The role of prokinetics in managing gastrointestinal involvement in systemic sclerosis: a systematic literature review

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The role of prokinetics in managing gastrointestinal involvement in systemic sclerosis: a systematic literature review

Short title: *Prokinetics for SSc-GI involvement*

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ABSTRACT

Objectives: Gastrointestinal involvement (GI) in systemic sclerosis (SSc) is frequent and heterogeneous, manifesting with different degrees of dysmotility. This systematic literature review aimed to summarize evidence on prokinetics for treating SSc-related GI dysmotility.

Methods: Studies investigating the effects of prokinetic agents on GI function and/or GI symptoms in patients with SSc were systematically identified on PubMed and Embase. A qualitative data synthesis was conducted, given the (anticipated) wide heterogeneity in study designs, interventions, and outcomes.

Results: Twenty-one studies evaluating the effects of prokinetics in patients with SSc were included. Thirteen studies focused on GI motility using objective tests, eight assessed clinical responses, and six evaluated both. Cisapride (n = 5 studies), Metoclopramide (n=7 studies), Octreotide (n=4 studies), and Prucalopride (n=1 study) were among the most studied prokinetics, with varying effects on different GI anatomical regions. While Metoclopramide consistently improved overall GI motility, other prokinetics provided selective benefits; Cisapride improved gastric emptying and colonic motility, but not esophageal motility, and Octreotide improved small bowel motility but delayed gastric emptying. Regarding symptomatic improvement, only prucalopride was evaluated using a validated patient questionnaire, showing improvement in both upper and lower GI symptoms.

Conclusions: Prokinetic drugs may improve GI motility and symptoms in patients with SSc. There is an unmet need for future well-designed studies to refine patient stratification and optimize treatment outcomes.

Keywords: Gastrointestinal, Systemic sclerosis, Scleroderma; Systematic Review, Prokinetics

Key messages:

- Prokinetic agents can improve gastrointestinal motility in patients with SSc, though their efficacy varies significantly between drugs.
- Patients with SSc experiencing both upper and lower GI symptoms may benefit from the judicious use of prokinetic agents.
- Better patient stratification, safety evaluation and treatment optimization are needed to enhance the effectiveness of prokinetic agents in managing gastrointestinal involvement in SSc.

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INTRODUCTION

Systemic sclerosis (SSc) is a complex connective tissue disease characterized by autoimmunity, inflammation, and vasculopathy, leading to excessive collagen production with deposition in the extracellular matrix and dysfunction in affected organs[1]. While cardiopulmonary complications most strongly drive mortality[2], the gastrointestinal (GI) system causes significant morbidity and affects up to 90% of patients. The esophagus is the most affected region of the GI tract (50-95%), followed by the small bowel and colon (around 50%)[1].

GI involvement in SSc is heterogeneous and likely driven by multiple effector mechanisms, including autoimmunity, vascular and neuropathic dysfunction, and dysbiosis, with the exact mechanism(s) still poorly defined. Although some tissue fibrosis of the GI structures is noted, later stages of GI dysfunction primarily demonstrate smooth muscle atrophy[3–6]. Many GI symptoms and complications are likely caused by abnormal motility of the GI tract and organs, commonly referred to as 'dysmotility"[7,8]. Dysmotility may range from subclinical or asymptomatic involvement to severe dysmotility, culminating in intestinal dilatation, bacterial overgrowth, and an inability to maintain adequate nutrition through oral intake. For example, Chronic Intestinal Pseudo-Obstruction(CIPO), represents one of the most severe forms of GI dysmotility due to SSc. It is marked by impaired GI propulsion and presents with symptoms and signs of bowel obstruction despite the absence of any mechanical lesion[3,4,9]. Importantly, the latest expert recommendations for the management of SSc[10,11], state that prokinetic drugs may be used to treat GI symptoms in patients with GI dysmotility on a case-by-case basis. However, they acknowledge that the effects of these drugs are currently speculative and often extrapolated from other fields[10].

Against this background, we aimed to systematicallyreview the extant literature, including qualitative and quantitative studies describing the effect of prokinetics on GI involvement in patients with SSc. We aimed to provide a comprehensive summary of the current evidence to help clinicians treat dysmotility-related GI symptoms in patients with SSc and to provide guidance for future research efforts.

METHODS

Systematic review strategy

We performed a systematic literature review (SLR) search of the PUBMED and EMBASE databases from inception to November 2023, using a pre-established study protocol registered in the International Prospective Register of Systematic Reviews **(Registration: PROSPERO CRD42023475388)**, developed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses recommendations[12]. Our research question was: In

patients with SSc, what is the effect of prokinetic agents compared to placebo/no treatment on GI motility or GI symptoms? Our objective was to evaluate the impact of prokinetics on GI motor function, considering all available methods for assessing motility, transit times, physiological surrogates, or clinical changes in GI manifestations, including symptoms. The scope of the analysis encompassed the entire GI tract. The search strategy was designed and conducted by two investigators (AED and LGAG) with help from an experienced librarian. The keywords and MESH terms used, as well as detailed information regarding the research question and search strategies are available (see **Supplementary Data S1***).* Articles published in both English and Spanish languages were considered. Due to the nature of the study design, ethical approval was not required.

Data extraction and data synthesis

After selecting the studies, the results were separated into two groups: a) the effect of prokinetic agents on GI motility test outcomes and b) the effect of prokinetic agents on clinical (GI symptoms) outcomes. General characteristics from publications were collected: first author, year published, study design, participant characteristics (age, sex, criteria used for SSc diagnosis), prokinetic agent used, duration and dose of treatment, and side effects reported. Regarding outcome data extraction, the following specific data were extracted in the GI motility tests studies: the effect of prokinetic treatment on physiological tests regarding the esophagus, gastric, small bowel, and/or colon. Regarding outcome extraction for studies in the clinical outcome group, data regarding GI involvement tests performed for patient inclusion baseline characteristics were retrieved. A high heterogeneity in study design, interventions, and outcome reporting was expected, which made a meta-analysis unfeasible. Therefore, we sought a qualitative synthesis of the study findings.

