives are suggested only in French guidelines as a second-line therapy; they are contraindicated in patients with dysphagia for the risk of lipoid pneumonia, and a possible malabsorption of fat-soluble vitamins must be considered.²³ Also, Spanish guidelines report a positive effect but without sufficient scientific evidence to recommend lubricant laxatives.

Stimulant laxatives are recommended by all the guidelines as a second-line therapy. The European guidelines recommend bisacodyl and sodium picosulfate, with moderate level of evidence, whereas a weak recommendation is made on the use of anthraquinones. Stimulant laxatives are usually well tolerated, the most common adverse effects being abdominal pain and diarrhoea.²⁴ Anthraquinones can cause *pseudomelanosis coli*, but no study demonstrated their association with a higher colon cancer risk.²⁵

By considering topical laxatives, all guidelines agree on their effectiveness. These formulations are strongly recommended because they have been traditionally used for a long time with good results and scarce adverse reactions. French guidelines confirm the recommendation of CO₂-releasing suppositories, alone and in association with biofeedback, with some scientific evidence in patients with constipation and dyschezia.^{26,27}

All guidelines recommend prokinetics, and particularly prucalopride (since 2015 also for men), as a second-line therapy. The Spanish guidelines, however, recommend it only in women, referring to previous studies. European guidelines also consider PAMORA (peripherally acting opioid agonists) that are strongly recommended in patients affected with opioid induced constipation, but may be also recommended in patients with constipation due to other causes (low level of evidence, weak recommendation).

European guidelines report a positive effect of secretagogues; at present, however, linaclotide in Europe is strongly recommended only in constipation-predominant irritable bowel syndrome, and lubiprostone is not available in most countries. Because of this, French and Spanish guidelines do not recommend secretagogues. Korean guidelines also do not recommend lubiprostone and linaclotide, because they are not available and there are still few studies on eastern patients. Moreover, Korean guidelines deal with the bile acid transporter inhibitor,

elobixibat, which is not yet available in most countries (see below).

Regarding the use of probiotics or fecal transplant as microbiota modulating agents, the French guidelines do not suggest any use, since significant actions were not reported with this approach.

Also, European guidelines state that there is no sufficient scientific evidence to recommend probiotics, although some positive effects have been observed in some studies, such as acceleration of intestinal transit time and improvements in stool frequency. Conversely, Korean guidelines recommend the use of probiotics together with other medical drugs, such as laxatives, due to a possible synergic action.

Non Pharmacological and Surgical Therapies

These are shown in Table 6. Transanal irrigation,²⁸ considering the low risk of perforation, is recommended by European guidelines in patients in whom laxative treatment failed, as positive results were reported by uncontrolled studies, although there is a low level of evidence and a low grade of recommendation. The French guidelines recommend transanal irrigation as a second-line therapy in patients with constipation resulting from neurological diseases and also (only as an expert recommendation) in constipated patients without neurological diseases after the failure of conservatives treatments.

Only French guidelines take into consideration the use of botulinum toxin, which showed good efficacy in the treatment of distal constipation, for its effect in decreasing resting anal pressure and improving puborectalis relaxation during straining with minimal adverse effects.

Concerning pelvic floor rehabilitation, the European guidelines report its positive effect, with good evidence, recommending it in subjects with constipation. The French guidelines also report a positive effect in patients with dyssynergia, but they distinguish the various parts of pelvic floor rehabilitation (eg, electrostimulation, kinesitherapy, biofeedback training and volumetric rehabilitation), asserting that biofeedback²⁹ is the most effective. The Spanish guidelines take into account only biofeedback, which, in dyssynergic patients, is more effective than laxatives or other treatments.³⁰ Comparing the different way of performing biofeedback (ie, manometric, electromyographic, verbal) no difference of effectiveness has been reported.³¹ The Korean guidelines state that

Table 6 Recommendation and Evidence of Non-Pharmacological and Surgical Therapies Suggested for Chronic Constipation According to the Different Guidelines

