Surgical options for intractable constipation: review of literature

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8/12/17

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PREFACE

In front of you lies the dissertation “Surgical options for intractable constipation: review of literature”. It has been written to fulfil the degree of Master of Medicine in Medicine at the University of Ghent. The research and the writing of this dissertation took place from September 2016 to December 2017.

As in every challenging task, the process went with ups and downs. It has been a period of intensive learning not only in the scientific area, but also on a personal level. I would like to thank some people who have supported me throughout this period.

First of all, I would like to thank Dr. Van de Putte. The longitudinal character of the assignment lead to an open relationship were issues could be discussed and questions could be asked without hesitation. Thank you for the pleasant cooperation. In addition, I would like to thank Dr. De Visschere and Prof. Dr. Pattyn for their wise advice and words of motivation.

Secondly, I would like to thank my family and friends not only for the discussions about the topic of this dissertation, but even more for their support and simply always being there for me.

Thank you and I wish you a pleasant reading experience!

Louis De Wispelaere

Ghent, December 6, 2017
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ABSTRACT

Aim To give an overview of the literature, mainly focused on the surgical approach of primary constipation, especially slow transit constipation, in adults after failure of conservative therapy. This literature review should lead to a flowchart as a proposal for a more systematic therapeutic approach of the constipated patient and if needed to make a choice between sacral neurostimulation (SNS), antegrade colonic enema (ACE), colectomy or a combination of ACE and colectomy.

Method MEDLINE, Embase and CENTRAL databases were searched for studies demonstrating the use of SNS and ACE as treatment for primary constipation. The search strategy is based on the PRISMA guidelines. For colectomy and other treatments for constipation, the data is mainly obtained from recent reviews and studies.

Results 17 articles for SNS and 12 articles for ACE were included for qualitative synthesis. Both techniques are relatively new in the context of constipation in adults. For SNS, the early retrospective studies were promising, but newer prospective studies are less positive. ACE in adults does not have as good success rates when compared with ACE in children. Approximately 50% of the patients can be helped with ACE. SNS and ACE both have minor complications, especially when compared with the last invasive resort of a constipated patient: colectomy with ileorectal anastomosis.

Conclusion The evidence of surgical options for primary constipated adult patients is based on poor quality studies. Further research with methodological good constructed studies are necessary to make solid conclusions possible. Despite this fact and looking at current available literature, no single surgical treatment can claim the position of ‘best practice’. Treatment of constipation must be seen as a gradually process, beginning with conservative treatment and building up to more invasive procedures until the symptoms of the patient are under control and improvement of quality of life (QoL) is obtained.

Keywords Constipation, slow transit constipation, sacral nerve stimulation, antegrade colonic enema, colectomy.
ABSTRACT

Doel Een overzicht te geven van de literatuur rond constipatie, waarbij de focus ligt op de chirurgische aanpak van primaire constipatie (voornamelijk trage transit constipatie) bij volwassenen na falen van conservatieve therapie. Dit literatuuroverzicht zou moeten leiden tot een flowchart als voorstel voor een meer systematische therapeutische aanpak van de geconstipeerde patiënt om zo nodig de keuze te kunnen maken tussen sacrale neurostimulatie (SNS), antegrade spoelingen (ACE), colectomie of een combinatie van antegrade spoelingen en colectomie.

Methode MEDLINE, Embase en CENTRAL databases werden doorzocht om studies te identificeren die rapporteren over het gebruik van SNS en ACE als therapie bij primaire constipatie. De zoekstrategie is gebaseerd op de PRISMA richtlijnen. Voor colectomie en andere behandelingen voor constipatie werd de informatie voornamelijk gehaald uit recente reviews en studies.

Resultaten 17 artikels voor SNS en 12 artikels voor ACE werden geïncludeerd. Beide technieken zijn relatief nieuw in de context van constipatie bij volwassenen. De vroege retrospectieve studies over SNS waren veelbelovend, maar nieuwe prospectieve studies zijn minder positief. ACE bij volwassenen hebben niet zo’n goede resultaten zoals bij kinderen. Ongeveer de helft van de patiënten kan geholpen worden met ACE. SNS en ACE hebben beide mineure complicaties, vooral wanneer vergeleken wordt met het laatste invasieve redmiddel van de geconstipeerde patiënt: colectomie met ileorectale anastomosis.

Conclusie De evidentie van chirurgische opties voor primair geconstipeerde volwassenen patiënten is gebaseerd op studies van zwakke kwaliteit. Verder onderzoek door middel van goede methodologisch onderbouwde studies is noodzakelijk om solide conclusies te kunnen maken. Ondanks dit feit en kijkend naar de huidige beschikbare literatuur, kan geen enkele chirurgische behandeling de positie van ‘best practice’ opeisen. De behandeling van constipatie moet gezien worden als een gradueel proces, startend met verschillende pogingen van conservatieve therapie en opbouwend naar meer invasieve procedures, totdat de symptomen van de patiënt onder controle zijn en verbetering van de kwaliteit van leven behaald wordt.

Trefwoorden Constipatie, trage transit constipatie, sacrale neurostimulatie, antegrade spoelingen, colectomie.
1 INTRODUCTION

1.1 Epidemiology and burden

Constipation is a common problem. It has been estimated that 14% of the adults population suffers from constipation, with rates of epidemiologic studies ranging from 1,9% to 40,1%. Older people, females and those of lower socioeconomic status have a higher incidence rate.

(1) Although many health care providers consider constipation as a benign process. Chronic constipation has a serious impact on quality of life and is a big cost for the health care system.

(2)

1.2 Constipation

There is no simple definition for constipation. In the past constipation was just described on the basis of the frequency of bowel movements per week: less than three times a week was defined as constipation. Looking on studies like the survey of Johanson et al. on 557 subjects, it became clear that by this way constipation is not fully defined. In this study most patients reported straining (79%). Other symptoms were hard stools (71%), abdominal discomfort (62%), bloating (57%) and feeling of incomplete evacuation (54%). Infrequent bowel movements were only reported by 57%. (3)

In 1989, the first version of the Rome criteria was written, which led to standardization. Recently (in 2016) the Rome III criteria have been revised, resulting in the Rome IV criteria.

Patients suffering from constipation have symptoms associated with difficult, infrequent, or incomplete defecation. Abdominal pain and/or bloating may be present but are not predominant symptoms in constipation, in contrary to irritable bowel syndrome (IBS) (4)

Table 1: Rome IV criteria. (Adapted from Lacy et al. (4))

<table>
<thead>
<tr>
<th>Diagnostic Criteria (i) for Functional Constipation (FC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Must include 2 or more of the following symptoms, which must be present for more than 25% of defecations:</td>
</tr>
<tr>
<td>a. Straining</td>
</tr>
<tr>
<td>b. Lumpy or hard stools (BSFS 1–2)</td>
</tr>
<tr>
<td>c. Sensation of incomplete evacuation</td>
</tr>
<tr>
<td>d. Sensation of anorectal obstruction/blockage</td>
</tr>
<tr>
<td>e. Manual manoeuvres to facilitate defecations (e.g., digital evacuation, support of the pelvic floor)</td>
</tr>
<tr>
<td>f. Fewer than 3 spontaneous bowel movements per week</td>
</tr>
<tr>
<td>2. Loose stools are rarely present without the use of laxatives</td>
</tr>
<tr>
<td>3. Insufficient criteria for irritable bowel syndrome</td>
</tr>
</tbody>
</table>

(i): Criteria fulfilled for the last 3 months (current activity) with symptom onset at least 6 months prior to diagnosis (chronicity).
Constipation can be either primary or secondary to another underlying disorder. Causes of secondary constipation are medications, medical disorders, and organic abnormalities that give a mechanical obstruction resulting in constipation. Secondary constipation must be excluded first. More often, however, constipation is caused by disordered colonic or anorectal function. (primary constipation)

**Table 2: Causes of chronic constipation. (Adapted from Tack et al. (5) and Pfeifer et al.(6))**

<table>
<thead>
<tr>
<th>Intestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colon</strong></td>
</tr>
</tbody>
</table>
| Functional: normal transit, slow transit  
| Organic: neoplasms, polyps, strictures, diverticular disease, aganglionosis  
| **Anorectum and pelvic floor**  
| Functional: anismus, dyssynergia  
| Organic: neoplasms, polyps, megarectum, anal stenosis, mucosal rectal prolapse, internal rectal prolapse, complete rectal prolapse, solitary rectal ulcer, rectocele, enterocele, descending perineum syndrome, Hirschsprung’s disease  |
| **Extra-intestinal**  
| **Endocrine:** hypothyroidism, diabetes  
| **Metabolic:** hypercalcemia, hypocalcemia  
| **Neurologic:** Parkinson’s disease, multiple sclerosis, systemic sclerosis, spinal cord lesions, muscular dystrophies, autonomic neuropathy  
| **Psychological:** depression, anxiety, eating disorders  
| **Myogenic:** myotonic dystrophy, dermatomyositis, scleroderma, amyloidosis  
| **Diet/lifestyle:** dehydration, low-fiber diet, immobility, poor bowel habits  
| **Medications:** narcotics, anticholinergics, antipsychotics, calcium channel blockers, anti-Parkinson’s therapy, anticonvulsants, tricyclic antidepressants, iron, calcium, aluminium antacids, sucralfate  |

### 1.3 Subtypes of primary constipation

This broad group of primary constipation can be divided into 4 categories after physiological tests: normal transit constipation (NTC), slow transit constipation (STC), functional obstructed defecation syndrome (ODS) and the combination STC and functional ODS. (4, 6, 7) Synonyms for functional ODS are pelvic floor dysfunction and evacuatory dysfunction.

In normal transit constipation the colon transit time and the function of the colon is fine, but people still experience symptoms of constipation, such as hard stools, sense of difficult or delayed evacuation and they may have increased psychosocial distress. (7) It is important to acknowledge that functional constipation and irritable bowel syndrome with predominant constipation (IBS-C) have a significant overlap. These disorders should thought of being on a continuum, rather than discrete disorders. (4, 5)

The precise cause of slow transit constipation is not known. In studies using colonic manometry, they observed fewer high-amplitude propagated sequences (HAPS) and reduced phasic contractile responses to a meal and to pharmacologic stimuli. There was also less spatial overlap between adjacent propagated sequences, which is crucial for colonic transit. (8) Autonomic dysfunction and reduced neurotransmitter levels (e.g. VIP, NO, 5-HT) have
been demonstrated in some patients. (4) Morphological changes in the myenteric and submucosal plexus with reduced numbers of interstitial cells of Cajal occurred in a couple of patients with STC. (4, 9) The result of STC is obvious. The faeces is longer present in the intestines. As a result, it hardens and becomes difficult to remove. Colon inertia is a term used for people with untreated STC and whose motor activity of the colon does not respond to meals or stimulants such as bisacodyl. (7)

Obstructed defecation syndrome occurs when patients have a difficulty in expelling stools form the rectum. ODS can be further subdivided into two groups: functional and structural ODS. Functional ODS is more common and is characterized by a dynamic failure of evacuation without structural abnormality. Changes in the normal sequence of the pelvic floor muscle activity may result in paradoxical anal contraction (anismus) or lack of coordination of the muscles involved in defecation (dyssynergia). Functional ODS is no indication for surgery. Such patients can be helped with physiotherapy and biofeedback. A high proportion of patients may also show impaired rectal sensation. (5)

Structural ODS is no primary constipation. It represents the subgroup of ODS with significant structural abnormalities (a large rectocele, rectal prolapse, anal stenosis, Hirschsprung’s disease, etc).

Figure 1: Schematic diagrams of normal physiology at rest and during defecation (top), and the pathophysiologic changes in faecal incontinence and dyssynergic defecation. (bottom) (Rao et al. (10))
1.4 Aim of the thesis

Epidemiology, burden, definition and categories of constipation are mentioned above. Usually patients can be helped with conservative therapy (e.g. laxatives, biofeedback, retrograde enemas), but for some this approach is insufficient. The quality of life of this small group decreases. To help these people, there are several surgical techniques: sacral neurostimulation (SNS), antegrade colonic enema (ACE), colectomy and stoma. In clinical practice however, there is still an empirical use and thus not evidence-based. These procedures should only be performed after a systematic assessment where they try to find the type of constipation and underlying etiology, making it possible to select the right patients for the procedure.

The aim of this thesis is to give an overview of the literature, focused on the therapeutic approach of primary constipation (especially slow transit constipation) in adults, where conservative possibilities are exhausted. The diagnosis (especially the physiological tests, because these are important in intractable constipation) and conservative management are mentioned in a short overview, but the focus is on sacral neuromodulation, antegrade colonic enema and colectomy. It is important to take into account that only a small part of patients with constipation are candidates for surgery. This literature study has led to a flowchart as a proposal for a more systematic therapeutic approach of slow transit constipation to make a choice between SNM, ACE and colectomy when conservative therapy fails.
2 Diagnosis

The first step in the treatment of constipation is a thorough clinical history and physical examination. In most cases, it will be sufficient in a first consultation to assess the severity, ask for alarm symptoms, and rule out organic and secondary cause. Thereafter diet, lifestyle changes and laxatives are introduced to alleviate the symptoms of the patients.