Risk of bias assessment

The risk of bias (RoB) for randomised and non-randomised controlled trials was assessed by both reviewers (AED and LGAG) using the RoB 2 tool[13] and the Newcastle-Ottawa Scale (NOS)[14], as appropriate. Eligible randomized studies were rated as either ‘high risk,’ ‘some concerns,’ or ‘low risk of bias,’ and non-randomized studies were of ‘high quality’ (if ≥8 points), ‘moderate quality’ (if 6–7 points), and ‘low quality’ (if ≤5 points), according to the RoB 2 tool and NOS, respectively. Risk of bias results can be found in **Supplementary Tables S1 and S2**.

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RESULTS

Overview

Of the 356 articles retrieved from the systematic literature search, 194 were screened, 41 were selected for full-text evaluation, and 21 were finally included (**Figure 1**). Excluded articles and the reason for exclusion can be found in **Supplementary Data S2**. Of the 21 studies included, 13 evaluated the effect of prokinetics on GI motility using objective tests, eight evaluated the clinical response to prokinetics, and six evaluated both the effect on objective tests and the clinical response. As previously explained in the Methods section, the findings from these last eight studies are shown separately.

Most studies (15/21) were non-randomized observational studies, while six involved randomized controlled trials (RCTs). Overall, serotonin receptor agonists had the strongest representation, (Cisapride n=3, Prucalopride n=1). The dopamine antagonists, motilin receptor agonists, somatostatin receptor agonists, and ghrelin receptor agonists were exclusively studied in non-randomized study designs. Seven studies investigated the longitudinal use of prokinetics in patients with SSc. Among these, six studies assessed treatment responses over a short duration, ranging from 7 to 30 days, while only one study, which evaluated octreotide, reported a longer treatment period of up to 24 months. Three of these studies did not report any adverse effects. In the remaining four, the prevalence of mild to moderate adverse events ranged from 5% to 55% (Nausea, headaches, dizziness, flushing and abdominal discomfort). Although no serious adverse events associated with the use of prokinetics were reported in longitudinal studies included in our review, the follow-up periods were limited, and the analysis were based on a small number of patients.

Patient population and outcome measures utilized to examine the effects of prokinetic therapy on objective GI outcomes

Table 1 summarizes the findings of the studies that evaluated prokinetics' effects on GI function using objective investigations.The median sample size across studies was 12 patients (interquartile range [IQR]: 10 to 16). The study populations were predominantly female (40% to 100%) and middle-aged, with a median age of 50.3 years (IQR: 49.4 to 55.9 years). Validated criteria were used to select patients in 15 (79%) of the included studies. Among these, 13 (87%) studies utilized the American Rheumatism Association (ARA) 1980 SSc classification criteria, and 2 (13%) studies utilized the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2013 SSc classification criteria. Six (31%) studies provided data on cutaneous subsets, showing that most patients had diffuse cutaneous SSc (median prevalence of 80%, IQR: 34% to 100%).

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In 14 (74%) studies, patients had documented GI involvement, confirmed by manometry, scintigraphy, and/or radiological tests. The esophagus was the most affected organ, with a median prevalence of esophageal dysfunction at 100% (IQR: 80% to 100%). The small bowel was the second most affected, as evidenced by abnormal findings on small bowel manometry or dilated bowel loops on radiological exams. Five studies included patients with CIPO, comprising a total of 17 patients with CIPO secondary to SSc [15–19].

Objective responses to prokinetic therapy in patients with SSc

Metoclopramide, a D2 receptor antagonist, consistently increased lower esophageal sphincter pressure (LESP)[20–23]. In two studies, Metoclopramide also enhanced esophageal peristaltic amplitude[20,23], and, even though two studies did not find an increase in esophageal body contractile activity[21,22], they found Metoclopramide improved esophageal clearance as assessed by scintigraphy[21,22]. Furthermore, Metoclopramide consistently improved gastric emptying in patients with delayed gastric emptying measured by scintigraphy (2 hours after meal), and also contractile motor activity in the antrum, duodenum, and jejunum was positively impacted, even in patients with severe GI involvement (i.e., CIPO)[16]. Metoclopramide also enhanced colonic motor activity by increasing colonic spike activity[15]. Cisapride, a 5-HT_4 receptor agonist, did not significantly change esophageal motility as assessed byesophageal manometry[24,25] and scintigraphy[26,27]. However, Cisapride positively affected gastric motility, improving both solid and liquid gastric emptying[26] and increased fundic gastric contractions compared to placebo[24]. It also improved colonic transit time in patients with SSc[27]. Erythromycin, a motilin receptor agonist, increased gastric motility and accelerated the gastric emptying of a semisolid meal[18,19]. Octreotide, a somatostatin analog, stimulated small bowel motility by inducing phase III activity during fasting[17,28,29]. Neostigmine, a parasympathomimetic, increased colonic spike activity[15], while Bethanechol, another parasympathomimetic, increased antral, duodenal, and jejunal motor activity[16]. Finally, Prucalopride, a high-affinity 5-HT_4 receptor agonist, indirectly improved GI motility, which was demonstrated by a reduction in orocecal transit time[30].

Patient population and outcome measures utilized to examine the symptomatic response to prokinetic therapy in SSc

Table 2 summarizes the results from studies reporting the clinical response to prokinetic treatment.The median sample size was 11 patients (IQR: 7.8 to 22 patients). The patient populations were predominantly female (40% to 100%) and middle-aged, with a median age of 54.4 years (IQR: 50.4 to 58.0 years). In 7 (88%) studies, patients met validated criteria for inclusion, with five using the ARA 1980 criteria and two using the ACR/EULAR 2013 criteria.

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Three (38%) studies objectively documented GI involvement using manometry, scintigraphy, or radiological tests.

