Efficacy of mast cell directed therapies in irritable bowel syndrome: a systematic review

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Abstract

Background and study aim: **Lately, mast cells (MCs) are increasingly implicated in the pathophysiology of irritable bowel syndrome (IBS). The aim of this systematic review was to assess the efficacy of mast cell directed therapies in reducing the main symptoms of IBS: abdominal pain and changes in stool frequency or consistency.**

Patients and methods: **Pubmed, Web of Science and Scopus were searched until December 19, 2022. Trials evaluating the efficacy of mast cell directed therapies, compared to placebo or any form of control group, were included. Trial selection was performed in two stages: screening titles and abstracts and reviewing full papers identified as relevant, taking into account the inclusion criteria.**

Results: **The search strategy identified a total of 1.384 citations. Eleven trials on 943 IBS patients and 197 controls were included: ten randomized controlled trials, two of which cross-over trials, and one cohort study. Of the 11 studies included in the systematic review, only three studies were found to be at low risk of bias. This limited evidence suggests a significant overall improvement in the key symptoms after treatment with disodium cromoglycate, ebastine, ketotifen or palmitoylethanolamide-polydatin compared to control groups.**

Conclusions: **Mast cell modulating therapies could be of significant value in therapy for IBS patients. Further high-quality research is needed to establish the therapeutic efficacy of mast cell targeted therapies in order to draw robust conclusions and improve the clinical management of irritable bowel syndrome.** (Acta gastroenterol. belg., **2024**, 87, **15-27**).

Keywords: Irritable bowel syndrome, mast cells, disodium cromoglycate (DSCG), ebastine, ketotifen, palmitoylethanolamide-polydatin.

Abbreviations: IBS: irritable bowel syndrome; RCT: randomized controlled trial; NNT: number needed to treat; DSCG: disodium cromoglycate; MC: mast cell; IBS-D: diarrhea predominant IBS; DC: reviewer D. Coppens; MK: reviewer M. Kips; TS: reviewer T. Stiévenard; IBD: inflammatory bowel disease; CBT: cognitive behavioral therapy; CM: reviewer C. Mertens; HDS: reviewer H. De Schepper; GI: gastrointestinal; RoB: risk of bias; RR: relative risk; ARR: absolute risk reduction; EER: experimental event rate; CER: control event rate; IBS-C: constipation predominant IBS; IBS-M: mixed IBS; IBS-A: alternating IBS; IBS-U: unclassifiable IBS; VAS: visual analogue scale; SPT: skin prick test; SGA: subgroup analysis; TSS: total symptom score; GSRS: gastrointestinal symptom rating scale; BSFS: Bristol stool form scale; b.i.d.: twice a day; t.i.d.: three times a day; o.d.: once a day; q.i.d.: four times a day; IG: intervention group; CG: control group; HSG: healthy subjects group; HS: hypersensitive; NS: normosensitive.

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by abdominal pain and an altered bowel habit. IBS results from dysregulated brain–gut interactions, leading to several underlying mechanisms, including increased intestinal permeability, dysmotility, food intolerance, and visceral hypersensitivity (1-2). The disorder affects approximately 10% of the population, depending on the criteria used to define its presence, and is more common in women and younger individuals (1,4). Risk factors for developing IBS include enteric infections, gastrointestinal inflammation as well as psychological comorbidities (5). The development of gastrointestinal symptoms at any point in time, with recurrent and remitting course, implies reduced quality of life, substantial morbidity, and high medical costs (2-3). Yet, the underlying mechanisms, including but not limited to alterations in mucosal immune function, gut microbiota, and central nervous system processing, that ultimately lead to IBS symptomatology remain incompletely understood (3). As a result, current treatment focuses mainly on symptom relief and includes patient education, dietary changes, intake of soluble fiber, and specific medication (2).

Lately, intestinal immune activation, and particularly mast cell activation, is increasingly implicated in the pathophysiology of IBS (6-7). Mature mast cells are granular cells derived from bone marrow myeloid-cell progenitors (6). Triggers of mast cell activation are immune (e.g., immunoglobulins, complement components, and interleukins) and non-immune stimuli (e.g., neuropeptides, hormones, and biological and physicochemical factors) (2-6). Other pathways of acute mast cell activation have been proposed, among which direct activation through the Mas-related G protein-coupled receptor X2 (MRGPRX2) , without requirement of circulating antibodies or priming of immune cells (8). In the gastrointestinal tract, mast cells regulate vascular and epithelial permeability, ion secretion, peristalsis, tissue repair, immunity, bacterial defense, chemotaxis, and nociception. Hence, uncontrolled or dysregulated activation of mast cells may interfere with gut homeo-

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stasis, generate tissue dysfunction, and promote inflammation in diverse gastrointestinal diseases, including IBS (1,3,6).