| | European GL | French GL | Spanish GL | Korean GL |
|---|--|--|--|---|
| Transanal irrigation | <p>Positive effect in patients where laxatives failed.</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak • Agreement: 100% | <p>Positive effect in patients with neurological disease</p> <ul style="list-style-type: none"> • Level I, Grade A • It may be proposed also in the absence of neurological diseases <p>Expert Recommendation</p> | NA | NA |
| Botulinum toxin | NA | <p>Positive effect in distal constipation</p> <ul style="list-style-type: none"> • Level II, Grade B | NA | NA |
| Pelvic floor rehabilitation with biofeedback | <p>Positive effect.</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • agreement: 100% | <p>Positive effect in patients with dyssynergia. Among the various techniques, biofeedback is the most effective</p> <ul style="list-style-type: none"> • Level I, Grade A | <p>Biofeedback has positive effect in people with dyssynergia</p> <ul style="list-style-type: none"> • Evidence Low • Recommendation: strong | <p>Biofeedback has positive effect in people with dyssynergic anorectal and pelvic floor muscles</p> <ul style="list-style-type: none"> • Evidence: A • Recommendation: I • Experts' agreement: completely agree (55.6%), mostly agree (44.4%) <p>Biofeedback therapy may be applied repeatedly, safely and can reduce the usage of laxatives</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree (34.6%), mostly agree (65.4%) |
| Pelvic floor rehabilitation without biofeedback | <p>Positive effect in chronic constipated patients non-responsive to standard care</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak • Agreement: 100% | NA | NA | NA |
| Stimulation techniques | <p>Positive effect of continuous direct nerve stimulation or sacral neuromodulation (SNS/SNM). It is the least invasive surgical option after all conservative treatments has failed</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak • Agreement: 75% | <p>Positive effects of sacral nerve stimulation</p> <ul style="list-style-type: none"> • Level II Grade B <p>Interferential therapy, positive effect, not recommended</p> <ul style="list-style-type: none"> • Expert Recommendation | <p>Positive effect of sacral nerve stimulation for people refractory to other treatments</p> <ul style="list-style-type: none"> • Evidence: low • Recommendation: weak | <p>Positive effect of sacral nerve stimulation (SNS), Extracorporeal magnetic stimulation therapy (EMST) and Electrical stimulation when other approaches have failed. Small, low-level evidence studies.</p> |

(Continued)

Table 6 (Continued).

| | European GL | French GL | Spanish GL | Korean GL |
|---------------------|--|--|--|--|
| Surgical treatments | <p>Positive effect. Surgical options, both resecting and non-resecting, might be considered for selected patients if all other conservative treatments were not effective</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • Agreement: 100% <p>Surgery can be an effective treatment for an evacuation disorder due to structural causes</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • Agreement: 92% <p>Surgery should be offered after performing physiological tests and only if the cause lies within the colon and/or rectum</p> <ul style="list-style-type: none"> • Evidence: Very low • Recommendation: Weak • Agreement: 100% <p>Total or segmental colectomy can be effective in highly selected patients with normal upper GI function and slow-transit constipation who did not respond to conservative therapy</p> <ul style="list-style-type: none"> • Evidence: Moderate • Recommendation: Strong • Agreement: 92% <p>The surgical method is chosen depending on the disease. In case of intussusception, rectocele or prolapse, the STARR or internal Delorme procedures are proposed.</p> | <p>Ventral mesh rectopexy (for rectal prolapse)</p> <ul style="list-style-type: none"> • Level I Grade A <p>STARR intervention, proposed for rectal intussusception and/or rectocele</p> <ul style="list-style-type: none"> • Level I, Grade A <p>Total colectomy (for slow-transit constipation)</p> <p>Expert Recommendation</p> <p>Malone procedure, may be proposed in case of failure of transanal irrigation</p> <ul style="list-style-type: none"> • Expert Recommendation | <p>Positive effect for colectomy, that should be considered only in people with severe chronic constipation refractory to other treatments and in whom extensive involvement of intestinal motility has been ruled out by specific tests, including gastrointestinal manometry</p> <ul style="list-style-type: none"> • Evidence: Low • Recommendation: Weak | <p>Positive effect of colectomy and others surgical interventions in patients with slow transit constipation who failed all non-surgical therapies.</p> <ul style="list-style-type: none"> • Evidence: C • Recommendation: 2 • Experts' agreement: completely agree (16.0%), mostly agree (64.0%), partially agree (16.0%), mostly disagree (4.0%) <p>Other surgical treatments can be effective in patients who have an outlet obstruction such as symptomatic rectocele and rectal prolapse.</p> <ul style="list-style-type: none"> • Grade of recommendation: 2. • Level of evidence: C. • Experts' opinions: completely agree (19.2%), mostly agree (61.6%), partially agree (19.2%) |

Abbreviations: STARR, Stapled Trans Anal Rectal Resection; NA, not assessed.

biofeedback has positive effect in people with dyssynergic defecation and, due to its safety, it can be repeated if needed, reducing the use of laxatives.

The European guidelines take into account also pelvic rehabilitation without performing biofeedback. This involves dietary advice to improve stool consistency and to maximize the gastro-colic response in order to ease defecation, and some simple pelvic floor exercises and abdominal muscular coordination training to improve the pushing effort.^{32,33} Before suggesting it for all patients with persistent constipation, it must be however taken into account that this is not an evidence-based treatment, and results from randomized clinical trials are pending.