Symptomatic responses to prokinetic therapy in patients with SSc

Five out of eight studies evaluating the effect of prokinetics on GI symptoms reported improvements in symptoms compared to baseline, with response rates ranging from 67% to 100%, depending on the agent used. Notably, only one study employed a validated PRO (UCLA SCTC GIT 2.0), while the remaining four relied on non-validated tools, with four using a 0-to-3 Likert scale. One study assessed the efficacy of Cisapride, showing it was effective in 11 out of 15 patients (67%) in improving lower GI symptoms[27]. Treatment with domperdone was associated with improved in GERD symptoms (heartburn, regurgitation, and night cough) compared to baseline in 33 out of 38 patients (87%), but the effect was not superior to alginate therapy[31]. Additionally, two studies evaluated the response in SSc-related CIPO, where Octreotide achieved a 100% GI symptom improvement compared to baseline in two studies involving 5 and 7 patients, respectively, where octreotide significantly improved abdominal pain and bloating, with a sustained effect over six months[32]. Treatment with Prucalopride demonstrated effects exceeding the minimally important difference (MID) threshold for the UCLA SCTC GIT 2.0 Reflux, Bloating, and Constipation domains. However, it showed worse outcomes for the UCLA SCTC GIT 2.0 Diarrhea domain and no significant differences for the UCLA SCTC GIT 2.0 Emotional Wellbeing or Social Activities domain, based on published cut-off values[33]. These effected we associated with an increase in the number of complete spontaneous bowel movements per month[30].

DISCUSSION

This is the first SLR that focuses explicitly on the impact of prokinetic therapies on GI motility and symptoms in SSc. The key findings that emerged from this work include: (a) the current approach to treating GI involvement in SSc primarily focuses on managing symptoms, as no therapies have been identified that can prevent or reverse GI organ dysfunction; and (b) prokinetic agents consistently enhance GI motility across affected GI organs, as demonstrated by objective studies used to quantify aspects of organ function.

The regulation of GI motor function relies on a complex interaction between the parasympathetic, sympathetic, and enteric nervous systems (ENS) [34]. Overall, prokinetic agents exert their effects by enhancing cholinergic transmission in the neuromuscular junction. Cholinergic agonists stimulate muscarinic M2-type receptors on smooth muscle cells. Cholinesterase inhibitors, on the other hand, work by inhibiting acetylcholinesterase, which

leads to the accumulation of acetylcholine. Similarly, 5-hydroxytryptamine(HT)4 receptor agonists facilitate the release of acetylcholine from myenteric neurons. Dopamine D2 receptor antagonists block the inhibitory action of dopamine on acetylcholine secretion and motilin analogues stimulate the release of both 5-HT and Ach[35].

Although the pathogenesis of SSc gastrointestinal dysmotility remains largely unknown, it was originally proposed by Sjögren to be a process involving three steps: neural dysfunction alone, where prokinetics may be more effective; smooth muscle atrophy, for which these medications are often less effective; and fibrosis, for which they are thought to be ineffective[36,37]. However, the findings from our review challenge this notion, demonstrating that even patients with the most severe forms of GI involvement, such as CIPO, can potentially benefit from prokinetic treatment. A summary of the evidence reviewed in this study is presented in **Figure 2**.

Severe GI involvement, including CIPO, can be one of the initial manifestations of the disease, as demonstrated by a study involving 536 patients with very early SSc, where CIPO was present in 4% of patients[38]. Over the course of the disease, the prevalence of CIPO among patients with SSc has been estimated to range between 6% and 8%[2,39]. Octreotide was the first prokinetic agent shown to be beneficial in treating symptoms of CIPO secondary to SSc. In the study by Soudah and colleagues[17], the administration of a single 100 mcg subcutaneous dose of Octreotide to five patients significantly improved small bowel motility by inducing phase III fronts of the migrating motor complexes. This enhancement in motility was accompanied by a reduction in GI symptoms when 50 mcg of subcutaneous Octreotide was administered at bedtime for three weeks. More recently, Boeckxstaens et al[40]. reported sustained benefits in two patients with severe enteric dysmotility, who had not responded to existing therapies (one patient had been treated with domperidone and cisapride, and the second with octreotide) but showed significant improvement after starting treatment with Prucalopride. Both patients underwent small bowel manometry and colonic transit studies before and after Prucalopride treatment, which documented improvements in contractile activity and decreased colonic transit time, highlighting the pan-enteric effects of Prucalopride. Organ-specific dysmotility plays a major role in GI manifestations in patients with SSc[8]. For example, a recent study suggested that gastric and/or small intestinal dysmotility were associated with PPI-refractory esophagitis independently of esophageal aperistalsis, which indirectly supports the use of prokinetic agents over more intensive anti-acid therapies for treating severe (including refractory) GERD[41]. Novel prokinetics with pan-enteric effects may improve future outcomes in patients with SSc.

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While SLR found no reports of serious adverse events associated with the use of prokinetics in patients with SSc, the studies includedevaluated short-term use. A recent comprehensive review by the American and European Neurogastroenterology and Motility Societies[42] provides a detailed evaluation of the efficacy and safety of prokinetic drugs. There is a notable absence of research evaluating the safety of long-term prokinetic therapy in patients with SSc. Future RCTs are needed to systematically assess the long-term benefit of these medications in the SSc population, including at different stages ofdisease evolution (e.g., where promotility agents may have differential benefit).

Patients with SSc have an increased risk of cardiac arrhythmias compared to the general population[43], and this risk should be carefully weighted before prescribing prokinetic agents. Over the last decade, the development of newer prokinetic agents has focused on addressing safety concerns.As a result, safety became a key focus in the clinical trials of newer agents, such as prucalopride, which underwent rigorous evaluations prior to approval, especially regarding potential cardiac adverse effects, making them overall safer. However, the safety profile of these agents in patients with SSc has not been fully established, and caution is warranted, particularly in patients with known cardiac disease. A summary of the most common serious adverse effects of prokinetic drugs is presented in **Table 3**.

Experts have proposed a symptom-based approach to selecting therapeutics for managing SSc-GI disease[7]. However, there remains uncertainty about whether specific patient characteristics or pathological thresholds on GI motility testing should guide the use of prokinetic therapy in patients with SSc, or if PROs combined with clinical judgment are sufficient. The diverse nature of GI involvement in SSc further complicates the identification of suitable candidates for therapeutic trials. In recent years, there has been a shift in focus from major morbid events to PROs, which reflect patients' perspectives on the benefits and harms of treatments and are often the most valued outcomes. The MID represents the smallest change in a PRO that patients consider meaningful—whether positive or negative—and that may guide management decisions by patients or clinicians[44]. In our review, only one study utilized the UCLA SCTC GIT 2.0, a validated PRO[45] with well-established MID cut-off values[33]. Given that our findings indicate minimal and non-severe side effects associated with prokinetic agents and that prokinetic drugs play a crucial role in managing symptoms related to dysmotility, our results support the more widespread use of prokinetics, and a tailored (personalized) treatment approach based on PROs.