If this approach repetitively fails, further assessment is needed (laboratory tests, colonoscopy and/or specific physiological tests). (9) In figure 2, a diagnostic flowchart is proposed. More detailed information is available in the text of this chapter.

Figure 2: Proposed diagnostic flowchart of chronic constipation.

1 Alarm symptoms: rectal bleeding, blood in the stool, anemia, unexplained weight loss (>10% in 3 months), sudden change in bowel habits, severe abdominal pain, fever and a family history of colon cancer. Especially in patients older than 45 years, one should not forget to ask.

2 Dotted line indicates that clinical history (e.g. digital evacuation – rectocele), physical examination (e.g. rectal toucher with squeezing not resulting in relaxation of the sphincter – animus) and colonoscopy (e.g. ulcer – sign of invagination) may be suggestive for a specific disorder.
2.1 **Clinical history and constipation scores**

In a first consultation the main concern is to exclude secondary constipation. Opioids, antidepressants, anticholinergics, calcium channel blockers and calcium supplements are medications that can cause constipation and may need to be stopped or modified. Patients may also suffer from an associated or undiagnosed endocrine, metabolic, psychiatric or neurologic disorder that will require treatment to help address constipation symptoms. (12)

It is important to ask the following alarm symptoms: rectal bleeding, blood in the stool, anemia, unexplained weight loss (>10% in 3 months), sudden change in bowel habits, severe abdominal pain, fever and a family history of colon cancer. Especially to patients older than 45 years, one should not forget to ask. (4, 12)

A detailed history should include onset and duration of constipation, frequency of bowel movements, shape and consistency of the stool, characterization of bowel habits: straining, need to anal digitation, etc. For the assessment of this information stool diaries might be useful.

The Bristol Stool Form Scale (BSFS) (figure 3) is an easy way to identify the type of stool. It is designed to classify the form of human faeces into seven categories. The form of the faeces depends on the time that it spends in the colon. Therefore, BSFS is a rapid and reliable indicator of colon transit time. (13) The stool form also affects the ease to evacuate it. (9)

A careful assessment of the symptoms may help to distinguish the subtypes of constipation. Abdominal pressure and bloating in the upper abdomen and infrequent, hard stools suggest STC. A sense of incomplete evacuation, straining, perineal pressure and the need for perineal/vaginal manipulation are more likely to indicate ODS. Predominant abdominal pain may indicate IBS. Many patients however will have symptoms associated with more than one subtype, which make it difficult to clearly establish a diagnosis without further testing. (12)

It can be helpful to use constipation scoring systems to objectify the complaints. By evaluating their course over time, scoring systems are useful to assess the response to therapy. They contain several variables and are fairly detailed. The most commonly used is the Cleveland Clinical Constipation Score (CCCS), also called the Wexner Constipation Score. (14)
Table 3: Cleveland Clinic Constipation Score/ Wexner Constipation Score. (Adapted from (6))

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of bowel movements</td>
<td>1-2x per 1-2 days</td>
<td>2x/week</td>
<td>1x/week</td>
<td>Less than 1x/week</td>
<td>Less than 1x/month</td>
<td></td>
</tr>
<tr>
<td>Difficulty: painful evacuation effort</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Usually</td>
<td>Always</td>
<td></td>
</tr>
<tr>
<td>Completeness: feeling incomplete evacuation</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Usually</td>
<td>Always</td>
<td></td>
</tr>
<tr>
<td>Pain: abdominal pain</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Usually</td>
<td>Always</td>
<td></td>
</tr>
<tr>
<td>Time: minutes in lavatory per attempt</td>
<td>&lt;5</td>
<td>5-10</td>
<td>10-20</td>
<td>20-30</td>
<td>&gt;30</td>
<td></td>
</tr>
<tr>
<td>Assistance: type of assistance</td>
<td>Without assistance</td>
<td>Stimulative laxatives</td>
<td>Digital assistance or enema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure: unsuccessful attempts for evacuation per 24 hours</td>
<td>Never</td>
<td>1-3</td>
<td>3-6</td>
<td>6-9</td>
<td>&gt;9</td>
<td></td>
</tr>
<tr>
<td>History: duration of constipation (years)</td>
<td>0</td>
<td>1-5</td>
<td>5-10</td>
<td>10-20</td>
<td>&gt;20</td>
<td></td>
</tr>
<tr>
<td>Total Score: (maximal 30; constipation &gt;15 points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2 Physical examination

Inspection of the abdomen for asymmetry, scars, distension and hernias is a beginning for a complete abdominal examination. Auscultation, percussion and palpation may help to detect air, ascites, masses (e.g. hard stools) in the abdomen. (4, 12)

Perineal and anal inspection may reveal fissure, prolapsing hemorrhoids, skin tags and scars. Digital rectal examination should be performed to exclude fecal impaction, stricture or neoplasm. Simultaneously the anal sphincter function at rest, squeeze and straining can be assessed. Normally the sphincter should relax together with a descent of the perineum. If not observed, pelvic floor dysfunction is presumable. (7, 15)

In women, special attention should be given to the posterior vaginal wall. A rectocele may be present. However, not every woman with a rectocele suffers from constipation. (6)

2.3 Laboratory tests

If there are no alarm symptoms or reasons to suspect a underlying metabolic or endocrine disorder, clinical history and physical examination are sufficient and symptomatic therapy can be applied. (6) In the other case, blood tests (with special attention to potassium, calcium and TSH) can be used to identify anemia, hypothyroidism, hyperparathyroidism or diabetes mellitus but are not specifically helpful in assessing constipation. (12)

2.4 Colonoscopy

Routine colonoscopy is not standard indicated for constipated patients. Colonoscopy is recommended when there is a suspicion of possible structural problems and especially for patients with alarm signs: rectal bleeding per anum, unexplained weight loss, sudden change in bowel habits, and a family history of colon cancer. (5, 16)
2.5 **Physiological tests**

When conservative therapy fails and no secondary cause can be detected, physiological tests are indicated. Those can help to find the cause or to assess the clinical meaning of abnormalities like rectocele, but are time-consuming. The use of this test requires clinical reasoning. Frequently one test is not enough to evaluate the pathophysiology. Those different tests should be interpreted together with the clinical presentation to make the correct diagnosis.

The American Gastroenterological Association (AGA) recommends to first rule out a defecatory disorder before testing the colonic transit. (16) Determination of colonic transit time is not recommended in the early diagnosis for two reasons. In the first place because 50% of patients with defecatory disorders have slow transit. Slow transit neither disturbs the anorectal tests nor it excludes the presence of defecatory disorders. These are treated with pelvic floor retraining regardless of colonic transit time. Secondly, the initial therapy (laxatives) for NTC and STC is the same. (9)

Anorectal manometry and rectal balloon expulsion test are therefore the first to be executed. If during clinical history and physical examination, findings are strongly suggestive for ODS, these tests can already be done before the use of laxatives.(9)

2.5.1 **Anorectal manometry**

The basal and maximal pressure in the anal canal are measured. Assessment of sphincter tone, rectal sensation and pressure changes during defecation takes place: the first sensation, the feeling of defecation and the maximal tolerable volume. Furthermore the rectoanal-inhibitory reflex can be analysed. If the reflex is normal, Hirschsprung's disease can be excluded. (6) During defecation, normally the intrarectal pressure should increase and the sphincter pressure should decrease. By using anorectal manometry, dyssynergic defecation can be evidenced by inadequate increase in rectal pressure, impaired sphincter relaxation or anal sphincter contraction, or a combination. (see figure 1) (9)

2.5.2 **Balloon expulsion test**

A balloon is introduced into the patient and is filled with 50 ml of water. Normally the balloon should be quickly evacuated, depending on the technique used, within one minute to five minutes. For individuals with ODS the evacuation can take more time or even may not succeed. (7)

2.5.3 **Defecography (MR and Rx)**

By using a defecography, the anatomy can be evaluated looking for structural abnormalities of the anterior (e.g. cystocele), medium (e.g. vaginal top prolapse) and posterior (e.g. rectocele) compartments. Also completeness of defecation and the function of the pelvic floor muscles
can be assessed, so that a functional disorder like anismus can be noticed. (12) The classic way to do this is through X-rays after administration of contrast (barium) in a sitting position. Besides barium defecography, there is also magnetic resonance (MR) defecography. A major disadvantage of MR, besides duration and cost, is the supine position, which is not the natural position for defecation. On the other hand, MR allows to examine internal organs such as bladder and vagina in more detail. Additionally, there is no harmful radiation with MR. (9, 12)

2.5.4 Colon transit studies (pellets/markers, scintigraphy, wireless pH-pressure capsule)

For the moment there are two major techniques used in practice for assessing colon transit time: pellets/markers and scintigraphy. In both, the patient is exposed to radiation. For the first one, the marker study, the patient has to ingest radio-opaque markers. Thereafter plain abdominal X-rays are taken to assess their movement through the gastrointestinal tract. Unfortunately, more than 10 methods exist to use those markers leading to no standardisation of the test. The ‘simple’ radio-opaque marker test is widely used: the patient swallows a gelatine capsule containing 20-50 markers on day 0 and an abdominal X-ray is taken on day 4 or 5 to determine the number of markers remaining in the colon. This technique is simple, cheap and widely available. (8)

The distribution of the pellets makes it possible to distinguish:
- A delayed transit: pellets throughout colon (colon inertia > 72 hours) (7)
- A normal transit: all pellets are gone (normal transit time is approximately 30h) (7)
- An unsuccessful evacuation: accumulation of pellets in the rectosigmoid

Secondly, there is radionuclide scintigraphy. The progress of a radio-isotopic chemical is followed through the GI tract using a gamma camera. The pH-sensitive coating breaks down in the mildly alkaline environment of the distal ileum. This is the desired location for evaluating the colon. Scans are taken after 4, 24, and 48h. (8)

The diagnostic capability for assessing slow transit is equivalent for the both techniques. Another new technique to assess colonic transit is by using a wireless pH-pressure capsule. The capsule is taken per os. It measures the temperature, pH and pressure along the GI tract. This information may help to investigate delayed gastric emptying and colonic transit. (17) Today the capsule is not yet in widespread use, partly due to the high cost. Further validation is required before being incorporated in practice. (8)

2.5.5 Transperineal ultrasonography

Transperineal ultrasonography is an imaging technique that is not often used. It is useful in identifying and assessing rectoceles, intussusceptions, muscle lesions, and levator muscle movement. Asynchronous movement and lesions of these muscles can lead to ODS.
Transperineal ultrasonography gives a dynamic visualization of the levator muscle. (18) Furthermore, it is a very cost-effective investigation compared to MR or other imaging techniques, but the use is limited by lack of availability and operator expertise. (12)

2.5.6 Electromyography (EMG)

EMG is mainly used in case of pelvic floor dysfunction. The primary goal is to assess the function of the pudendal nerve, which is done by placing an electrode capable of stimulating and recording simultaneously into the rectum. Thereafter a intramuscular electrode is used to record the electric potentials generated by activation of the muscle cells. It can demonstrate the failure of the puborectalis muscle or the external anal sphincter to relax during defecation. (7) For the purpose of diagnosing other subtypes of constipation, this test has no contribution.

2.5.7 Colonic manometry and barostat testing

The colonic contractility can be recorded with colonic manometry. It is recommended for patients with severe constipation, who are unresponsive for conservative treatment and have evidence of slow colonic transit in the absence of an evacuatory dysfunction. (19) Mainly in pediatric literature, it is suggested that colonic manometry may guide clinical decision making. However, until today there are no clear clinical guidelines.(20)

Because of limited (but growing) understanding of normal colonic physiology and of pathophysiology of colonic motor function in constipation, manometric (and also transit) biomarkers have restricted implications for defining constipation subtypes and guiding treatment. Only through further device development and acquisition of large data sets, this can be accomplished. (8)

Colonic barostat can record colonic tone, phasic contractile events, compliance and visceral sensation. It has the same problems as colonic manometry: lack of data and standardisation. Nevertheless, this is also an important research area, given the impact of colorectal sensory dysfunction in functional gastrointestinal disorders. (8) These tests are currently only available in highly specialized centers with a research interest and their role in diagnosing constipated patients is not yet established. (9)

After the diagnostic tests it should be possible to classify every single patient into one of the following categories: normal transit constipation, slow transit constipation, obstructed defecation syndrome (functional or structural), combination of STC and ODS, structural cause seen by colonoscopy (e.g. neoplasms), and at last extra-intestinal cause (e.g. hypothyroidism).
3 CONSERVATIVE MANAGEMENT OF CONSTIPATION

Diet and lifestyle modification are the first step of conservative treatment. If necessary, laxatives can be prescribed. For the majority of patients, these interventions are sufficient. More recently some new drugs are on the market, such as prucalopride, linaclotide, and lubiprostone. They are considered as a next level after repetitive failure of laxatives. Biofeedback is an effective treatment for patients with dyssynergic defecation. For patients resistant to these treatment options, surgery can be the final solution.