All guidelines report positive effects of sacral nerve stimulation as a last chance, before surgery, in patients who failed to improve with non-surgical therapies. However, this approach has both a low level of evidence and recommendation.

All guidelines agree that a surgical treatment must be taken into account only after an adequate evaluation of the constipated patient. There are two main conditions that can benefit from surgery. The first is represented by patients with normal function of the upper GI tract showing abnormal colonic motility (ie, inertia coli). In this situation, the most appropriate intervention will be a total colectomy with ileorectal anastomosis. The second is represented by patients with normal colonic motility displaying obstructed defecation provoked by rectal intussusception and/or rectocele (Stapled Trans Anal Rectal Resection or internal Delorme procedures can be suggested), or by rectal prolapse (a ventral mesh rectopexy can be suggested). Another surgical procedure, reported only by the French guidelines, is the Malone procedure, which can be proposed in treatment refractory patients in whom transanal irrigation has failed.

Complementary and Alternative Medicine

These approaches are shown in Table 7. The European and French guidelines take into consideration complementary and alternative therapies. The French ones, due to the lack of reliable studies, state that it is impossible to express a definite opinion about their positive or negative effect. Any judgement can be formulated only as an expert recommendation, even if a positive effect can be obtained mainly in patients confident on the efficacy of these therapies (ie, as a placebo effect). Also the European guidelines, attempting to analyze different therapies, due to the absence of high-quality study and the difficulty of

comparing products without a well specified composition, conclude that level of evidence is low or very low and the recommendation is weak. With respect to the psychological approaches, European guidelines state that these did not show any positive or negative effect on constipation, even though the quality of life can be improved.

Commercially Available but Scarcely Investigated/Not Approved Drugs for CIC

It is surprising that some common commercially available drugs are used to treat CIC patients or have been investigated with controlled trials for this purpose, although in a quite scattered manner. For instance, oral colchicine has been shown to be effective, at least in the short-term period, for CIC treatment, even in double-blind, placebo-controlled trials.^{34,35} However, likely due to possible important side effects, to date the drug has not been approved for such an indication. The same limitations apply to the use of misoprostol, a potentially useful agent to treat CIC patients.^{36,37}

The combination sodium picosulphate/magnesium citrate is frequently used as a cleansing preparation for colonoscopy; its efficacy to treat CIC patients has been assessed in a pilot study carried out on a small group of subjects with refractory symptoms, and was shown to be of benefit.³⁸ No other studies are, however, available.

Of interest, in a small randomized double-blind placebo-controlled pilot trial it was shown that the nonabsorbable antibiotic rifaximin (400 mg tid for two weeks) was able to ameliorate CIC symptoms by improving methane production and colonic transit,³⁹ no other studies have been, however, published on this topic.

Emerging Treatment Options

In the last years, some new drugs for the treatment of CIC have been developed,⁴⁰ and a few are close to be commercially available or have been recently commercialized, although only in some Countries. Plecanatide is a guanylate cyclase C (GC-C) agonist that belongs (together with the similar drug linaclotide, already commercially available⁴¹) to the secretagogues class of laxatives and shares the structural and physiological characteristics of uroguanylin.⁴² Plecanatide at the dosage of 3 mg once a day proved to be effective for the treatment of CIC,^{43,44} with a very favourable safety profile due to its low systemic availability with a low (about 10%) incidence of

Table 7 Recommendation and Evidence of Complementary and Alternative Therapies Suggested for Chronic Constipation According to the Different Guidelines

| | European GL | French GL | Spanish GL | Korean GL |
|--|---|--|------------|-----------|
| Complementary and Alternative Medicine | <p>Positive effect of Chinese herbal medicine, (but it is not known which formulation is best)</p> <ul style="list-style-type: none"> ● Evidence: Low ● Recommendation: Weak ● Agreement: 100% <p>Insufficient evidence to recommend or not acupuncture, moxibustion or herbal remedies (other than Chinese herbal medicine)</p> <ul style="list-style-type: none"> ● Evidence: Very low ● Recommendation: Weak ● Agreement: 100% <p>Abdominal massage may have a positive effect, but it needs to be standardized before it could be recommended</p> <ul style="list-style-type: none"> ● Evidence: Very low ● Recommendation: Weak ● Agreement: 100% | It is impossible to express a definite opinion about their positive or negative effect but any judgement can be formulated only as an expert recommendation. | NA | NA |
| Psychotherapy, cognitive behavioral therapy and hypnotherapy | <p>Not positive, not negative on constipation, even if they improve quality of life</p> <ul style="list-style-type: none"> ● Evidence: Very low ● Recommendation: Weak ● Agreement: 100% | NA | NA | NA |

Abbreviation: NA, not assessed.

diarrhea resulting in treatment interruption in less than 6% of patients.⁴⁵ In addition, the drug has been shown to be effective and safe also in patients older than 65 years.⁴⁶ An important issue related to this (and other recently marketed) class of drugs to treat CIC is the cost that featured some critical comments on patients' affordability.^{47,48} To date, plecanatide is commercially available only in the USA.