Expert (BSR and EULAR) recommendations for the management and treatment of SSc agree with this concept and also promote the use of prokinetic drugs to manage symptomatic

dysmotility associated with the disease, despite the absence of relevant randomized-controlled trials in patients with SSc[10,11]. Nonetheless, the current recommendations focus exclusively on esophageal dysmotility, specifically dysphagia and GERD, while providing no guidance on conditions like gastroparesis or chronic intestinal pseudo-obstruction (CIPO). We believe our review also supports the potential role of prokinetics in managing symptoms associated with gastric and intestinal dysmotility. While prokinetics have demonstrated positive effects on GI motility, our review has also highlighted several critical gaps in the current literature that should be prioritized as future research focuses. Notably, the existing evidence on prokinetics in SSc largely focuses on cisapride (5 out of 21 studies) and metoclopramide (7 out of 21 studies). However, cisapride has been withdrawn from the market in many countries due to its association with cardiac side effects[46], and metoclopramide is unsuitable for chronic use because of the risk of tardive dyskinesia and other potentially irreversible neurotoxicities[42,47]. While Erythromycin is often well tolerated, its use is hindered by the development of tachyphylaxis, limiting its long-term efficacy. Additionally, the use of parenteral cholinesterase inhibitors carries a risk of cardiac side effects[42], which limits their widespread use. However, a case-series study by Ahuja et al[48]. reports the effect of an oral cholinesterase inhibitor, pyridostigmine, in 31 patients with SSc and GI symptoms unresponsive to conventional therapies. The study found that nearly half of the patients reported clinical improvement in their GI symptoms, particularly in alleviating constipation. Despite the frequent occurrence of mild side effects, no cardiac complications were observed.

Our findings demonstrate an urgent need for confirmatory RCTs evaluating the effects of prokinetics in patients with SSc and gastrointestinal involvement. These RCTs should incorporate a comprehensive range of outcome measures, including assessments of digestive symptoms using validated PROs such as the UCLA SCTC GIT 2.0, Incorporating MID into sample size calculations ensures that RCTs are appropriately powered to detect changes. This is important so that changes that patients perceive as meaningful are differentiated from statistically significant changes that do not meaningfully impact patient's quality of life together with the objective results of GI motility tests (relevant to the intended target GI organ/s), assessment of nutritional status and physical activity, and overall health-related quality of life(HrQoL). Additionally, such future studies should focus on relevant clinical scenarios, including refractory GERD, patients with significantly reduced oral intake, or CIPO. Such studies are essential for identifying which treatments and diagnostic tests can most effectively stratify patients and predict their response to therapy, which will likely ultimately lead to improved outcomes (including HrQoL) for patients with SSc.

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We adopted an inclusive approach to studies evaluating the effects of prokinetic agents to reduce the risk of selection bias. The inclusion criteria across the studies varied significantly, with some using the 2013 ACR/EULAR criteria and others relying on the 1981 criteria. Additionally, there was considerable variability in how GI involvement was defined. In some studies, inclusion was based solely on clinical assessment and GI symptoms (6/21, 29%), although in most included studies (15/21, 71%), objective motility or radiological tests were used to define GI involvement. Additionally, our study did not evaluate the effects of mucosal protective agents or immunomodulation on GI motor function or symptoms, and these topics remain to be addressed.

A significant strength of our study is that we utilized a comprehensive search methodology to identify all relevant studies evaluating the effects of prokinetics in patients with SSc, irrespective of study design. However, we acknowledge the inherent limitations in our review, including the variability in sample sizes, limited number of patients, methodologies, and study populations, which contributed to the high heterogeneity across study designs and patient characteristics. These factors (as expected) rendered a meta-analysis unfeasible. However, despite these limitations, our SLR has consistently indicated that prokinetic treatment has a beneficial impact on both GI organ motility by objective tests and GI symptoms by clinical outcomes in patients with SSc, irrespective of the extent or severity of GI involvement. However, the response to treatment is highly heterogeneous between patients, as the anatomical areas within the GI tract where the response is expected vary by individual drug therapies. Our review has also shed light in that there is a notable absence of well-designed studies assessing the impact of prokinetic drugs on both validated PROs and clinically relevant endpoints. Furthermore, there is a notable absence of research evaluating the safety of long-term prokinetic therapy in patients with SSc, a critical consideration given the life-long nature of the disease. Our findings have synthesized the best available evidence, underscoring the efficacy of prokinetic agents in managing symptoms secondary to the frequent GI complications associated with SSc, and may serve as a highly helpful source of reference for clinicians in practice. Future studies are needed to confirm the safety and efficacy of prokinetic therapies for GI involvement in SSc; particular attention should be given to generating robust data on the safety of long-term use, especially concerning cardiovascular effects. Additionally, research should explore and validate potential biomarkers to guide patient selection and optimize treatment strategies.

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CONFLICTS OF INTEREST: The authors have declared no conflicts of interest.

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FIGURE LEGENDS

Figure 1: Flowchart of studies in the systematic literature review following PRISMA guideline and recommendation.

Alt text: Flowchart showing the process of identifying and screening articles for inclusion in the systematic literature review. Of 194 records identified, 21 studies were included in the final literature review.

Figure 2: Evidence summary of objective motility effect of prokinetics on gastrointestinal motor function in patients with systemic sclerosis.

Alt text: Illustrated summary table. Arrows show increasing or decreasing contractile activity, while two other symbols indicate either no effect or where the effect was not evaluated.