3.1 Diet and lifestyle modification
The first to recommend is a diet and lifestyle modification.

Increase water and fibre consumption are important. Natural sources of fibre are fruit (e.g. prunes), vegetables, wholegrain bread and pasta. Simultaneous intake of water and fibres lead to water retention in the intestinal lumen to enlarge the mass and to promote bowel movements. For 85% of patients without an underlying pathological problem dietary fibre treatment leads to improvement. However, there is a huge difference between those without an underlying pathological problem and the group with STC and ODS. From the STC and ODS patients respectively 80% and 63% did not respond to increased fibre intake. (21) A systematic review, comparing soluble and insoluble fibres (bulk-forming agents) with placebo or no therapy in adult patients with chronic idiopathic constipation, found most evidence in soluble fibre. Compared with placebo, soluble fibre (e.g. psyllium) led to improvements in global symptoms (86.5% vs. 47.4%), straining (55.6% vs. 28.6%), pain on defaecation, and stool consistency. Also an increase in the mean number of stools per week was observed. (3.8 stools per week after therapy compared with 2.9 stools per week at baseline) (22)

Toilet training, for example going to the toilet after a meal (using the gastro-colic reflex), and physical activity might help as well. A food and stool diary can be useful to correlate the food intake and bowel movements. Also medications that can cause constipation, need to be stopped or changed if possible. (16)
3.2 **Laxatives**

Liquid paraffin is an example of a lubricant laxative. The faeces is coated with lipids and colonic absorption of water is made more difficult, so that the stool slipped through the colon more easily. It is mostly used for children with good results. (23)

The osmotic laxatives, such as polyethylene glycol and lactulose, are more commonly used in the management of chronic constipation. A Cochrane systematic review evaluated the efficacy of polyethylene glycol and lactulose in treating chronic constipation and faecal impaction. The meta-analysis concluded 10 randomized controlled trials (RCT). The findings indicated better outcomes in frequency and form of stool, relief of abdominal pain, and the need for additional product use in the group using polyethylene glycol. They concluded that polyethylene glycol should be preferred to lactulose in the management of chronic constipation. (24)

For the stimulant laxatives, such as bisacodyl, less evidence is available. Some studies showed good results on short term. However, the long-term effects (e.g. fluid and electrolyte imbalance) of chronic stimulant laxative use were not assessed. (25)

The emollient laxatives, also called the stool softeners, prevent hardening of the faeces by adding moisture to the stool. These anionic surfactants (e.g. docusate) promote luminal water binding to soften the faeces. (15)

Most of these laxatives can be taken by mouth or rectally, as an enema or suppository. There is still a lack of head-to-head comparisons for most of these laxatives. This makes it difficult to determine whether one laxative class is superior to another. (5)

3.3 **Newer agents**

A major group of constipated patients do not get a satisfied feeling of defecation with laxatives, mainly due to concerns about efficacy and safety. (3) Additionally, laxatives do not target the pathophysiology that may contribute to the symptoms. So in recent decades, new agents have been produced to tackle this problem.

Prucalopride (Resolor®) is a selective agonist of the 5-HT4 receptor. Increased colonic motility and transit is observed as a result of the interaction between agonist and receptor. Lubiprostone (Amitiza®) and linaclotide (Constella®) are drugs acting on the intestinal enterocyte, more specifically on an intestinal type-2 chloride channel (lubiprostone) and guanylate cyclase receptor (linaclotide). By activating the channel/receptor the chloride concentration of intestinal fluid increases, leading to stimulation of the intestinal fluid secretion and acceleration of the transit. (26)
In 2010, the number needed to treat (NNT) was estimated from placebo-controlled clinical trials that compared following medications with placebo in constipation. The estimation of NNT for osmotic and stimulant laxatives NNT = 3, lubiprostone NNT = 4, and prucalopride and linaclotide both NNT = 6. This might suggest some difference in efficacy, but the different end points used in the studies do not make it possible to make robust conclusions. (26)

A recent systematic review of 22 RCTs investigated the current drugs for chronic constipation: selective 5HT4-agonist (prucalopride, tegaserod, velusetrag), lubiprostone, linaclotide, inhibitor of the ileal bile acid transporter (elobixibat), bisacodyl and sodium picosulphate. The researchers conclude that the current drugs show similar efficacy for primary end points: ≥3 complete spontaneous bowel movements (CSBM)/week and increase over baseline by ≥1 CSBM/week. Nevertheless, these authors emphasize the need for head-to-head trials of active agents to determine the optimal selection of pharmacological agents. Furthermore, they mention the need for selecting the appropriate drug according to the underlying pathophysiology. For example prokinetics for patients with STC in the absence of rectal evacuation disorders. (27)

There is still a lack of guidelines to use these newer agents in practice, mainly because of the recent discoveries so not all effects have yet been examined. A comprehensive summary of all medications used in constipation is difficult to make. Comparative studies with long term effects are needed. Nowadays, it is assumed that these newer agents are indicated after failure of diet modification and laxatives.(15)

3.4 Biofeedback
Biofeedback is an useful option for patients with constipation and dyssynergic defecation. Major symptom improvement for 70-80 % of patients undergoing biofeedback therapy have been demonstrated in randomized controlled trials after correct diagnosis. Their chronic constipation was resistant to standard therapy. In those RCTs, biofeedback has been determined to be superior to polyethylene glycol laxatives, diazepam or sham therapy. Long-term results for major symptom improvement are varying from 55% to 82%. (28)
3.5 Retrograde enema

Retrograde enema or trans-anal irrigation (TAI) is designed to help evacuate the faeces from the rectosigmoid by introducing water via the anus. By regularly using this technique, it often enables the patient with constipation or faecal incontinence (FI) to re-establish a controlled bowel function, resulting in a self-chosen time and place to evacuate. The effect of TAI can vary considerably between patients: some report full satisfaction while others do not feel a difference and abandon therapy. Besides patient motivation and perseverance, no other factors could be found to explain this variation of success. (29) In constipated patients, consistently performed TAI may lead to an acceleration of transit time through the whole colon. (30)

Emmett et al. reviewed TIA in 254 adults with chronic functional constipation. In the seven studies included, the mean reported success rate is about 50% with a great variation among the different studies, probably due to varying methodology and context. (31) Given the chronic and refractory nature of the symptoms, 50% may be considered as adequate, especially looking at the simple and reversible way of treatment. The limitations of retrograde enema compared with antegrade colonic enema are mentioned below (see 4.2.2).

![Retrograde enema: classic system with conus (left) and Peristeen system (right).](image)

Figure 4: Retrograde enema: classic system with conus (left) and Peristeen system (right).
4 SURGICAL MANAGEMENT OF CONSTIPATION

4.1 SACRAL NERVE STIMULATION

4.1.1 Introduction
Sacral nerve stimulation (SNS) is a relative new technique. It has already shown his efficacy in an urological setting. SNS was first used for the treatment of urinary urge incontinence and non-obstructive urinary retention. (32) In subsequent studies simultaneous improvement in bowel symptoms was observed. Matzel et al. (33) were the first in 1994 to use SNS for faecal incontinence (FI). Several studies followed and finally in 2010 it was approved by the FDA for its use in faecal incontinence. It is now considered as the first line invasive procedure for patients with FI failing conservative approaches. Success rates of SNS for FI were reviewed by Thin et al. resulting in a median of 63% on short term (less than 1 year) and 54% on long term (>36 months). (34) In the 21st century, researchers observed also some potential for SNS to help patients with constipation who are refractory to conservative therapy. The literature in this area is complicated due to the heterogeneity of constipation.

It has to be mentioned that SNS is only useful for people who are not helped with conservative treatment (e.g. high fiber diet, laxative, prucalopride); who have major symptoms, which have an impact on quality of life and who are psychological suited for intervention. Contraindications to SNS are pregnancy, anatomical limitations to place the device, psychiatric disease, cardiac pacemaker and when the need for repeated MRI is expected.

4.1.2 Procedure and mechanism of action
The foramina of the sacrum are used to stimulate the nerve plexus. The best nerve response with the least side-effects is usually achieved on the level of S3. How SNS exactly works, is not known. It is tempting to assume a single mechanism of action for as well the urinary as bowel function, because of its impact in both using the same technique (electrode position, stimulation parameters). Unfortunately, this is not yet evidenced, partly due to heterogeneity in literature of both urinary and bowel systems. (35)

There is evidence that the effect of SNS is not a placebo effect. (36) They found that SNS is not only acting on the efferent nerves to the end organs (bladder and intestines), but also on afferent and reflex pathways. Furthermore SNS has the potential to act on all the structures that are involved in continence and defecation. This may be a reason that SNS could be clinically superior to other techniques that address only one aspect. (37)
In addition, there is also an important central effect. SNS leads to modulation of brain regions that play a role in the regulation of the defecation. For example, in an acute stimulation with SNS the contralateral cortex, involved in focused attention will be activated. After prolonged therapy (2 weeks in humans) the ipsilateral caudate nucleus is stimulated. This region is involved in learning and reward processing. (35)

Before implanting a permanent device, a percutaneous nerve evaluation (PNE) is performed. This is mostly done under general anesthesia, but can also be done under local anesthesia. In the past an open approach was performed. Nowadays, the test electrode is placed by puncture with standardized anatomic reference points. The position of the electrode is correct if motor responses are visible (sphincter contraction, big toe flexion). Under local anesthesia, sensation of the stimulation in the anal, perineal region is also a sign of good positioning.

This test period is often two weeks for faecal incontinence. Experts believe two to four weeks is better for the evaluation of constipation. (38) In most studies so far, a period of three weeks was the standard. Holzer et al. suggest that it might be beneficial to add a period without stimulation to the PNE phase in those patients who report improvement in order to minimize any potential placebo effect. A potential disadvantage is the prolonged use of the external test electrode that could increase the risk of infection. (36) This test period is almost painless and without consequences. This is extremely rare in a surgical technique and represents a considerable advantage. (37) If there is more than 50% improvement in symptoms, the implantation of a final device is the next step. The final implant is placed by surgery that is safe and without major side effects, especially compared to alternative surgical options. (39)

SNS is normally set to a pulse width of 210 µs and a frequency of 14 Hz. The only settings that have been varied among studies are the amplitude of the stimulation (µV) and the position of the electrode. These parameters used for constipation are similar to those used for incontinence, that have been based on settings where SNS was applied for urinary dysfunction. In faecal incontinence, there have been several studies investigating the effect of shorter pulse width and higher frequencies. The results of those studies suggest higher efficacy of SNS with shorter pulse width (90µs) and higher frequency (31Hz). Thomas and colleagues examined this in constipation. They saw the best Cleveland Clinic constipation score in standard settings (210 µs; 14 Hz). A limitation of the study is the small number of patients (n = 11). A reason for the difference with faecal incontinence could be the large heterogeneity of the underlying pathophysiology in constipation. Further studies with a larger population are needed to find the best settings. (24)
### 4.1.3 Methodology

MEDLINE and Embase databases were searched for studies demonstrating the use of SNS as treatment for primary constipation. The final search was on 28/7/2017. Keywords were: ‘constipation’ AND (‘sacral nerve stimulation’ or ‘sacral neuromodulation’). Further selection was done by selecting only English written articles and selecting articles acting on adults. The Cochrane Central Register of Controlled Trials database (CENTRAL) was consulted, looking for articles that have ‘constipation’ and ‘sacral nerve stimulation’ in their title, abstracts or key words. Inclusion criteria were clinical studies, like RCT, comparative studies and case series. Articles were screened by reading title and abstract. Only studies that mentioned clinical outcome of SNS for primary constipation in adults were eligible for reading of full-text. Exclusion criteria were case reports, transcutaneous sacral stimulation, and articles that after reading the full-text did not meet the including criteria (primary constipation, adult, clinical outcome). The aim of this review was to assess the clinical efficacy of SNS for primary constipation in adults based on the current published literature. After reading the selected articles, 2 more records could be retrieved out of the reference lists. (40, 41) The methodology of the included studies was scored using the Oxford CEBM summary levels of evidence. (see table 4) A study was categorised as prospective if it was stated by the authors or if patients were ‘enrolled’ or ‘recruited’ to a study and pre- and post-operative data was systematically recorded. A cohort study was defined when specified analytical methods were used to address a clear stated aim. Generally, this means a comparison group related either to the relative efficacy of two or more procedures or to patient selection where a specified baseline risk factor was analysed in relation to relative success of the intervention. When observations were reported based on clinical practice, the study was defined as a case series.

![Figure 5: PRISMA flow diagram of the search for sacral nerve stimulation and constipation.](image-url)
<table>
<thead>
<tr>
<th>Summary level of evidence</th>
<th>Type of studies</th>
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<tbody>
<tr>
<td>I</td>
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<td>a</td>
<td>Systematic review of high quality of RCT</td>
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<td>b</td>
<td>High quality RCT</td>
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<td>c</td>
<td>All or none studies</td>
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<tr>
<td>II</td>
<td></td>
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<tr>
<td>a</td>
<td>Systematic review of cohort studies</td>
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<tr>
<td>b</td>
<td>Poor quality RCT, individual high quality cohort study</td>
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<tr>
<td>c</td>
<td>Ecological study</td>
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<tr>
<td>III</td>
<td></td>
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<tr>
<td>a</td>
<td>Systematic review of case-control studies</td>
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<tr>
<td>b</td>
<td>Individual high quality case-control study</td>
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<td>IV</td>
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<td>Case series and poor quality cohort and case-control studies</td>
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<td>V</td>
<td>Expert opinion, bench research</td>
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### 4.1.4 Results

17 studies were found to report clinical outcome of SNS in adults: 4 double-blind crossover trials, 2 long term follow-ups of patients who completed the RCTs, 6 prospective uncontrolled and 5 retrospective uncontrolled studies. 517 patients had PNE and 313 patients were implanted a permanent SNS-device. Follow-up after implanted device was ranging from 4 weeks to 60 months. Only some studies reported the outcome of permanent SNS at end of follow-up. Both intention to treat and per protocol results are presented are showed in table 6.