Numerous studies were conducted to identify the mechanisms that underlie the role of mast cells in gut mucosal barrier disruption, mucosal immune dysregulation, visceral hypersensitivity, dysmotility, and stress at the site of irritation in combination with centralised stress responses in IBS (4,6-7). Recently, Aguilera-Lizarraga *et al*. identified and characterized an IgE-mediated mechanism of mast cell activation caused by an inflammation-induced break in oral tolerance to dietary antigens, and resulting in food-induced abdominal pain (7).

Several studies have investigated mast cell-targeted therapies in patients with IBS, further supporting the potentially important role of mast cells in the pathophysiological process of IBS, and particularly visceral hypersensitivity (2). Several factors cause the onset of IBS symptoms, in which the role of mast cells has been established mainly in IBS-D patients (6). This subset of patients could therefore benefit from mast cell targeted therapy. Possible mechanisms of action of these therapies include stabilizing the plasma membrane of MCs, preventing cell membrane lysis, preventing MC degranulation, and targeting their mediators and receptors (e.g., ebastine), resulting in a reduced release of inflammatory mediators, including histamine and tryptase (2,12). These clinical studies with mast cell-targeted therapies, such as mast cell modulators and antagonists of histamine and serotonin receptors, demonstrated considerable efficacy (2).

However, the lack of cohesion in existing studies and the lack of insight into the efficacy of mast cell directed therapies implies a critical gap in literature. With a growing population of patients facing IBS symptoms, we need to gain a better understanding of pathophysiology-directed and effective therapies. The aim of this systematic review was to assess the efficacy of mast cell directed therapies in reducing key gastrointestinal symptoms: abdominal pain and changes in stool frequency or consistency. The information provided in the present study may be useful for the clinical management of IBS patients in whom mast cells are an important symptom onset factor.

Methods

Design

The systematic review consists of ten randomized controlled trials, two of which cross-over trials, and one cohort study.

Search strategy

The literature search was conducted by three independent reviewers (DC, MK, TS) on PubMed, Web of Science, and Scopus. All databases were first consulted on 18 November 2022 and last on 19 December 2022. Following criteria were adopted to select studies for analysis: patients diagnosed with IBS based on clinicians' opinion or international symptom-based criteria (e.g., classifications of the Rome foundation), studies examining the efficacy of - any dose of - mast cell directed therapies, which were compared with placebo or any form of control group. The following exclusion criteria were applied during the study selection process: no specific IBS diagnosis (e.g., IBD, fibromyalgia, microscopic colitis, functional dyspepsia, Crohn's disease, and ulcerative colitis), animal models or in vitro studies, no specific mast cell directed therapies (e.g., mesalazine, cognitive behavioral therapy (CBT), electroacupuncture), review articles, case reports as study design, and non-academic English. Other language or publication year restrictions were not applied.

Query terms of IBS were considered and identified by: *irritable bowel syndrome* (both MeSH and free text term), *IBS* or *visceral hypersensitivity*. These terms were combined using the set operator AND with therapy terminologies defined by the terms: *mast cell* (both MeSH and free text term), *MC*, *mast cell degranulation stabilizer*, *mast cell stabilizers* (both MeSH and free text term), *mast cell stabilizing compounds*, *mast cells therapy* (MeSH term when possible), *histamine antagonists* (both MeSH and free text term), *antihistamin*, *ketotifen* (both MeSH and free text term), *cromoglycate*, *loratadine* (both MeSH and free text term), *desloratadin*, *olopatadin*, *rupatadin*, *mepolizumab*, *omalizumab* (both MeSH and free text term), *pemirolast*, *nedocromil* (both MeSH and free text term), *azelastin*, *tranilasat*, *palmithoylethanolamide*, *GW876008*, *DNK333*, *FUT175*, *mesalazin*, *acrivastin*, *cetirizine* (both MeSH and free text term), *ebastine*, *fexofenadin*, *levocetirizin*, *mizalastin*, *cromolyn sodium* (both MeSH and free text term), *olopatadine hydrochloride* (both MeSH and free text term), *mesalamine* (both MeSH and free text term), *futhan* and *nafamstat mesilate*. MeSH-applications were not available in Web of Science and Scopus, thus every term was labeled by a field search in title or abstract.

Three reviewers (DC, MK, TS) screened each retrieved article in an independent and blinded manner. Web application Rayyan (Rayyan Systems Inc.) assisted the review authors in study selection. No filters or automation tools were integrated into the overall selection process to decide whether a study met the review's inclusion criteria, in order to minimize the risk of errors and bias. The second stage, the disagreement resolution process, was carried out together with two additional investigators (CM, HDS).