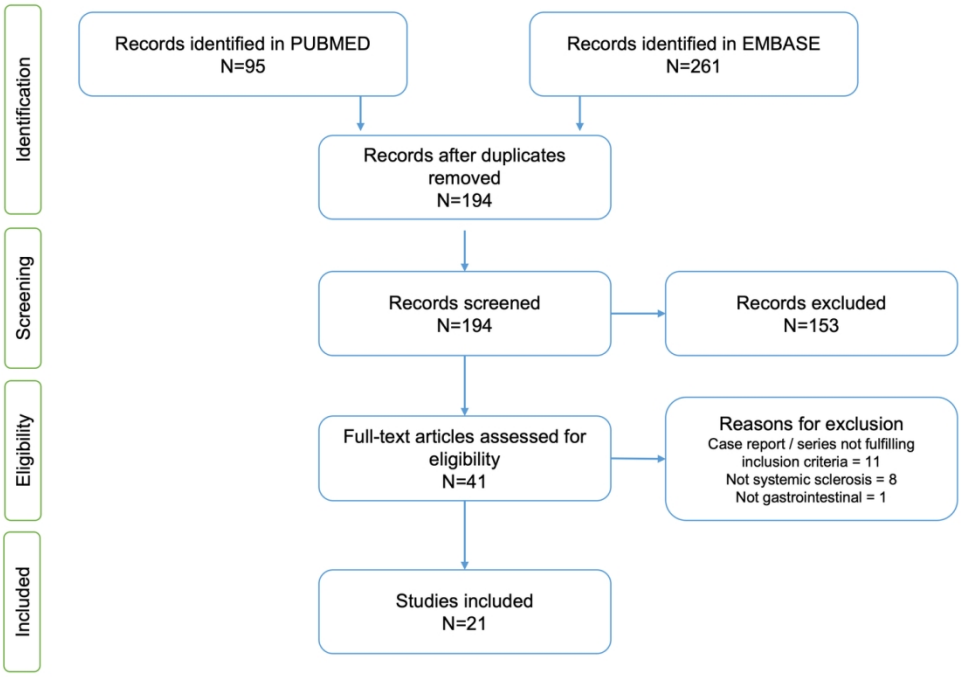

Figure 1. Flowchart of studies in the systematic literature review following PRISMA guideline and recommendation.

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Table 1: Effect of prokinetics on objective gastrointestinal motility in patients with systemic sclerosis

Author and year	Design	Number of patients	Age (Years) Mean (range)	Female sex (%)	Classification Criteria	Cutaneous subset, n (%)	GI involvement	Prokinetic agent. Dose and Duration	Esophagus	Stomach	Small bowel	Colon	Side effects
Ramirez-Mata M. 1977	Before and after study	14 patients	46.4 (31 – 66)	78.6%	N/A	N/A	100% esophageal disfunction by manometry	Metoclopramide 20 mg ev (single dose)	CEM: - increased in LESP (average 4.9 mmHg) in 50% patients. -100% patients with hypomotilty increased peristaltic amplitude. - 45% patients with aperistalsis showed contractile reserve	Not evaluated	Not evaluated	Not evaluated	No side effects reported during the intervention (single dose)
Battle WM. 1981	Cohort	10 patients	50 (34 – 71)	80%	N/A	N/A	2 (20%) CIPO	Metoclopramide 10 mg ev (single dose). Neostigmine 1 mg im (single dose)	Not evaluated	Not evaluated	Not evaluated	CM and MSWA: Metoclopramide and Neostigmine increase colonic spike activity40 % patients without severe GI involvement ($p<0.05$) no effect in patients with severe intestinal dismotility ($p>0.05$).	No side effects reported during the intervention (single dose)

Rees. W. D. 1982	Cohort	15 patients. 9 without GI disease and 6 with GI disease.	Without GI disease: 46 (21-60) GI disease 58 (46-70)	N/A	N/A	N/A	6 (40%) CIPO	Metoclopramide 10 mg ev (single dose). Bethanechol 2.5 mg sc (single dose)	Not evaluated	CADM: -Metoclopramide increased antral, duodenal and jejunal motor activity ($p<0.05$) with diminished effect in patients with GI involvement. -Bethanecol increased antral, duodenal and jejunal motor activity ($p<0.05$) but reduced compared to metoclopramide.		Not evaluated	No side effects reported during the intervention (single dose)
Horowitz. M. 1987	Cohort	8 patients	(31 – 69)	87.5%	N/A	N/A	100% Delayed gastric emptying in the Gastric Emptying Scintigraphy	Cisapride 10 mg ev (single dose)	RES: No improvement in esophageal emptying ($p=0.1$)	GES: Improved solid (average retention at 100 min, 31%, $p<0.001$) and liquid gastric emptying (average half-emptying time 8 min, $p=0.01$)	Not evaluated	Not evaluated	No side effects reported during the intervention (single dose).
Johnson DA. 1987	Before and after study	12 patients	43.3 (25 – 65)	83.3%	American Rheumatism Association (1980)	N/A	100% esophageal disfunction in manometry and 33% delayed gastric emptying in the Gastric Emptying Scintigraphy	Metoclopramide 10 mg ev (single dose).	CEM: Increased LESP (average 9.0 mmHg). No augmentation in the peristalsis amplitude. RES: Mean esophageal clearance improved (averaged 10%, $p<0.05$)	GES: Improved solid-phase gastric emptying (average $T_{1/2}$ 56 minutes, $p<0.05$)	Not evaluated	Not evaluated	No side effects reported during the intervention (single dose)
Drane WE. 1987	Before and after study	14 patients	49.8 (33- 69)	85.7%	American Rheumatism Association (1980)	N/A	100% esophageal dysfunction in radionuclide esophageal scintigraphy (RES)	Metoclopramide 10 mg ev (single dose).	CEM: Increased LESP (average 6.8 mmHg, $p<0.01$). No augmentation in the peristalsis amplitude. RES: Increased the average percent of esophageal emptying	Not evaluated	Not evaluated	Not evaluated	There is no data regarding side effects evaluation