In 2001 Ganio and co-workers investigated the effect of SNS in 40 patients with anorectal and urinary problems, of whom 12 had constipation. Eventually, 10 patients had a PNE for 10 days. In this group no increase in weekly bowel movements was seen. However, there was an improvement in the start of evacuation, a decrease in the number of unsuccessful visits to the toilet and a reduced time required for evacuation. The number of patients with constipation who felt better was not clear. (43)

In 2002, researchers at St Mark's Hospital in London examined this further. Malouf et al. (44) did PNE for 3 weeks on 8 subjects with slow transit constipation. 2 patients had an increase in frequency of bowel movements and an improvement of the bowel function via the VAS score. Colonic transit time did not normalize. The same year Kenefick et al. (45) brought more convincing results. Originally, PNE was beneficial to the four persons included to the study, 2 with STC and 2 with dyssynergia. After this test period of 3 weeks and before a permanent device was planned, they observed a return to baseline values of the percentage of abdominal pain, bloating and symptom analog score after 3 days. The bowel frequency also returned to baseline levels over a longer period. In a follow-up of 6 months after a permanent implementation, the symptoms of 3 out of 4 persons improved. In addition to an increase of stool frequency, an improvement in the VAS, Wexner score and quality of life was seen. The transit time normalized in one person. In a subsequent study by the same working group (36) two patients of the previous study were selected into a double-blind placebo-controlled crossover study. They observed a marked improvement in spontaneous defecations, abdominal pain, bloating and VAS, when the stimulator was turned ‘on’ compared with ‘off’.

<table>
<thead>
<tr>
<th>Summary level of evidence</th>
<th>Type of studies</th>
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<td>I</td>
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<td>a</td>
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<td>b</td>
<td>High quality RCT</td>
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<td>c</td>
<td>All or none studies</td>
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<td>b</td>
<td>Poor quality RCT, individual high quality cohort study</td>
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<tr>
<td>c</td>
<td>Ecological study</td>
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<tr>
<td>III</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Systematic review of case-control studies</td>
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<td>b</td>
<td>Individual high quality case-control study</td>
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<td>V</td>
<td>Expert opinion, bench research</td>
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<tr>
<td>Reference</td>
<td>Year</td>
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<td>-----------</td>
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</tr>
<tr>
<td>Ganio[43]</td>
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<tr>
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<tr>
<td>Naldini[40]</td>
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<tr>
<td>Kamm[47]</td>
<td>2010</td>
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<tr>
<td>Sharma[48]</td>
<td>2011</td>
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<tr>
<td>Govaert[49]</td>
<td>2012</td>
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<tr>
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<tr>
<td>Ortiz[51]</td>
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<tr>
<td>Ratto[52]</td>
<td>2014</td>
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<tr>
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</tr>
<tr>
<td>Patton[55]</td>
<td>2016</td>
</tr>
<tr>
<td>Maeda[56]</td>
<td>2017</td>
</tr>
</tbody>
</table>

NA: clear data not available; STC: slow transit constipation; ED: evacuatory dysfunction; FU: follow-up; BM: bowel movements; DM: digital manipulation; PCS: prospective case series; PCH: prospective cohort study; RCS: retrospective case series; RDBCT: randomized double-blinded cross-over trial;
Table 6: Studies reporting data about successful use of permanent SNS at end of follow-up.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Follow-up after SNS (months)</th>
<th>Successful use at end follow-up</th>
<th>Definition of long term success</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Number of people</td>
<td>Intention to treat</td>
<td>Per protocol (implanted SNS device)</td>
</tr>
<tr>
<td>Kamm(47)</td>
<td>2010</td>
<td>28</td>
<td>39</td>
<td>63% (39/62)</td>
</tr>
<tr>
<td>Maeda(56)φ</td>
<td>2017</td>
<td>60</td>
<td>18</td>
<td>29% (18/62)</td>
</tr>
<tr>
<td>Sharma(48)</td>
<td>2011</td>
<td>34</td>
<td>10</td>
<td>47% (10/21)</td>
</tr>
<tr>
<td>Knowles(50)</td>
<td>2012</td>
<td>19</td>
<td>9</td>
<td>69% (9/13)</td>
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<tr>
<td>Ortiz(51)</td>
<td>2012</td>
<td>26</td>
<td>14</td>
<td>29% (14/48)</td>
</tr>
<tr>
<td>Govaert(49)</td>
<td>2012</td>
<td>37</td>
<td>61</td>
<td>52% (61/117)</td>
</tr>
<tr>
<td>Ratto(52)</td>
<td>2014</td>
<td>51</td>
<td>32</td>
<td>52% (32/61)</td>
</tr>
<tr>
<td>Graf(53)</td>
<td>2015</td>
<td>24</td>
<td>5</td>
<td>11% (5/44)</td>
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<tr>
<td>Patton (55)b</td>
<td>2016</td>
<td>24</td>
<td>3</td>
<td>5% (3/59)</td>
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<tr>
<td>Zerbib(41)</td>
<td>2017</td>
<td>12</td>
<td>11</td>
<td>31% (11/36)</td>
</tr>
</tbody>
</table>

φlong term follow-up of Kamm et al.

blong term follow-up of Dinning et al. where also a SNS was implanted in patients after negative PNE
Holzer et al. (46) examined in 2008 the effect of SNS in 19 people (8 with STC, 9 with ODS, 2 mixed). For persons with STC, the primary endpoint was more than 2 bowel movements per week. For persons with ODS, the primary endpoint was defecation without digital manipulation. Eight of them met these criteria after PNE and they got a permanent device. In addition to an increase in quality of life, the Wexner constipation score increased significantly compared to baseline level. In concrete terms, baseline median of 23 (range 18-27) decreases after 11 months implantation to 8 (range 4-13).

In 2010, a retrospective study of Naldini et al. (40) was published. They looked at 15 people with slow transit constipation treated from March 2003 to May 2006. 9 finally got a permanent implant. There was a significant increase in frequency of defecation and reduction in the need of enemas. The Wexner Constipation Score fell from a mean of 21 (range 11-27) to 11 (3-20 range). The SF-36 (QoL) score increased from 95.8 (range 88-104) to 102.0 (range 96-113).

Kamm et al. (47) have produced in 2010 the largest multicentre prospective study of sacral neuromodulation for constipation: 62 patients of whom 81% had slow transit constipation were followed up during 28 months. 45 of the 62 progressed after successful PNE to permanent stimulation. 39 out of 62 patients (63%) achieved treatment success at the latest moment of follow-up. Bowel frequency improved from a mean of 3.5 to 7.1/week (p<0.001). They also demonstrated statistically significant decreased straining (75.3% of time to 40.5%), reduction in incomplete toilet, decreased abdominal pain and bloating and improved SF-36 (QoL) scores in four domains. Kamm et al observed a change in the visual analogue score of severity of symptoms (0=worst, 100=best) for bowel function from 8 before treatment to 66 after treatment. The Wexner score improved from 18 at baseline to 10 at 28 months. Both patients with slow and normal transit time benefited. After 6 months, colonic transit time normalized in half of those with baseline slow transit with a corresponding increase in defaecatory frequency. Rectal sensation was altered by stimulation. There was a reduction in the sensory, urge, and maximal thresholds to rectal balloon distension. Maeda et al (56) recently published the long-term follow up of this study. 18 patients of the 45 originally implanted with SNS attended at 60 months of follow-up. 27 premature study exits occurred, of whom 7 had loss of efficacy and 1 had infection of the implant. In 14 out of 18 patients attending 60-month follow-up, the Wexner score was available. Improvement was sustained (18 at baseline vs 10 at 60 months).

Sharma et al. (48) did a retrospective study in 2011. They implanted temporary neuromodulation wires in 21 patients, of whom 18 had slow transit constipation. Patients with more than 50% improvement in bowel diaries were candidates for a permanent implant. Such an improvement was seen in 12 patients. One person refused further intervention. 11 patients received a permanent implant. The median stool frequency increased from one per week at
baseline to four per week at 34 months of follow-up. 8 of the 11 patients completely stopped the use of laxatives and 2 of them reduced laxative use by more than 50%. One person lost therapeutic response after permanent implant.

One year later, in 2012, Govaert and colleagues (49) published a retrospective study of 117 patients who had PNE with a median follow-up of 37 months. Of these, 68 patients had a successful PNE and underwent implantation of a permanent device. Patients who had a successful PNE were younger than those who had a failed PNE. (mean age, 43.2 years vs 48.9 years, p = 0.02). Age was a statistically significant predictive factor of PNE outcome (p = 0.02). Success rate of PNE was higher in patients who had normal colonic transit time compared with those who had slow transit (NTC: 76% vs STC: 52%; p = 0.048).

In 2012 there was a prospective randomised double-blind placebo-controlled crossover of Knowles et al. (50) 13 patients with evacuatory dysfunction and demonstrable rectal hyposensitivity completed the trial. Inclusion was also based on the absence of delayed colonic transit time. During a 4-week period of temporary stimulation, patients were randomised ON-OFF/OFF-ON for two 2-week periods. Defecatory desire volumes to rectal balloon distension were normalised in 10 of 13 patients and maximum tolerable volume in 9 of 13 patients. This illustrates a normalisation of their rectal sensation, which was the primary outcome of the study. There was also a significant increase in proportions of successful and complete bowel movements, and Wexner Constipation Scores improved in 11 of the 13 patients. There were no significant changes in other symptoms and in quality of life measures. In the end 11 patients progressed to permanent stimulation, of whom 9 with success at 19 months. This study was limited because of the small sample size of highly selected patients.

Ortiz and co-workers (51) retrospectively reviewed 48 patients. 23 were implanted with a permanent stimulator. On an intention-to-treat basis, 14 of 48 patients met the definition of a successful outcome at 26 months. The Wexner Constipation Scores decreased from a mean of 20,2 at baseline to 5,4. Nevertheless, 6 of 14 patients were still using laxatives and/or enema at the last follow-up.

In 2014 Ratto et al. (52) did a retrospective study on 61 patients. 42 received a definitive SNS implant. At a mean follow-up of 51 months, the mean baseline Wexner Constipation Score of 17 (SD 6) dropped to 9 (SD 6). Threshold and urgency rectal sensation significantly decreased, while anal pressures did not change. The SF-36 (QoL) Score significantly improved following SNS. All these findings above were more marked in patients with obstructed defecation.

Graf et al. (53) published in 2015 a report of 44 patients with chronic constipation. They were treated with a 3-week test stimulation. In 15 patients there was a 50% reduction of symptoms
and they received a permanent implant. Four were explanted during the course of the study. Five subjects reported sustained symptom relief at final follow-up after a mean of 24 months. The mean ODS score did not change during the treatment.

In 2015 the largest double-blind randomized controlled crossover study on SNS in slow transit constipation was published. Dinning et al. (54) evaluated the efficacy of suprasensory and subsensory SNS compared with sham. After 3 weeks of PNE, all patients had permanent implantation and were randomized to subsensory/sham (3 weeks each) and then re-randomized to suprasensory/sham (3 weeks each) with a 2-week washout period between each arm. Of the 59 patients, 16 (28%) responded positively to PNE. Regardless of how they responded to PNE, a permanent device was placed, after dropout of 4 people, in 55 patients. The reason was to determine the positive and the negative predictive value of the initial PNE results. The primary outcome measurement was the proportion of patients who, on more than 2 days/week for at least 2 of 3 weeks, reported a bowel movement associated with a feeling of complete evacuation. The proportion of people who achieved the primary endpoint did not differ between suprasensory stimulations (30%) and sham (21%), nor between subsensory (25%) and sham (25%) stimulation. In addition, there were no significant changes in QoL scores. When compared with baseline measures, suprasensory, subsensory and sham stimulation caused significant changes in a number of measured characteristics. The positive and negative predictive value of the initial PNE results for a response on a permanent SNS for short-term (3 weeks) were, respectively, 50% and 78% (p = 0.04). Straightforward, this can be translated to: a positive PNE in patients with STC is a poor predictor of short-term success of a permanent pacing. A negative PNE is a fairly good predictor of the failure of continuous therapy.

One year later, in 2016, Patton and colleagues (55) published the long-term follow-up results of the patients, who completed the randomised controlled trial (RCT) of Dinning et al. The primary endpoint was identical to the RCT in 2015. 53 patients completed the trail and entered long-term follow-up. By the end of the second year, 44 patients withdraw from the study due to patient dissatisfaction and adverse events leading to treatment failure. At 1 and 2 years, 10 and 3 patients achieved the primary outcome measure. As a secondary endpoint, they looked at improvement of the colonic transit time, as measured by scintigraphy. The amount of isotope in the colon after 72 hours did not differ between the beginning and 1-year follow-up. At last the positive and negative predictive value of PNE results for a response to permanent SNS after 2 years were 6% and 94%.