Flow of studies throughout the review

The search strategy identified a total of 1.384 citations, of which 71 published articles appeared relevant after screening and were retrieved for further assessment (Figure 1). Three reviewers (DC, MK, TS) assessed each

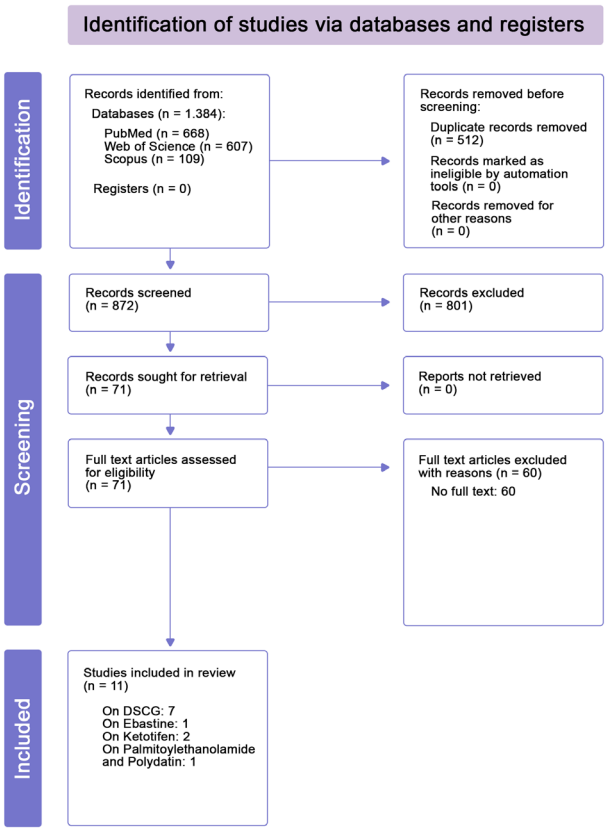

Figure 1. — Flowchart of study selection.
DSCG = disodium cromoglycate.

retrieved article in an independent and blinded manner. The second stage, the disagreement resolution process, was carried out together with two additional investigators (CM, HDS). Full agreement was reached after discussion between all reviewers and investigators. Eleven full text articles met all inclusion criteria for the systematic review and were eligible for inclusion.

Data collection process

The following clinical data were collected for each individual study: setting (type of clinic or study center and country), year of data collection, study design, participant's sex, participant's age, inclusion criteria, exclusion criteria, IBS diagnosis criteria, outcome IBS, results, and control group type (e.g., placebo, no treatment, et cetera).

Outcome assessment

All articles specified changes in gastrointestinal (GI) symptoms as one of the main outcomes. Most frequently, abdominal pain and changes in stool frequency or form were assessed. As a primary outcome, the therapeutic efficacy of compounds on improving the three key symptoms compared to control groups was assessed. In addition, the efficacy between all included mast cell directed therapies was assessed as a secondary outcome.

Risk of bias assessment

Three reviewers (DC, MK, TS) performed the risk of bias (RoB) assessment of individual studies together by consensus. Afterwards, a fourth reviewer (CM) performed the assessment independently. The Cochrane RoB-2 and ROBINS-I tools were used for assessing the risk of bias in randomized and non-randomized clinical trials, respectively (9-10).

Synthesis methods

All results were grouped by outcome and active substance, allowing medical professionals to easily determine which pharmaceutical therapy is most efficacious for the symptoms of IBS patients according to current international guidelines.

Therapies were compared relatively by expressing the impact of the intervention with a dichotomous relative risk (RR), p-values, and number needed to treat (NNT) if applicable. NNTs were calculated using the formula 1/absolute risk reduction (ARR), which can be obtained by subtracting experimental event rate (EER) from control event rate (CER).

Results

Quality of evidence

Of the 11 studies included in the systematic review, only three studies were found to be at low risk of bias (14-15,17). Risk of bias in all domains for all included trials is reported in Table 1. Ten RCTs were assessed using the RoB-2 Cochrane tool (9). Overall, only three RCTs had low risk of bias, in which no concerns were present in any of the domains. Two studies raised some concerns and were judged to have moderate risk of bias. The low quality was mainly due to insufficient randomization processes (Domain 1) (12,21). All five studies assessed as high risk of bias, involving a total of 564 subjects, appeared to present additional concerns particularly related to missing outcome data and measurements of reported outcomes (Domain 3 and Domain 4) (13,17-19,22). To assess risk of bias in the results of non-randomized studies, the ROBINS-I Cochrane tool is indicated for pre-experimental cohort studies with interventions (10). One study had a critical overall risk of bias, mainly due to serious concerns about classification of interventions and measurement of outcomes (Domain 3 and Domain 6) (20). Of the seven RCTs investigating disodium cromoglycate (DSCG), solely one trial was not assessed to be at high risk of bias (21). There was one RCT involving ebastine that was judged to be at low risk of bias (15). The two RCTs of ketotifen did not show a high risk of bias, one of which was considered to be at low risk of bias (16) and one raised some concerns (12). The only trial of palmitoylethanolamide-polydatin was assessed as having a low risk of bias (14).