									(average 10%, p<0.01).				
Soudah HC. 1991	Cohort	5 patients	60 (55 – 65)	40%	American Rheumatism Association (1980)	Diffuse = 5 (100%)	100% CIPO	Octreotide 100 µg sc (single dose).	Not evaluated	CADM: Octreotide induced intestinal propagative phase III activity.		Not evaluated	No side effects reported during the intervention (single dose)
Kahan A. 1991	Crossover trial	20 patients	50 (3)* *Standard deviations	80%	American Rheumatism Association (1980)	N/A	None	Cisapride 10 mg ev (single dose)	CEM: Cisapride increased LESP vs placebo (8.3 (2.1) cmH_2O vs 0.1 (0.3) cmH_2O, p <0.001)	CEM: Cisapride increased number of fundic gastric contractions vs placebo (7.7 (2.3) vs 0.9 (0.6), p <0.01)	Not evaluated	Not evaluated	11 (55%) mild adverse effects: dizziness, flushing, headache and palpitations
Limburg A.J. 1991	Crossover trial	10 patients	(30 – 74)	70%	American Rheumatism Association (1980)	N/A	100% esophageal disfunction in manometry	Cisapride 10 mg ev (single dose)	CEM: Non-different Cisapride vs placebo in LESP (p=0.4) and mean amplitude of esophageal contractions (p=0.4).	Not evaluated	Not evaluated	Not evaluated	There is no data regarding side effects evaluation
Fiorucci S. 1994	Cohort	12 patients	57.3 (31 – 80)	92%	American Rheumatism Association (1980)	N/A	100% esophageal disfunction in manometry 4 patients (33%) CIPO	Erythromycin 2mg/kg ev (single dose)	Not evaluated	GEU: Increased gastric motility index (p<0.001) and reduced the $T_{1/2}$ of gastric emptying (p<0.01) Gallbladder ultrasound Accelerated gallbladder emptying (p<0.001)	CADM: (5 (41.6%) patients): Increased the antral motility index (p<0.01) without affecting the small bowel.		There is no data regarding side effects evaluation

Fiorucci S. 1994	Cohort	12 patients	57.3 (31 – 80)	92%	American Rheumatism Association (1980)	N/A	100% esophageal disfunction in manometry 4 patients (33%) CIPO	Erythromycin 250 mg p.o t.i.d (4 weeks)	Not evaluated	GEU: Reduced the $T_{1/2}$ mean gastric emptying ($p<0.01$) Gallbladder ultrasound Accelerated gallbladder emptying ($p<0.001$)	Not evaluated	Not evaluated	1 (9.3%) mild adverse effects with oral erythromycin : vomits (not withdraw)
Sridhar KR. 1998	Cohort	20 patients	50.3 (26 – 75)	85%	American Rheumatism Association (1980)	N/A	16 (80%) esophageal disfunction in manometry 10 (50%) delayed gastric emptying in the Gastric Emptying Scintigraphy	Metoclopramide 10 mg im in 4 (20%) patients with delayed gastric emptying (single dose)	Not evaluated	GES: accelerated the gastric emptying rate 2 h after meal (average 33.4%, $p<0.05$)	Not evaluated	Not evaluated	There is no data regarding side effects evaluation
Wang SJ. 2002	Cohort	16 patients	48 (28 – 69)	75%	American Rheumatism Association (1980)	N/A	Clinical assessment 12 (75%) patients had chronic constipation.	Cisapride 10 mg p.o t.i.d (7 days)	Not evaluated	Not evaluated	Not evaluated	CTS: Reduced colonic transit time (average median GC at 24 h was 0.55, $p=0.038$)	There is no data regarding side effects evaluation
Wang SJ. 2002	Crossover trial	12 patients	(28 – 70)	83.3%	American Rheumatism Association (1980)	N/A	Clinical assessment Esophageal symptoms (dysphagia, heartburn or regurgitation)	Cisapride 10 mg p.o t.i.d (3 days)	RES: No improvement esophageal transit after cisapride administration vs placebo ($p>0.05$)	Not evaluated	Not evaluated		There is no data regarding side effects evaluation
Sjölund K. 2005	Cohort	10 patients	53 (30 – 72)	90%	American Rheumatism	Diffuse = 6 (60%)	Esophageal disfunction in manometry or	Octreotide 50 µg sc	Not evaluated	CADM:		Not evaluated	No side effects reported

					Association (1980)	Limited = 4 (40%)	malabsorption syndrome	(single dose).		Octreotide induced migrating motor complex (MMC) phase III activity complex			during the intervention (single dose
Mercado U. 2005	Before and after study	27 patients: - Early disease: 21 patients. - Late disease: 6 patients	Early disease: 41.4 (9.8)* Late disease 52.6 (9.1)* **Standard deviations	92.6%	American Rheumatism Association (1980)	Diffuse = 27 (100%)	95% patients with early disease esophageal disfunction in manometry and 100% patients with late disease esophageal disfunction in manometry	Metoclopramide 10 mg ev (single dose).	CEM: Increased LESP, peristaltic contraction velocity and esophageal contractions amplitude ($p<0.05$)	Not evaluated	Not evaluated	Not evaluated	No side effects reported during the intervention (single dose)
Marie I. 2007	Cohort	8 patients	63 (37 – 73)	100%	American Rheumatism Association (1980))	Diffuse = 2 (25%) Limited = 6 (75%)	6 (75%) patients abnormal small-bowel manometry and 8 (100%) patients abnormal small-bowel manometry at 5 years follow up	Octreotide 50 µg sc (single dose).	Not evaluated	Not evaluated	CADM: Alterations of small-bowel motility (decreased median number phase III MMC and one patient no phase III) in response to octreotide infusion at 5 years follow up.	Not evaluated	No side effects reported during the intervention (single dose)
Ariyasu H. 2014	Crossover trial	10 patients	67.5 (48 – 80)	70%	American College of Rheumatology (ACR)/EULAR 2013	Diffuse = 10 (100%)	Clinical assessment Grading of Gastrointestinal Involvement in Systemic Sclerosis (Draft Guidelines of Japan)	Ghrelin (5.0 µg/kg ev) (single dose)	Not evaluated	^{13}C-acetate breath test Gastric emptying time was accelerated by ghrelin vs placebo (43.3 min vs 53.4 min, $p=0.03$)	Not evaluated	Not evaluated	2 (20%) mild adverse: flushing and sweating
Vigone B. 2017	Crossover trial	40 patients. 29 patients completed the study	54.4 (10.5)* *Standard deviations	100%	American College of Rheumatology	Diffuse = 7 (24.2%) Limited = 22 (75.8%)	Clinical assessment Rome III criteria	Prucalopride 2 mg p.o/24 h (30 days)	Not evaluated	OCTT by lactulose breath test (17 (58.6%) patients completed the lactulose breath test)		Not evaluated	7 patients (17.5%) did not tolerate prucalopride

					(ACR)/EULAR 2013		for functional constipation and had mild-to-severe subjective symptoms of constipation			Prucalopride reduced the OCTT vs placebo (difference -65.9 min, p = 0.035)		due to side effects: headache, abdominal pain, dizziness and nausea.