The latest randomized controlled trial of SNS for refractory constipation is from Zerbib et al. (41) 36 subjects underwent PNE. 20 responded and received a permanent stimulator. A least
three bowel movements per week and/or more than 50% improvement in symptoms was observed in 12 of 20 and 11 of 20 patients after active (‘ON’) and sham (‘OFF’) stimulation respectively. Both active and sham period took 8 weeks. At 1 year of permanent stimulation, 11 of the 20 patients continued to respond. Statistically significant improvement was seen in sensation of incomplete evacuation, number of days with pain and Wexner, VAS and QoL scores. There was found no significant effect of stimulation on colonic transit time.

Due to inconsistent and no standardized representation or not reporting of complications, coherent analysis is difficult. Maeda et al. reported about this issue and stated that lead displacement was the most common problem in the PNE stadium. After implantation, loss of efficacy, pain and infection around the device site were most reported. Overall, almost all complications were minor and easily treated. (57)

4.1.5 Discussion
The opportunity of a minimally invasive treatment for constipation refractory to standard therapies, is attractive. A test period of 3 weeks without any major complications is a big advantage. This is particularly true for the heterogeneous group of constipation where the alternative might be a severe invasive surgical procedure, such as a colectomy. The question is, can SNS be a valid treatment for constipation?

This review summarizes the results of 17 studies, of whom 4 studies have level IIb of evidence and the others have level IV of evidence. With this in mind, it can be concluded that open-label, uncontrolled older studies showed some promising results in constipation, but lack high evidence. (36, 40, 44, 45) The large prospective study of Kamm et al. enlarged the evidence of efficacy of SNS for constipation. (47) Recent RCTs, however, showed less positive results. Thus, it is still unclear which results can be expected in clinical practice. (41, 54) More robust data is needed to incorporate SNS in clinical practice and make reimbursement of this expensive technique possible. Nowadays, SNS for constipation is not reimbursed in Belgium.

PNE has been a reliable screening test for patients suffering from faecal incontinence. Those with a positive effect during PNE are highly likely to benefit from a permanent device.(58) In the context of constipated patients, the value of PNE is less well established. Looking at studies with more than 10 subjects, the success rates are ranging from 28% in the RCT of Dinning et al. (54) to 85% observed in Knowles’ RCT of a small sample size (n=13) of highly selected patients with functional ODS and rectal hyposensitivity and no slow transit.(50)

After a positive PNE (per protocol analysis), between 33% and 90% of people showed a successful use at the end of follow-up. (48, 53) The high success rates of 90% were seen in two retrospective studies of Sharma et al. (48) and Govaert et al.(49). The latter study
considered retained implant as definition of long term success. When looking at studies with a comparable follow-up (between 24 months and 28 months), the success rates were between 33% and 87% of people. (47, 51, 53) This illustrates the great variability in success. The results of the study of Graf et al. are not mentioned here, because in this study a permanent SNS device was also implanted in patients after negative PNE.

On an intention to treat analysis, these rates are between 5% in the study of Patton et al. (55) and 69% observed in Knowles’ RCT (59) of a small sample size of highly selected patients. The latest well-constructed (level IIb) study of Zerbib et al. reported 31% of success on an intention to treat basis. This variability needs to be further clarified, because pacemakers are too expensive to implant without some assurance of success. Further research is needed to develop strict criteria for a positive PNE and to determine a generally accepted definition of long-term success.

In the European consensus statement of 2015 of Maeda and colleagues, they asked 22 experts if SNS for constipation could be considered for patients who have had symptoms for more than one year and after failed conservative therapy. The patient should have slow transit constipation and/or symptoms of outlet obstruction without a mechanically correctable cause. 73% of the experts agreed, which was not enough for a recommendation. This illustrates until this date the disunity for the use of SNS for constipation. (38) Recently (2017), another expert panel headed by Knowles, agreed about following practice recommendation: “Patients should be counselled that the evidence base does not support the use of SNS for chronic constipation”. (Evidence level II, Grade B) (60)

Furthermore in all studies, they could not identify any clinical or physiological factor associated with sustained response to SNS in patients initially tested, what makes it difficult to predict the best candidates for this treatment. Knowles and co-workers observed only a highly selected group with evacuatory dysfunction and demonstrable rectal hyposensitivity without delayed colonic transit time. The results of their RCT were good. 69% of people were still using their SNS. (50) The results of the retrospective studies from Govaert et al. and Ratto et al. where different according to the type of constipation. The outcome was better in subjects with normal transit time and evacuatory dysfunction compared to subjects with slow transit time. (49, 52) However, the results of these studies can’t be generalised due to the study design and the incomplete data regarding pathogenesis of constipation. Other studies reported no difference between the effect of SNS on slow transit constipation or evacuatory dysfunction. (46, 47, 51, 53) In the study of Kamm et al. colonic transit time normalized in half of those with baseline slow transit after 6 months of therapy. (47) Such a marked change in physiology was not
confirmed in other studies. No consistent changes in physiological parameters can be found in literature.

Another important factor is the individual’s psychological status, illustrated by the study of Carriero et al. (61) 68 patients with STC were offered psychological assessment using the Minnesota Multiphasic Personality Inventory (MMPI) questionnaire. 45 completed the MMPI questionnaire. A normal score was found in 13 patients and they underwent PNE. Eventually, 11 received a permanent implant. Nine of those who had refused to complete the questionnaire or had an abnormal score, also underwent PNE. Only three of them progressed to permanent stimulation. A complete and accurate psychological evaluation could have an important role in management of constipated patients and should be a selection criteria for SNS.

Discrepancies among studies are likely to be multifactorial. Comparisons between these studies are difficult because of differences of study design. The retrospective studies may have recall bias. While RCT and the long follow-up studies, such as Maeda et al. (56), may have attrition and reporting bias, because maybe only the patients who had good outcome from the therapy filled in bowel diary and completed the constipation scores and questionnaires of quality of life. Also patient selection, definition of constipation, measurement tools, follow-up period, management during the follow-up, criteria used to evaluate outcomes were different. Most studies used frequency of defecation as one of their measurements. It is important to take into account that although symptoms may significantly improve, none of them completely resolved. Measuring the satisfaction of bowel function (for example with VAS) and quality of life were used in recent studies and should be a standard for following studies.

Finally, there were no studies found that compared SNS to another treatment. This makes it difficult to assess the relative value of each treatment option. More studies are needed to further assess the position and efficacy of SNS in constipation. This is also mentioned in the Cochrane systematic review of Thaha et al. in 2015. (58)

4.1.6 Conclusion
Older studies showed some promising results for SNS in constipation, but lack an adequate methodology to prove its results. Recent randomized controlled trials with higher levels of evidence showed less positive results on short and long term. There is also no evidence that SNS is best for a specific subtype of constipation (STC, NTC, ODS). SNS for constipation needs larger prospective studies to enlarge the current evidence base before incorporation of SNS in clinical practice can be advised.
4.2 ANTEGRADE COLONIC ENEMA

4.2.1 Introduction
The antegrade colonic/continence/continent enema (ACE) is an alternative technique for the treatment of faecal incontinence (FI) or constipation after failed conventional treatments. It is an option for those who prefer to avoid colectomy or/and an end stoma. These more invasive procedures do not have ultimate efficacy and are unacceptable in some subgroups, such as children. (11) ACE was first described in 1990 by Malone et al. for the treatment of FI in children. (62) In the subsequent years, it has become a popular treatment option in the paediatric world for both FI and severe constipation.

The ACE procedure in a pediatric setting was reviewed by Siminas et al. including 25 studies (total of 505 patients). Good outcomes were estimated in 82% of the cases. (63) The role of ACE in the treatment of constipation in adults is not well established, because the success rates tend to be less satisfactory. The aim of this literature study is to review the clinical outcomes of ACE in a constipated adult population.

4.2.2 Procedure and mechanism of action
As mentioned, Malone et al. were the first in 1990 to use ACE as treatment for FI in children. They created a continent stoma based on the Mitrofanoff principle, where the appendix was used to create a conduit between the skin surface and the urinary bladder. First, they resected the appendix and a cuff of caecum with preservation of the appendiceal arterial supply. Subsequently, a submucosal tunnel was constructed in the tenia of the caecum. The distal end of the appendix was sutured to the caecum and then the proximal part was brought out on the right side of the lower abdominal wall as a stoma. Malone et al. thought the inversion of the appendix would act as an valve mechanism to prevent leakage. Later, equally good results appeared when the appendix is left in situ, only its tip is excised and brought out as an appendicostomy. (64) Throughout the years several modifications have been described using the terminal ileum (65), caecum, left colon, as a conduit instead of the appendix. (66) All these techniques have complications like leakage, stenosis and pain at the site.

More recently, a gastrostomy tube button in ceacum or ileum and a percutaneously placed cecostomy catheter are also used to get access to the colon. A percutaneous endoscopic cecostomy (PEC) is an innovative procedure proposed as a minimally invasive alternative. There is no need for general anesthesia, laparotomy or laparoscopy. There is no stoma stenosis possible due
to the indwelling tube/button. Also less wound problems can be expected compared to more invasive surgical Malone procedures. (67) Wrong position, spillage of stool and leakage along the catheter are some of the reported complications.

Such procedure could also be done under radiological guidance, but the endoscopic method offers the advantage of direct visualization of the cecostomy site. In this way, selection of desirable spot (and not the terminal ileum or any other undesirable spot) and both direct observation and treatment in case of luminal bleeding is possible. (68)

After adequate surgery and resting period, water or enema solution are injected in the colon, resulting in removal of faeces out of the colon in an antegrade manner after a mean time of 20-30 minutes. The frequency and quantity of fluid administration are adapted to each patient to achieve the most satisfaction. The effectiveness of irrigation is thought to rely on the induction of colonic propagating waves, direct mechanical lavage and weakening of the stool. The optimal volume needed to achieve the two effects varies among patients. (69) It can be used in both constipation and FI to alleviating symptoms.

The administration of fluid can also be done via the retrograde route. However, the volume is frequently limited by the patient’s ability to resist the urge to evacuate and the sphincter’s ability to effectively retain the fluid, resulting in only a cleared distal colon. Using an antegrade route via administration in the right side of the colon, these limitations can be tackled, resulting in a more effective evacuation of both sides of the colon. (70)

4.2.3 Methodology

The MEDLINE and Embase databases were searched for studies demonstrating the use of ACE as treatment for constipation, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). The terms used in the search builder were: ‘constipation’ AND 'antegrade colonic/continent/continence enema’. The latest search was on 27/7/2017. Further selection was made by selecting people older than 18 years and only English written articles. The Cochrane Central Register of Controlled Trials database (CENTRAL) was consulted, looking for articles that have ‘antegrade continence enema’ in their title, abstracts or key words.

The articles were then further selected by looking at title and abstract. Inclusion criteria were clinical studies, such as RCTs and case series. Also endoscopically placed cecostomy tubes were included. Exclusion criteria were case reports, studies including patients younger than 16 years despite the mean/median age above 18 years, no full text available, and studies conducted at the same institution and including the same patients, but with shorter follow-up.
By reading the reference lists of the selected articles, two more articles could be included. (71, 72)

The focus in SNS (see 4.1) was on primary constipation in adults. Because of the limited amount of studies reporting ACE in primary constipation also studies describing results of population with secondary causes of constipation were selected. Additionally, studies reporting both the results of ACE in FI and constipation were read to enlarge the total count of constipated patients to review. In this way, eventually 12 studies were withheld. The methodology of scoring studies is already mentioned in the methodology of sacral nerve stimulation. (see 4.1.3)

Figure 6: PRISMA flow diagram of the search for antegrade colonic enema and constipation.