Elobixibat is an ileal bile acid transported inhibitor that represents a new class of treatment for CIC patients; its administration causes increased delivery of bile acids to the colon,⁴⁹ accelerating large bowel transit and increasing colonic secretion. Elobixibat, in both Phase II^{50–52} and Phase III studies^{53,54} proved to be efficacious and well tolerated even in real-life conditions,⁵⁵ with a good safety profile even in elderly patients,⁵⁶ suggesting its possible role as first-line approach to treat patients complaining of CIC.⁵⁷ The use of elobixibat is currently approved only in Japan.

One of the main research issue in the last years has been the selective targeting of 5-HT₄ receptors. One drug with this effect, prucalopride, is already commercially available in Europe and in the US due to its proven beneficial effects on CIC patients⁵⁸ (see also above), and other drugs belonging to this class have been developed for this purpose. Tegaserod, although effective and approved for the treatment of CIC,⁵⁹ has been subsequently withdrawn due to the risk of cardiovascular ischemic events and reintroduced on the market in the US with only one indication (women aged <65 years with constipation-predominant irritable bowel syndrome and no cardiovascular risk)⁶⁰ However, some promising data on other highly selective 5-HT₄ agonist are available. Phase II studies showed that various doses of velusetrag⁶¹ and naronapride (data published only in abstract form)⁶² display beneficial effects in CIC patients, with relatively favourable safety profile.⁶³ However, as for other recently investigated drugs, data on velusetrag and naronapride are

still quite scarce, the evidence is of moderate quality, and the long-term effects of these drugs unknown.^{64,65}

Relamorelin, a pentapeptide selective agonist of ghrelin receptor 1a, significantly reduced constipation symptoms and accelerated colonic transit in a Phase II, placebo-controlled randomized trial.⁶⁶ These effects have been related to the stimulation of colonic high-amplitude propagated contractions in these patients,⁶⁷ even though this effect appears to be weaker compared to other laxatives.^{68,69} To date, no other studies have been published with this drug in CIC patients.

In a small randomized double-blind placebo-controlled pilot trial the effects of CSP01, a novel superabsorbent hydrogel, were evaluated IN CIC patients; although the hydrogel was able to decrease colonic transit time compared to placebo, no effects on symptoms were documented.⁷⁰ Once again, no other data are available on this agent concerning CIC.

Mizagliflozin, a novel oral sodium-glucose cotransporter 1 inhibitor that increases luminal glucose and water, has been recently tested in CIC patients in a randomized double-blind placebo-controlled Phase II trial.⁷¹ The drug, at doses of 5 and 10 mg once a day, showed favorable efficacy and tolerability, suggesting a potential alternative approach to target CIC. However, more data are needed to confirm its efficacy and safety in the time course.

Conclusions

CIC is a frequent functional digestive disorder with a relevant impact on the QoL. Several therapeutic approaches have been proposed to ameliorate symptoms associated with CIC. European, French, Spanish and Korean therapeutic guidelines have been compared and discussed with respect to the different methodological criteria and results. Based on the available evidence, a high fiber diet and PEG represent the recommended first-line therapeutic approach,^{72,73} it is worth noting that this approach is useful also as over-the-counter therapy.⁷⁴ Stimulating laxatives and new agents like prucalopride and plecanatide can be proposed as a second-line therapy in patients unresponsive to osmotic laxatives; of interest, literature evidence suggest that prucalopride has the potential for being a first-line treatment for CIC.⁷⁵ There is also evidence that some drugs currently approved for constipation-predominant IBS might in the near future be approved also for CIC, due to their efficacy also in this condition.⁷⁶ In patients with ano-rectal dyssynergia, pelvic floor rehabilitation is the principal recommended method. In

constipated patients refractory to any therapeutic approach sacral nerve stimulation and surgery can represent the last therapeutic chance. Finally, new promising emerging agents have been demonstrated effective to treat CIC patients⁷⁷ although only some of these medicaments are commercially available.

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Disclosure

The authors report no conflicts of interest in this work.

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