CADM = conventional antroduodenal manometry; **CEM** = conventional esophageal manometry; **CIPO** = Chronic Idiopathic Pseudo-obstruction; **CM** = Colonic manometry; **MSWA** = Myoelectric slow wave activity; **CTS** = Colonic Transit Scintigraphy; **GC** = geometric centre of colonic activity **GES** = gastric emptying scintigraphy; **GEU** = gastric emptying ultrasonography; **LESP** = lower esophageal sphincter pressure; **OCTT** = Orocecal Transit Time; **RES** = Radionuclide esophageal scintigraphy;

Table 2: effect of prokinetics on clinical outcomes in patients with systemic sclerosis

Author and year	Design	Number of patients	Age (Years) Mean (range)	Female sex (%)	Classification Criteria	Cutaneous subset, n (%)	Gastrointestinal involvement evaluation for inclusion	Prokinetic agent. Dose and Duration	Prokinetic effect on clinical outcomes	Side effects
Horowitz. M. 1987	Cohort	8 patients	(31 – 69)	87.5%	N/A	N/A	100% Delayed gastric emptying by Gastric Scintigraphy	Cisapride 10 mg ev (single dose) and Cisapride 10 mg p.o q.i,d before meals for 30 days.	Non validated questionnaires. Likert scale 0 (none) to 3 (severe) for each symptom. Total score upper GI symptoms 27: 18 for gastric symptoms and 9 for esophageal symptoms. -Improved the score upper GI symptoms (median 1 (range 0-12), p<0.001) -Improved Gastric symptoms (median 0 (range 0-3), p<0.001) -Improved Esophageal symptoms (median 1 (range 0-9), p<0.025) -No improved frequency bowel movement/week	No side effects were reported during follow up (30 days)
Soudah HC. 1991	Cohort	5 patients	60 (55 – 65)	40%	American Rheumatism Association (1980)	Diffuse = 5 (100%)	100% CIPO	Octreotide 100 µg sc (single dose). Octreotide 50 µm/24 h 3 weeks	Non validated questionnaires. Likert scale 0 (none) to 3 (severe) for nausea, bloating and abdominal pain. Abdominal pain decreased mean 1.5 points (p=0.002) Nausea decreased mean of 1.5 points (p=0.05) Bloating decreased mean of 2.1 (p=0.003) Number of episode of vomits decreased mean 3.6/week (p=0.05)	No data on side effects
Fiorucci S. 1994	Cohort	12 patients	57.3 (31 – 80)	92%	American Rheumatism Association (1980)	N/A	100% esophageal disfunction in manometry 4 patients (33%) CIPO	Erythromycin 250 mg p.o t.i.d 4 weeks	Non validated questionnaires. Likert scale 0 (none) to 3 (severe) for early satiety, abdominal pain, nausea, bloating, vomiting and constipation. At 4th week of treatment: -Early satiety decreased mean of 1.8 (p < 0.01) -Abdominal pain decreased mean of 1.8 (p < 0.01) -Nausea decreased mean of 1.5 (p < 0.01) -Bloating decreased mean of 1.7 (p<0.01) -Vomiting episodes decreased mean of 2.5 (p<0.01) -Increased mean number of bowel movements/week mean of 5.7 (p<0.05)	1 (9.3%) patient had mild adverse effect: vomits (not withdraw)
Wang SJ. 2002	Cohort	16 patients	48 (28 – 69)	75%	American Rheumatism	N/A	Clinical assessment	Cisapride 10 mg p.o t.i.d 7 days	Non validated questionnaires. 66.7% response of constipation symptoms	No side effects

					Association (1980)		12 (75%) chronic constipation.			reported during the intervention (7 days)
Nikou G.C. 2007	Before and after study	7 patients	(37 – 64)	100%	American Rheumatism Association (1980)	Diffuse = 4 (57%) Limited = 3 (43%)	100% gastrointestinal symptoms (abdominal pain, nausea, vomiting, bloating and disturbed defecation). 43% reported a previous episode of sub occlusive crisis (suggestive of CIPO)	Octreotide 4 patients: 0.1 mg/12 h sc 3 patients ocretoide LAR 20 mg/mo Duration range 9 - 24 months	Non validated questionnaires. Likert scale 0 (none) to 3 (severe) for abdominal pain, nausea, vomiting, bloating and disturbed defecation. Maximum score: 15. -Reduction of symptom severity in the first month (decreased mean of 1.6 points, p = 0.0006). -Bloating symptom didn't improve, p > 0.05. -Remission of symptoms after 6 months of treatment.	2 (28.6%) patients stopped the treatment: 1 died due to myocardial infarction and the other for disease progression.
Ariyasu H. 2014	Crossover trial	10 patients	67.5 (48 – 80)	70%	American College of Rheumatology (ACR)/EULAR 2013	Diffuse = 10 (100%)	Clinical assessment: Grading of Gastrointestinal Involvement in Systemic Sclerosis (Draft Japanese Guidelines)	Ghrelin (5.0 µg/kg ev) single dose	Assessment of satiety VAS scores (10 cm in length) -Ghrelin administration did not improve early satiety vs placebo (1.04 (0,54) vs 1.54 (0.34), p=0.43)	2 (20%) mild adverse: flushing and sweating (single dose)
Foocharoen C. 2017	1:1 Trial	75 patients -38 domperidone group -37 Algycon group	54.4 (9.7)* *Standard deviations	62.5%	American Rheumatism Association (1980)	Diffuse = 58 (77.3%) Limited = 17 (22.7%)	Clinical assessment: Symptoms of refractory GERD: GERD-Q >7 + GERD improved <50% after omeprazole 20 mg/twice daily for 4 weeks.	Domperidone 10 mg p.o t.i.d 4 weeks	QoL by EQ-5D Frequency of symptoms (FSSG) VAS score of severity of heartburn and regurgitation -Severity, frequency of the symptoms and QoL after treatment in the domperidone and algycon groups were not significantly different. -13.2% in domperidone vs 21.6% in algycon did not response to the treatment (p=0.12)	2 (5.3%) patients mild side effects in the domperidone group: Nausea and infected calcinosis cuti)
Vigone B. 2017	Crossover trial	40 patients. 29 patients completed the study	54.4 (10.5)* *Standard deviations	100%	American College of Rheumatology (ACR)/EULAR 2013	Diffuse = 7 (24.2%) Limited = 22 (75.8%)	Rome III criteria for functional constipation	Prucalopride 2 mg p.o/24 h 30 days	UCLA GIT 2.0 questionnaire Total score improved with prucalopride (decrease of -0.147. p = 0.047) 5-point Likert scale for constipation Improved with prucalopride -1.282, p <0.001 4-point Likert scale for GERD symptoms Improved with prucalopride -0.678, p <0.001	7 patients (17.5%) did not tolerate prucalopride due to side effects: headache,