4.2.4 Results

100 studies could be identified with the search, of which 12 could be included in the studies. All were nonrandomized, uncontrolled studies. Only 3 of them had a prospective design. 6 studies only included constipated patients. All, except one (73), observed a heterogeneous group of constipation. The other 6 studies included patients identified with constipation, FI or both. In total, 319 patients could be reviewed over a follow-up period ranging from 6 to 75 months. Meta-analysis was not an option, given the heterogeneity in pathology, type of ACE conduit, follow-up time and the reported outcomes.
Table 7: Results of published studies about ACE for constipation.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>N</th>
<th>Type of constipation</th>
<th>C</th>
<th>Fl</th>
<th>Both</th>
<th>Follow-up (months)</th>
<th>Successful use at end follow up (%)</th>
<th>Definition of success</th>
<th>Type of ACE conduit</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biyani (73)</td>
<td>2007</td>
<td>5</td>
<td>idiopathic constipation</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>5 (100)</td>
<td>Patient-reported great satisfaction</td>
<td>Endoscopic tube cecostomy MIC-KEY button</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Uno (68)</td>
<td>2006</td>
<td>15*</td>
<td>neurogenic bowel</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>11 (73)</td>
<td>Patient-reported satisfaction</td>
<td>Endoscopic tube cecostomy + Chat</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Duchalais (87)</td>
<td>2014</td>
<td>21</td>
<td>STC(12), neurogenic(5), anorectal malformation(2), scleroderma(1), opioid analgesics(1)</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>11 (52)</td>
<td>Still performing ACE (No clear data about success)</td>
<td>Endoscopic tube cecostomy CHAIT</td>
<td>PCH</td>
<td>IV</td>
</tr>
<tr>
<td>Rongen (72)</td>
<td>1999</td>
<td>12</td>
<td>idiopathic(9), neurological(2), medication(1)</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>8 (67)</td>
<td>'considered successful' (No clear definition of success)</td>
<td>A, INA, CDC</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Lees (74)</td>
<td>2004</td>
<td>32</td>
<td>STC(6), ODS(9), STC and ODS(8), unknown(8)</td>
<td>32</td>
<td>0</td>
<td>0</td>
<td>36</td>
<td>15 (47)</td>
<td>Still performing ACE (No clear data about success)</td>
<td>A, INA, CeA, 2 distal colonic conduits</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Meurette (71)</td>
<td>2010</td>
<td>25</td>
<td>STC(17), neurogenic(3), previous anoperineal surgery for constipation(5)</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>55</td>
<td>13 (52)</td>
<td>Still performing ACE (No clear data about success)</td>
<td>A, CeA, INA</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Portier (75)</td>
<td>2006</td>
<td>28</td>
<td>FC, Fi; perineal colostomy after abdominoperineal resection, imperforate anus with FI</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>27</td>
<td>26 (93)</td>
<td>Still performing ACE (No clear data about success)</td>
<td>A, CeA, INA</td>
<td>PCH</td>
<td>IV</td>
</tr>
<tr>
<td>Krogh (76)</td>
<td>1998</td>
<td>16</td>
<td>neurological(2), STC(1), systemic sclerosis(1), ODS(1), postoperative(1)</td>
<td>6</td>
<td>10</td>
<td>0</td>
<td>17</td>
<td>12 (75)</td>
<td>Still performing ACE: satisfaction high(8) very high(2) 2 no longer used it because no symptoms</td>
<td>A, CeA</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Hirst (77)</td>
<td>2005</td>
<td>20</td>
<td>ODS</td>
<td>7</td>
<td>0</td>
<td>13</td>
<td>6</td>
<td>15 (75)</td>
<td>'13 satisfied with the outcome 2 remained the same and still used ACE'</td>
<td>A, CeA</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Altomare (65)</td>
<td>2007</td>
<td>11</td>
<td>Fi and FC (4 with PC)</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>44</td>
<td>9 (75)</td>
<td>Still performing ACE (No clear data about success)</td>
<td>INA</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Patton (70)</td>
<td>2015</td>
<td>54</td>
<td>STC(31), OD due to gracilis neosphincter(5), cong anomalies(8), spinal injury(2)</td>
<td>46</td>
<td>6</td>
<td>2</td>
<td>66</td>
<td>35 (65)</td>
<td>Still performing ACE (No clear data about success)</td>
<td>A or CeA + Chat cecostomy catheter</td>
<td>RCS</td>
<td>IV</td>
</tr>
<tr>
<td>Worsoe (78)</td>
<td>2008</td>
<td>80</td>
<td>idiopathic FC (19), anorectal disease or surgery (8), neurologic (20), scleroderma (1)</td>
<td>48</td>
<td>20</td>
<td>12</td>
<td>75</td>
<td>51 (64)</td>
<td>43 still performing ACE 8 no longer needed it</td>
<td>A, CeA, INA or A/NA + colostomy</td>
<td>RCS</td>
<td>IV</td>
</tr>
</tbody>
</table>

*Uno et al. observed 20 patients, but the 5 patients with bowel obstruction were excluded.
C: constipation; Fl: faecal incontinence; STC: slow transit constipation; ODS: obstructed defecation syndrome; A: appendicostomy; CeA: cecal tube neoappendicostomy; INA: ileal neoappendicostomy; RCS: retrospective case series; PCH: prospective cohort study; PCS: prospective case series
No strict definition of success is observed in the different studies. In all studies, the proportion of people still using their ACE at the end of follow-up was reported. Several studies mentioned this is probably comparable to the success rate, because the reason to stop irrigating via ACE could be no symptomatic relief or suffering from complications. Other studies just mentioned 'successful' without given an clear definition of success. In four studies the subjective satisfaction of patients was asked to determine success. Only one study explicitly defined successful treatment as: “patients who were still using ACE at follow-up or patients whose symptoms had resolved as a result of the treatment and who, therefore, no longer required treatment” (78) Such heterogeneity in definition of success makes it difficult to compare the several studies. With this in mind, following results were reported. The results of the studies reporting only on patients with constipation and the studies reporting on both constipated and/or faecal incontinent patients are presented separately.

4.2.4.1 Constipation only

Studies with a short follow-up time (< 3 years) have a success rate varying from 52 to 100%. (67, 68, 72, 73). Three out of four studies used a percutaneous endoscopic caecostomy (PEC). (67, 68, 73)

Biyani et al. placed a caecostomy (MIC-key) button endoscopically in 5 patients. 3 patients were satisfied with their caecostomy buttons and so did not undergo formation of surgical ACE. The other 2 subsequently had a permanent ACE. After a median follow-up of 19 months, all patients reported great satisfaction, increased self-esteem, energy, confidence and appetite. However, 4 out of 5 patients reported pain at the caecostomy site, which was controlled adequately by mild analgesics. (73)

Uno et al. observed 15 patients. All of them had undergone PEC. Nine were changed to the Chait Trapdoor caecostomy catheter. One person died from unrelated cause before the end of follow up. Three moved to other hospitals and were lost to follow up. Of the 11 patients available for follow up, all continued to use ACE and were satisfied with the results. (68)

In the most recent study of Duchalais et al., a Chait Trapdoor caecostomy catheter was successfully placed in 19 patients of the 21 included for the study. At 1 year of follow up 11 patients were still using their Chait catheter to irrigate their colon. They all were regularly performing ACE. On an intention-to-treat basis, in 11 out of 21 (52%) the procedure was successful. Of the other 8 patients implanted with a Chait catheter, one person died in follow-up unrelated to ACE or its complications. The remaining 7 people stopped ACE due to chronic wound pain (n=5), accidental removal and closure of the abdominal wound (n=1), or catheter
handling difficulties (n=1). 14 patients didn’t use laxatives or retrograde irrigations during the period of ACE administration. (67)

This study of Duchalais et al. had data on functional outcome and QoL before and after placement. Median KESS (Knowles Eccersley Scott constipation Score) decreased from 25 (12-39) to 17 (6-34) one year after PEC placement in 15 out of 21 patients of whom clear data were available independently of ACE success (p< 0.05). Also quality of life improvement was observed. The GIQLI (Gastrointestinal Quality of Life Index) scores increased from a median of 65 (25-104) to 95 (48-119) after the procedure. Remarkably 3 out of 4 patients, who had PEC removal after several months and were available for follow-up after 1 years, reported decreased KESS and increased GIQLI scores although none of them underwent surgical procedures during the follow-up. (67)

In a Dutch prospective study of Rongen et al. the Cleveland Clinical Constipation Score (CCCS) dropped from a median of 21,5 to 5,5. An important remark is that they only calculated the mean of the scores of the successful patients (8 of 12). They did not incorporate the scores of 4 patients for who ACE was not successful. Besides the improvement in CCCS, the constipation associated symptoms showed significant improvement regarding rectal pain, incompleteness of defecation, use of laxatives or manual evacuation. Changes in abdominal pain or bloating were not significant. As regards QoL, alternative tools like the State Trait Anxiety Inventory, Zung test and Nottingham Health Profile levels were used. The first two tests significantly improved in successfully treated patients. The third had a tendency to decrease. (72) Analogous to the studies of Duchalais et al. (67) and Muerette (71) et al. QoL remained elevated in comparison with the general population. This study of Rongen et al. is the only study with shorter follow-up that mentioned additional procedures. Four patients, who do not use their ACE anymore, underwent subtotal colectomy. Thereafter two of them needed an ileostomy for persisting symptoms. (72)

On longer term (> 3 years) the sustained-use-rates reduce to range from 47 to 52% in patients using ACE at 36 and 55 months of follow-up. (71, 74) In these studies, failure of ACE could not be predicted by pathophysiological, demographic or clinical indices. After failure, further surgery was common.

In the study of Lees et al. ACE had failed in 17 out of 32 patients. 12 (71%) had undergone further surgery to treat their constipation at 36 months of follow-up: 9 had end stomas, 2 right hemicolecctomies and 1 left hemicolecctomy. (74)
In the other long-term follow-up study of Meurette et al., 13 of 25 (52%) patients continued to irrigate their colon. This study, only reporting post-operative KESS and GIQLI scores, confirmed that the mean QoL score and the mean constipation score did not reach the general population level (KESS < 7 and GIQLI > 125). The effects of ACE on functional outcome or QoL cannot be deduced in this last study, because of no preoperative evaluation of these scores. 8 out of 12 people (67%) who had stopped irrigations needed further surgery: 2 total colectomies with ileostomy, 3 colectomies with ileorectal anastomosis and 3 segmental colectomies. At the end of follow-up, 5 people in this group had subsequent an end colostomy. (71)

Thus, approximately 50% of patients still used their ACE at more than 3 years of follow-up. The patients with failed ACE, often required further surgery: colectomies and/or stomas. The functional outcome and QoL was better after ACE, but did not reach general population levels.

4.2.4.2 Constipation and FI

Successful use on short term (< 3 years) at end of follow-up of 3 studies was reported to range from 75% to 93%. Both appendicostomy (A) and cecal tube neoappendicostomy (CeA) were used in every individual study. (75-77) Ileal neoappendicostomy (INA) was an additional technique in the study of Portier et al. In this study, all patients with an INA and CeA could use their conduit after a median follow-up of 27 months. Failure to use ACE at end of follow-up was seen in 2 out of 7 appendicostomies, because of intra-abdominal sepsis. (75)

In the study of Krogh et al. 12 of 16 patients were satisfied with the results, although only 10 patients were still irrigating their colon with ACE. The two no longer used the stoma because the symptoms had disappeared or because of serious illness during the median follow-up of 17 months. (76)

The role of the ACE procedure in 20 female patients, suffering from obstructed defecation with (65%) or without (35%) faecal incontinence, was investigated by Hirst et al. On a median period of 6 months still 15 were irrigating via ACE. 13 of them had an subjective improvement of their symptoms. Two women had no improvement and one person felt much worse after ACE due to pain while flushing. Another women stopped ACE, because she was unable to manage it. From 3 persons no data could be retrieved. Hirst et al. used the bowel-related questionnaire (BRQ) for obstructed defecation and Cleveland continence score (CCS) for Fl. In this study, BRQ (41.5 versus 25.6; p<0.001) and CCS (9.3 versus 5.5; p=0.001) improved significantly postoperatively. There was no significant change in quality of life as assessed on SF36 (101.5 versus 99.5; p=0.154) (77)
Of the 3 studies with longer follow-up (>3 years), the success rates decreased to 64%-75%. (65, 70, 78) Again different techniques to perform ACE were used (see table 6).

Altomare et al. included patients with functional constipation, FI and perineal colostomy formation for constructing a modified Marsh and Kiff ACE (ileal neoappendicostomy). 75% still used their ACE at median follow-up of 44 months. Altomare et al. used the American Medical System (AMS, maximus score = 120) for FI and Cleveland Clinic Constipation index (CCC, maximum score 30). Both mean AMS (77 versus 11) and CCC (23 versus 8.5) score were significantly decreased during the postoperative period. GIQLI scores were available for 6 out of 11 patients. A significant increase of the mean value from 92 pre to 102 points postoperatively was observed. (65)

In the most recent study of Patton et al., a significant relationship, between patients’ confidence in their ability to manage the irrigation procedure and their satisfaction with the procedure (p<0.01) was seen. Majority of failure was due to irrigation failure rather than surgical complications. Only some components of QoL were evaluated with VAS postoperatively. VAS for patients with successful ACE were high regarding confidence to partake in social activities (VAS=82) and all-day activities (VAS=71). (70)

In the study with the longest follow-up (75 months), 11 of 80 patients operated were not available for follow-up. 43 patients (54%) were still performing ACE. Additionally, 8 people did not need ACE anymore as symptoms were resolved. So the procedure was determined by Worsoe et al. to be successful in 51 cases (64%). By using VAS before and after procedure, they measured the bowel function and QoL. For the bowel function the VAS increased from 12 preoperatively to 81 postoperatively in the patients with sustained use at end follow-up. (P<0.01) For the QoL, VAS increased from 28 before to 81 after of the procedure on a scale of 100 (P<0.01). (78)

The results of the subgroup of only constipated patients was available in 4 out of 6 studies. There seems to be a trend of slightly lowered rates when compared with the whole study population: constipation and FI. (70, 76-78) Constipated people still using ACE at end follow-up were 25 (52%) out of 48 (78), 4 (57%) out of 7 (77), 18 (58%) out of 31 STC patients (70) and 4 (67%) out of 6 (76).

Although most individual studies tried to assess functional outcome and QoL, it is difficult to compare due to lack of use of validated tools. Despite this, the functional outcome and the quality of life in all studies improved after the procedure, regardless of the tool to measure. In some studies this improvement was significantly.
4.2.4.3 Complications

Due to no standard representation, lack of data, no standardized definition of complications and different techniques of ACE, it is difficult to make a coherent analysis of complications. Therefore only the most common complications are mentioned to maintain the bigger perspective.

In 4 studies no stoma stenosis was observed. (67, 68, 73) Remarkably, 3 of these studies only used the PEC technique. (67, 68, 73) However, the need for reinsertion of the catheter in these studies was often observed. In the other studies, where surgical Malone procedures were used, the stoma stenosis rate varied from 5% to 34%. (65, 71, 72, 74-78) Lees et al. (74) and Portier (75) et al. reported some lower stenosis rates for ileal neoappendicostomy compared with appendicostomy. The most common reason for revision of the stoma was stenosis. Chronic wound pain, especially with the PEC technique, and wound infection were also common reported. They were treated conservatively.

4.2.5 Discussion

This review summarizes the results of 12 studies on the use of ACE in adults for constipation (and faecal incontinence). All the reports have level IV of evidence. Hence, no strong conclusions can be drawn. Despite this fact and looking at the long term results, the mean overall success is approximately 50%. Functional outcome and quality of life, improved in most studies, but did not reach general population levels. Complications were common present, of which some like leakage and stoma stenosis after Malone surgical approaches needed revision surgery. It is important to set this in the context of the complexity of functional problems, like constipation. Patients need to have realistic expectations. It should be educated that ACE is a long-term management process and not a cure for their condition. (70)

Factors that may have an influence on the results are the technique of operation, type of constipation and commitment of the patient towards ACE. There is still no consistent evidence preferring one technique. Some have found that the frequencies of leakage, stenosis and reflux all favor ileal neoappendicostomy. (75) However, other studies, demonstrating different surgical procedures did not observe significant differences favouring a surgical procedure. In all studies the conduit was created on the right side of the abdomen. No single study presented results of left antegrade colonic enema (LACE). Several studies in the paediatric setting reported good results with LACE. (79) This still has to be confirmed in the adult setting.

Studies, describing the PEC technique with an indwelling catheter showed some benefits when compared with surgical Malone procedures like A, ILA, CeA. (67, 68, 73) First of all, less
major complications that can require revision surgery were observed, for example stoma stenosis is not an issue with PEC. Secondly, it is also minimally invasive throughout endoscopically placement, and has been done under sedation with local anaesthesia. (67) This could be extremely helpful in treating severe constipation, especially for patients who are not optimal candidates for surgery. Thirdly, performing a PEC demands less technical skills of the surgeon, so less mistakes can be expected. Finally, PEC is reversible. It allows to assess whether the patient may benefit ACE in the long term. In case of absence of efficacy or complications, simply gentle traction of the PEC tube is sufficient for removal. Within days spontaneous closure of the stoma will follow. (67) This procedure does not compromise further surgery when required in the long run. Feasibility and safety of PEC has been demonstrated by Biyani et al. (73) Now recently, Duchalais et al. reported that functional results are comparable to other approaches of ACE. (67) An indwelling catheter has also issues. Complications like pain, leakage along the catheter, granuloma formation and dislocation are reported. It is also expensive due to frequent (annualy) replacement. For some patients, the feeling of a foreign object in their abdomen can be enough to quit ACE irrigation.

According to the type of constipation, no consistent differences in success could be retrieved. Thus, it is unclear who (STC, ODS or secondary constipation) benefits the most from the ACE procedure. Beside the vagueness about the best technique to use and most suitable constipation type to treat with ACE, it is sure that the success of the ACE procedure is dependent on the motivation and dedication of the patients for the therapy. This should be asked properly before application.

A moderate rate of complications like stoma stenosis, infection and the chronic wound pain were reported. However, on balance, the ACE procedure appears to be safe. Nevertheless, complications should be better prevented to improve long-term durability of the device. Morbidity and complications are quite unacceptable, keeping in mind that the main goal of ACE is to improve digestive function and quality of life.

Remarkably was the improvement in functional outcomes in 3 out of 4 people despite the PEC removal. However, some studies investigating ACE in children showed similar results. They demonstrated that the colonic motility can improve after using ACE for at least 6 months. (80) Such studies had not been done on adults, but the observations in the study of Duchalais et al. raise curiosity. Further research on this topic in adults is necessary.

Several limitations exist in the studies included in this literature review. First, the number of patients in every single study is small. This may be due to rare indication and that ACE is not commonly done on adults. Second, every single study included a very heterogeneous group of constipation (see table 6) making it impossible to determine whether the therapy could be
more beneficial for a subgroup of constipated people. Third, most studies have a retrospective design which is vulnerable for bias, especially recall bias. Finally, differences in follow-up time, measurement tools and poorly defined end points make it difficult to compare. It was chosen to present sustained use as marker of success of treatment in most studies. The disadvantage of this decision is that this is pure technical success. It was stated that patients stopped their ACE because of development of complications or no symptomatic relief. However, in some studies, ACE was stopped as symptoms resolved or other reasons unrelated to ACE itself, such as disease progression or increasing disability. Hence, the chance of bias is high. Additionally, it is better to use markers of symptomatic or functional improvement, but these were not consistently reported.

Therefore, it is recommended for future studies to use the same tools to measure functional outcome, quality of life and for reporting complications (see 5. Flowchart and future perspectives). Especially for ACE, registration of irrigated volume, frequency of irrigation and fluency of evacuation is needed. Similarly to SNS, there are no randomized trials comparing ACE with other treatment options. This should be a priority for further research. Also better patient selection and bigger study population are required (which is possible with multicentre studies) to establish which ACE procedure is the best and which constipation subgroup benefits the most from the procedure.

4.2.6 Conclusion
The ACE procedure for constipation in adults is evolving. Approximately in 50% of the patients ACE will be successful and so able to avoid more aggressive approaches, like colectomy. Because of the mostly easily treated complications and relatively cheap procedure, ACE via PEC technique can be an option in clinical practice. If not successful, surgical Malone approaches are still possible or the patient can progress to other surgical procedures (colectomy and/or stoma) which are often required after ACE failure. Surgical Malone procedures can also be done as first choice after discussion with the patient. Further research is needed, especially RCTs or prospective studies with bigger power, to firmly establish the evidence of the ACE procedure for constipated adults.
4.3 COLECTOMY

4.3.1 Introduction

At first sight, colectomy for constipation looks like unnecessary overpowering a benign condition. However, in some cases conservative therapy and less invasive procedures like SNS and ACE do not help the patient. Colon resection is for these patients a radical resort to elucidate or at least improve symptoms and restore quality of life to an acceptable level.

4.3.2 Procedure and mechanism of action

The principal looks easy: removing the part of the intestines that cause the delay of defecation. On the other hand, this means major surgery, which inevitably harms the patients. This can be expressed by peri-operative complications and/or negative long-term functional outcomes in a undeniable part of operated patients.

The idea to treat constipation through resection of the colon originates in the beginning of the previous century. Back then, Arbuthnot Lane removed the whole colon with anastomosis of the terminal ileum to the upper rectum. (81) Approximately one century later, no radical modifications have taken place and colectomy with ileorectal anastomosis (CIRA) still remains the most used surgical approach.

Total colectomy was/is not generally accepted and several other less radical colonic resections have been applied, but no sufficient data in terms of clinical outcome is present to conclude a certain benefit in comparison to CIRA. A subtotal colectomy with ileosigmoid anastomosis (SCISA) is used to preserve more colon. A more and more popular technique is the subtotal colectomy (SC) with ceacorectal anastomosis (CRA). SCCRA is not frequently done by a colorectal surgeon, and no standard technique exist for creating a CRA. By preserving the ileocaecal junction, more absorptive functions (bile, vit B12 and electrolytes) can be expected, which may reduce diarrhea. Another option is segmental resection after regional transit studies. Studies describing this procedure, reporting variable results and again no robust benefit could be found compared to CIRA. (82) Studies describing the combination of antegrade colonic enemas and colectomy were not found.

Table 8: Success rates of the different colectomy procedures. (Summarized results of table 4 from Knowles et al. (82))

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N</th>
<th>Follow-up Mean (in months)</th>
<th>Success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medium (%)</td>
</tr>
<tr>
<td>CIRA</td>
<td>1069</td>
<td>54</td>
<td>87,1</td>
</tr>
<tr>
<td>SCISA or SCCRA</td>
<td>169</td>
<td>49</td>
<td>84,5</td>
</tr>
<tr>
<td>Segmental colectomy</td>
<td>86</td>
<td>40</td>
<td>80,2</td>
</tr>
</tbody>
</table>
4.3.3 **Methodology**

During this literature review a systematic review of Knowles et al. was published on colonic resection for constipation, including different procedures like CIRA, SCISA, SCCRA and segmental colectomy. They reviewed English written studies reporting primary data of patients (n>20) treated for constipation with colon resection. Studies were included when they mentioned clinical outcome: efficacy, harm or both over a minimum mean/median follow up of 12 months. The final search of Knowles et al. was on 22 of February 2016. Because of nearly full analogy with this intended literature review, no new search strategy based on PRISMA guidelines was conducted. Instead, after consulting the supervisors of this thesis, it was chosen to narrative review data about colectomy for constipation.

4.3.4 **Narrative review**

Knowles et al reviewed in 1999 32 studies, published between 1981 and 1998. (83) The latest review of them in 2017 included 40 studies, reporting outcomes in 2045 patients and published between 1988 and 2015. (82) The major differences in inclusion criteria were that the latest only included studies with a study population of minimum 20 patients and follow-up of 12 months or more, while in 1999 no restriction of follow-up was made and studies with a population between 10 and 20 patients were also included. Most of the studies included in the 2017 review are evidence level IV, just a few are methodological better constructed, resulting in an evidence level IIB. (84-86)

4.3.4.1 **Criteria for successful colectomy**

As earlier mentioned, the first report of colectomy for chronic constipation was written in 1908. (81) Since then, no major publications were found until the 80’s where an remarkable increase of studies is observed. Knowles et al. reviewed this topic in 1999 when knowledge about colectomy for constipation was just little. Keeping this in mind, they already had some interesting findings. For example a wider variability in outcome in the group with incomplete physiology testing than in the group with complete physiology test (minimum of anorectal manometry, defecography, and transit study). Studies only including patients with proven slow transit constipation generally had better outcomes to these with incomplete investigation of transit (median outcome 90% vs 67%, respectively). (83)

A study of 106 patients demonstrated that patients with a nonrelaxing pelvic floor (n=16), despite preoperative biofeedback, had significantly higher rates of recurrent defecatory difficulties and lower satisfaction rates after colectomy. (87) Another study, also compared patients with (n=52) and without ODS (n=22). Nyam et al. found no significant difference in result between the both groups. (88) This makes it still unclear if colectomy is suitable for patients who have also obstructed defecation.
Looking at the whole gastrointestinal tract, it is known that a generalized gastrointestinal disorder (GID) (so also upper GI tract involvement) have poorer outcomes than other patients after colectomy. In the prospective study of Redmond et al. a drop in long-term success rate was seen, 90% success rate in the no GID group vs 13% in the GID group. (84)

Also the specific symptoms which the patients present are crucial for colectomy to succeed. Kamm et al. noted that symptoms such as abdominal pain and bloating are not generally improved by surgery. Furthermore, they noticed that patients with psychological problems have lower tolerance for abdominal pain and are faster seeking salvation in surgical treatment, although outcome is adversely influenced by presence of severe psychological problems. (89) Hasegawa et al. confirmed these findings in a population group of 61 patients. Failure rate was significantly higher in patients with a psychological disorder (n=10) when compared to the remainder, 70% vs 18% (P=0.002). (90)

4.3.4.2 Success rates, harms and laparoscopy

Success rates of colectomy for constipation are difficult to establish, because of inconsistent reporting and usually obtained by a variety of methods (increase of bowel frequency, changes in summative symptom scores). Nevertheless, overall outcome is approximately 85% for more than 12 months of follow up (see table 9). An important remark is the difference in follow up time, which may be responsible for time confounding. (74)

Table 9. Results of meta-analysis of Knowles et al. (82) on colonic resection for constipation.