									Improved number of complete spontaneous bowel movements/month ($p<0.001$).	abdominal pain, dizziness and sensation of feeling sick.

QoL = Quality of Life; **CIPO** = Chronic idiopathic Pseudo Obstruction **GERD** = Gastroesophageal Reflux Disease **VAS** = Visual analogue scale;

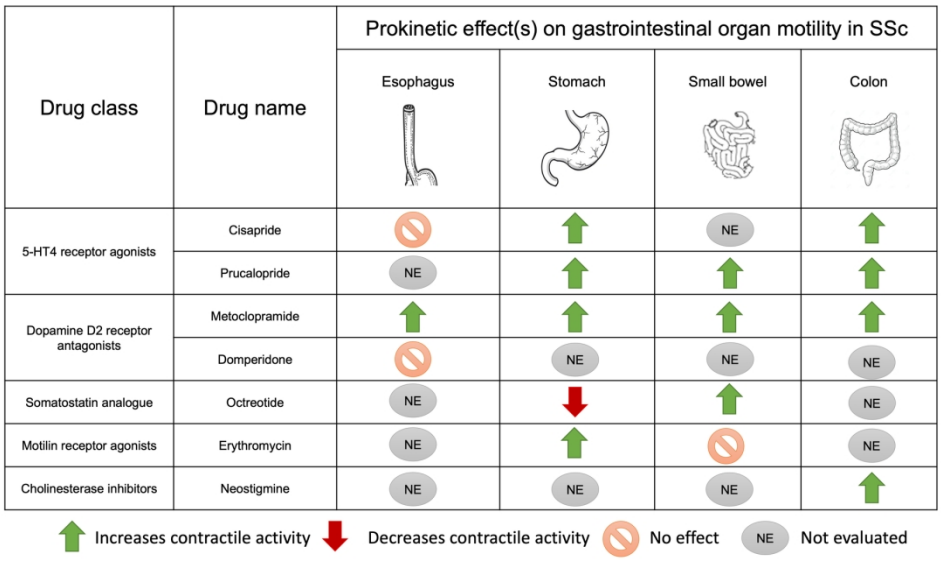

Figure 2. Evidence summary of objective motility effect of prokinetics on gastrointestinal motor function in patients with systemic sclerosis

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Table 3: Summary of evidence and recommendations for the use of prokinetics in managing GI involvement in systemic sclerosis

Drug class	Drug name	Drug dose	Indications	Warnings and drug precautions
5-HT4 receptor agonists	Cisapride	10 mg PO TID before meals	• **Gastroparesis** • **Chronic constipation**	Withdrawn from the market due to risk of ventricular arrhythmia.
	Prucalopride	1-2 mg PO daily	• **Refractory gastroesophageal reflux disease** • **Gastroparesis** • **Enteric dysmotility / Chronic idiopathic-pseudo obstruction** • **Chronic constipation**.	Up to 20% of patients may report side-effects [Headache, dizziness, nausea]
Dopamine D2 receptor antagonists	Domperidone	10-30 mg PO TID	• **Refractory gastroesophageal reflux disease** • **Gastroparesis**	Potential cardiac side effects, including QTc prolongation with doses > 40mg day, Prolactin related adverse events
	Metoclopramide	10 mg PO TID	• **Refractory gastroesophageal reflux disease** • **Gastroparesis** • **Enteric dysmotility / Chronic idiopathic-pseudo obstruction**	**FDA Warning:** avoid treatment with metoclopramide for longer than 12 weeks because of the risk of developing tardive dyskinesia.
Somatostatin analogue	Octreotide	Octreotide sc 50 µm daily at bedtime Octreotide LAR IM 20 mg/mo	• **Enteric dysmotility / Chronic idiopathic-pseudo obstruction**	Increases risk of biliary gallstone disease. Administer at bedtime or apart from meals, as octreotide reduces gastric motility.
Motilin receptor agonists	Erythromycin	Erythromycin 2mg/kg IV	• **Gastroparesis**	Development of tachyphylaxis, limiting its long-term efficacy.

		Erythromycin 250 mg PO TID every 4 weeks		
Cholinesterase inhibitors	Neostigmine	1 mg IV, single dose	• **Acute colonic pseudo-obstruction**	Risk of bradycardia and hypotension. The use of telemetry monitoring is mandatory.
	Pyridostigmine	30-60 mg PO TID	• **Enteric dysmotility / Chronic idiopathic-pseudo obstruction** • **Chronic constipation**	Up to 45% patients report side-effects [Headache, diarrhea, salivation]

GERD Gastroesophageal reflux disease **IM** intramuscular **IV** intravenous **LAR** Long-acting release **PO** by mouth **SC** subcutaneous
TID three times a day