<table>
<thead>
<tr>
<th></th>
<th>Random effects meta-analysis (%)</th>
<th>95%CI (%)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall global satisfaction</td>
<td>85,6</td>
<td>81,4-89,3</td>
<td>76,9</td>
</tr>
<tr>
<td>Perioperative complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>general</td>
<td>24,4</td>
<td>17,8-31,7</td>
<td>88,1</td>
</tr>
<tr>
<td>POI</td>
<td>9,7</td>
<td>5,7-14,6</td>
<td>87,9</td>
</tr>
<tr>
<td>SBO</td>
<td>9,7</td>
<td>5,7-14,6</td>
<td>87,9</td>
</tr>
<tr>
<td>Long-term adverse outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBO</td>
<td>15,2</td>
<td>10,2-20,9</td>
<td>85,5</td>
</tr>
<tr>
<td>re-operation rate</td>
<td>13,3</td>
<td>8,6-18,7</td>
<td>87,7</td>
</tr>
<tr>
<td>Symptom outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhoea</td>
<td>9,8</td>
<td>4,7-16,4</td>
<td>76,9</td>
</tr>
<tr>
<td>incontinence</td>
<td>7,4</td>
<td>2,2-14,7</td>
<td>90,8</td>
</tr>
<tr>
<td>ungoing or recurrent constipation</td>
<td>18,2</td>
<td>9,3-29,2</td>
<td>91,4</td>
</tr>
<tr>
<td>persistent (or worsening)</td>
<td>39,3</td>
<td>28,8-50,1</td>
<td>89</td>
</tr>
<tr>
<td>abdominal pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bloating</td>
<td>23,9</td>
<td>11,9-38,1</td>
<td>92,7</td>
</tr>
</tbody>
</table>

POI= postoperative ileus; SBO= small bowel obstruction
The harms that are associated with surgery form a major counterbalance for selecting patients for colectomy. Between different studies, there is high variability and inconsistently reporting of complication rates. Consequently estimations here presented from Knowles et al. are necessarily tentative (see table 8). 20-30% of operations have immediate complications. Postoperative ileus and small bowel obstruction on short notice are seen in 5-15% of patients. On long-term, small bowel obstruction (10-20%), diarrhoea/incontinence (5-15%), abdominal pain (30-50%) and bloating (10-40%) is reported. The recurrence of constipation is seen in 10-30% of patients treated with colectomy. (82)

In the prospectively, randomized, single-blind study of Xu et al., they compared laparoscopic and open-surgery colectomy of STC in 64 patients. The patient group, who underwent a laparoscopic procedure, had less perioperative blood loss and a shorter hospital stay than patients who underwent an open colectomy. (86) Another potential advantage of laparoscopic approach is cosmesis, especially because the majority of patients are female. Little is known about the long-term differences between laparoscopic approach and open surgery. Ho et al. found similar results of global satisfaction rate for both groups after mean follow-up of 24 months (100% laparoscopic (n=7) vs 96% open (n= 40)). Small bowel obstruction was more frequent after open surgery in this study, but their study population was too small to call these differences significantly. (91) In the US study of Dudekula et al. on a large study group (n=2377) no significant differences in complications could be demonstrated between laparoscopic and open surgery. (92)

This recent study showed some new insights about this topic. By using the US Nationwide Inpatient Sample and the State Inpatients Database, data from 2377 patients who underwent colectomy for constipation between 1998-2011 could be obtained. The number of procedures rose from 104 in 1998 to 311 in 2011. 42,7% of the operations were associated with complications over a period of 30 days after surgery. The most frequent were gastrointestinal complications (27%): nausea/vomiting/hemorrhage, ileus and intestinal obstructions. (92)

Also longitudinal data from 166 patients, recorded on State Inpatient Databases of Florida and California, was analysed. Analogue with the nationwide data of 2377 patients, a high rate of complications was observed. More revealing was the resource utilisation (ED encounters and hospitalisations). Excluding the incident colectomy, these 166 patients had 2355 encounters: 1494 ED visits by 149 patients and 861 hospitalisations by 144 patients. 45% of the 1494 ED visits occurred after colectomy, shared by 120 patients, of whom 28 had ED visits exclusively after colectomy with main reasons of visit were abdominal pain and migraines, which both increased after colectomy. 57% of the 861 hospitalisations occurred after colectomy by 110 patients. 42 out of 110 had no admissions prior to colectomy. The main reasons for
hospitalisation after colectomy were gastrointestinal problems or complications of medical and surgical therapy. By excluding a 30-day period immediately before and after colectomy, the potential impact of immediate post-operative complications was corrected. Despite this correction, no differences in the number of ED visits and hospitalisations was seen before and after colectomy. In other words, healthcare resource utilisation remained high after surgery. Healthcare utilisation was seen by Dudekula et al. as a surrogate marker of functional status and well-being. It is acceptable to think that colectomy should not only improve subjective well-being, but also reduce the need for care and use of healthcare sources. The results of this recent study argue for caution about colectomy for constipation.(92)

Using a surrogate marker like Dudekula et al. is not always reliable. As counter example the study of FitzHarris et al. can be mentioned. It is one of the few studies assessing quality of life. 75 of the intended 112 patients filled in the questionnaire. Although 41% had abdominal pain, 21% had incontinence and 46% had diarrhoea at least some of the time, 92% of patients stated they would undergo colectomy again if given an second chance. (93) A serious limitation is that only postoperative quality of life was available. Assessing quality of life wasn’t a major focus in the past. Most studies mainly focused at efficacy of the procedure. Particularly in a functional disorder, quality of life must be the key outcome measure.

4.3.5 Conclusion

Colectomy and ileorectal anastomosis (CIRA) is only an option for highly selected patients when patients suffer and have low quality of life even after a constructive trial of conservative therapy and trying less invasive procedures, like antegrade enemas. Complications occurred frequently, so selecting patients for surgery must be adequate. Such patients are suitable for CIRA after further testing of clinic, psychology and physiology. The mean success rate is approximately 85%. Best success rates of CIRA are seen in patients with slow transit constipation, normal psychological condition, no suffering from abdominal pain or bloating, normal upper gastrointestinal motility, no concomitant defecation disorder and with functional anal sphincter. These criteria are orderly presented in a proposed therapeutic flowchart (see 5. Flowchart and future perspectives). Further prospective research with performant assessment of symptom scores and quality of life before and after colectomy is needed.
4.4 **STOMA**

Sometimes a stoma is created to elucidate the symptoms of patients with constipation. By creating a stoma, a discontinuity of intestines is caused. It can also be made for the purpose of constructing a way for administer antegrade enemas throught the colon (see 4.2 antegrade colonic enema). A stoma is often voluntarily chosen by people or after failure of other surgery. Complications such as hernia, prolapse or retraction may occur. Corrections of these complications may require surgery. It may be offered as first surgical procedure to patients with psychiatric disorders, STC combined with refractory ODS, or patients with significant pain and/or bloating. (94)

Just one publication was found presenting the outcomes of constipated patients by constructing an end stoma. Van der Sijp et al. found that subjective improvement (including decrease of bloating, abdominal pain and less use of laxatives and enemas) was present in 82% of the group with primary constructed stoma (n=11, one ileostomy and 10 colostomies) and 50% of the group with constructed ileostomy after failure of colectomy with ileorectal anastomosis (n=10). (95) Because of limited study population and unavailable data about reason for failure of colectomy, these results may not be extrapolated. Further research in needed to confirm these findings.
5 FLOWCHART AND FUTURE PERSPECTIVES

Patients with constipation represent a complex group. The management is very difficult. Many patients undergo multiple treatments without any benefit. A step-wise approach from conservative treatment to more invasive surgery is advised. Several study groups have published recommendations for the diagnosis and treatment of constipation, but there is still no standardized treatment guidelines that gained full acceptance in medical practice. (5, 96)

In general, the treatment pathway is as followed:

1. Ask for alarm symptoms and exclude secondary causes.
2. Start treatment with diet/lifestyle, laxatives if necessary and biofeedback if indicated.
3. Constructive trial of different laxative types and if needed newer agents, suppository and enemas.
4. Refer to a center specialized in surgery for constipation as last resort after repetitive failure of conservative therapy.

The proposal of therapeutic approach of normal and slow transit constipation is visualized in a flowchart (see figure 7). The reasoning behind the making of this flowchart and the criteria for patient selection are mentioned throughout this thesis. In general, first a constructive trial of conservative therapy is advised for normal and slow transit constipation. If not successful, further clinical, psychological and physiological testing is needed to include the right patients for surgery. It seems obvious to first try less invasive procedures like ACE and SNS before performing CIRA.

The choice between ACE and SNS is not simple to make. Recent trial data (level II) suggest no overall benefit of SNS for chronic constipation. In the meantime, level IV evidence suggests approximately 50% success rate of ACE for constipation. Before making practice recommendations, some considerations have to be mentioned. First, the large variance in success rates is a great concern that the treatment might not be useful for an individual. SNS has the advantage of having a test phase without major morbidity or costs for indicating potential good responders to a permanent implant. However, clear criteria for positive PNE and predictive value is not yet established. Secondly, some statistically significant differences were found in bowel frequency, Wexner score, squeezing, etc. However, the question still remains: will a treatment with SNS or ACE give a clinical relevant result in a specific case in a daily setting? Discussion with the patients about their views and circumstances is vital. Thirdly, another therapy could be ‘better’ with respect to both the desired beneficial and adverse events, or another therapy may simply have a different benefit/harm profile (but be perceived to be more favorable by some people). For example, literature suggest that ACE is successful in half of the patients with refractory constipation, which tend to be better success rates than
SNS. However, SNS can be preferred by an individual patient (after proper counseling about the low success rates), because it is more acceptable to the patient than irrigate the colon on a daily basis. SNS should not be completely banned for constipation. It is still an interesting research item. Future trials have to confirm recent disappointing findings.

Future studies should be conducted in a prospective manner with carefully obtained data from patients. These data must include clinical, psychological and physiological information about the patients, so clear stratification of patients is possible to allow reasonable interpretation of outcome results. Comparative studies are needed. It might be an option to randomize people for ACE or SNS, because both procedures are minimally invasive and reversible. Because of the limited indications for these procedures, multicentre studies are useful to obtain a bigger study population to make firm conclusions.

The primary end point of future studies should be quality of life. In the past, most studies were focused on efficacy of the procedure. Because of technical success, this is interesting for the executive surgeon, but the patient has more benefit from improved quality of life, then just a successful procedure. Besides efficacy of the procedure and quality of life, symptoms should be properly reported using validated tools, like PAC-QoL and PAC-SYM .(97, 98) Also complications reported in an uniform manner is recommended. The Clavien Dindo classification (99) is suggested. This classification is based on treatment consequences of the complication, with higher grade when treatment is more invasive. By this way, it is possible to compare the severity of complications of several procedures (e.g. SNS, ACE, colectomy) who normally have specific complications (e.g. small bowel obstruction – colectomy) that are impossible to compare.

In this manner, it is possible to further collect evidence of good quality on efficacy, harms and patient selection for the different procedures. This would help to further establish the criteria that are presented in the proposed flowchart.

In figure 8, an alternative flowchart is presented. This flowchart is based on expert opinion. No evidence in literature is found. This alternative flowchart is more an stimulant for further research. Besides therapeutic studies, also more research is needed on the pathophysiology of constipation, physiological tests like colonic manometry and mechanism of action of SNS. Better understanding of the aforementioned will also lead to better treatment.
Figure 7. Proposed therapeutic flowchart of normal and slow transit constipation.
ACE = antegrade colonic enema; SNS = sacral nerve stimulation; CIRA = colectomy and ileorectal anastomosis. The Oxford CEBM (2009) summary levels of evidence and grades of recommendation here displayed, are derived by Knowles et al. in the systematic review ‘Surgery for constipation: systematic review and practice recommendations’. (60)

Figure 8: Proposed alternative therapeutic flowchart of more invasive procedures for normal and slow transit constipation resistant to conservative approach, merely based on expert opinion. These are areas for future research.
(L)ACE: (left) antegrade colonic enema; CIRA: colectomy with ileorectal anastomosis; SCCRA: subtotal colectomy with caeco-rectal anastomosis.
The arrows that are thickened, indicates pathways with most evidence in the literature.
6 CONCLUSION

Constipation is a common problem. It is a complex disorder, heterogenic in etiology and symptoms. Constipation is more than just a deranged defecation frequency. Other symptoms like bloating, straining, hard stools, feeling of incomplete evacuation, abdominal discomfort may be present. Because of the heterogeneity, a systematic approach of constipation should be executed. Most people can be helped with conservative therapy, but for some this is not sufficient and they are seeking other therapy to alleviate symptoms and increase their quality of life.

Looking at the literature on primary constipation in adults, SNS and ACE were two relatively new approaches to help these constipated people. Both SNS and ACE are minimal invasive options compared with colectomy, which is especially in a functional disorder like constipation a great advantage. Thus, patients and researchers were excited. However, after two decades of research, both SNS and ACE are not established as ‘best practice’ for patients refractory to conservative therapy. Articles with level IV of evidence reported good results for both SNS and ACE. Recently, some level II trials have been reported on SNS for constipation, which are less positive, with the result that SNS cannot be recommended as clinical practice. In 2017, an expert panel headed by Knowles, agreed about following practice recommendation: “Patients should be counselled that the evidence base does not support the use of SNS for chronic constipation”. (Evidence level II, Grade B) (60) New well-constructed trials are needed to further collect evidence for treatment options for constipation.

So for now, a step-wise therapeutic approach is recommended. Starting with conservative therapy, and if not successful, further assessment to point out the suitable patients for surgery. ACE (and SNS) are surely options to avoid a colectomy, but do not help all patients. Some patients will directly choose for a stoma to end the therapeutic trial and error. Other patients, suitable for major surgery, can benefit from a colectomy with ileorectal anastomosis.

7 LIMITATIONS

The majority of studies included in this review, are of poor quality, as reflected in the Oxford CEBM summary levels of evidence. It was chosen to conduct a structural narrative review, which is a helpful design to present a broad perspective on a topic and can be used to describe the history of management. Especially for constipation, because of the heterogeneity in pathophysiology, patient selection for therapy, outcome measurements and the poor quality studies in this area, a structural narrative review seems to be an adequate approach to maintain the bigger picture. By not choosing for a systematic review, we acknowledge that the conclusions and proposed flowcharts are based on lower evidence.
REFERENCES


2. Sanchez MIP, Bercik P. Epidemiology and burden of chronic constipation. Canadian Journal of Gastroenterology. 2011;25(SUPPL.B):11B-5B.


81. Lane WA. Remarks on the results of the operative treatment of chronic constipation. British medical journal. 1908;1(2455):126.