Table 1. — **Risk of bias within and between studies**

RoB-2 framework Study (year)	**Domain 1:** Risk of bias arising from the randomization process	**Domain 2:** Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)	**Domain 3:** Missing outcome data	**Domain 4:** Risk of bias in measurement of the outcome	**Domain 5:** Risk of bias in selection of the reported result	**Overall risk of bias**
Wang, J. *et al.* (2020)	?	+	+	+	+	Some concerns
Lobo, B. *et al.* (2017)	?	?	+	-	+	High
Cremon, C. *et al.* (2017)	+	+	+	+	+	Low
Wouters, M. M. *et al.* (2016) - Part 2	+	+	+	+	+	Low
Klooker, T. K. *et al.* (2010)	+	+	+	+	+	Low
Daryani, N. *et al.* (2008)	?	+	?	+	+	High
Leri, O. *et al.* (1997)	?	+	+	?	+	High
Stefanini, G.F. *et al.* (1995)	?	+	?	?	+	High
Lunardi, C. *et al.* (1991)	?	+	+	+	+	Some concerns
Paganelli, R. *et al.* (1990)	-	?	-	?	?	High

ROBINS-I framework Study (year)	**Domain 1:** Bias due to confounding	**Domain 2:** Bias in selection of participants into the study	**Domain 3:** Bias in classification of interventions	**Domain 4:** Bias due to deviations from the intended interventions	**Domain 5:** Bias due to missing data	**Domain 6:** Bias in measurement of outcomes	**Domain 7:** Bias in selection of the reported result	**Overall risk of bias**
Stefanini, G.F. *et al.* (1992)	?	+	-	?	+	-	+	Critical

+ = Low risk of bias
? = Some concerns
- = Serious or high risk of bias

The reviewing team decided to use only provided information that had been published. The initial agreement among the three reviewers (DC, MK, TS) for the quality assessment was moderate, and reached full agreement after discussing the differences together with investigator CM (moderate to good secondary agreement, kappa statistics = 0.48). Most discussions arose from concerns about blinding and randomization processes, and measurement of the outcomes. Table 3 shows the quality of evidence determined by the GRADE approach (11). Every cluster of results is assessed according to a common, sensible, and transparent approach to grading the quality or certainty of evidence and the strength of recommendations.

Study characteristics

Of the 71 articles that appeared to be relevant, 60 papers were excluded due to a lack of full text (available yet no results or a comment), leaving ten RCTs and one cohort study (20) (Table 2). Of these, six RCTs compared mast cell directed therapies with placebo (12,14-16), including two cross-over trials consisting of treatment with either DSCG or placebo for 6 (17) or 8 (21) weeks, followed by the cross-over treatment for a further 6 or 8 weeks, respectively. Two RCTs compared the therapeutic role of exclusion diet versus both exclusion diet and oral DSCG (18,22). Two RCTs compared control groups,

in the form of exclusion diet or no treatment to assess natural evolution, with DSCG (13,19).

Ten RCTs involving 869 subjects reported data on the proportion of patients who showed relevant global IBS symptoms. Of these participants, 641 patients were randomly assigned to the intervention groups.

Study population

Diagnostic criteria for IBS differed considerably between the study protocols. Only one trial selected IBS patients according to the most recent Rome IV criteria defined by the Rome foundation (12). In two trials, patients were included based on Rome III criteria (14-15). Rome II criteria were an inclusion criterion in three RCT (13,16-17). Five studies qualified IBS patient enrollment based on a clinical diagnosis, e.g., chronic diarrhea with exclusion of other GI diseases, clinical history, and other GI symptoms (18-22).

Two studies did not specify the subtype(s) of IBS (21-22), whereas nine studies included only IBS-D patients (12-20), in four other subtypes such as IBS-C, IBS-M or IBS-U were considered (14-17).

Treatment interventions

Therapy administration varied significantly in terms of active pharmacological substance, dose, duration, and frequency of administration. In the seven trials on DSCG, daily intake showed great heterogeneity between studies, ranging from 150 mg to 2000 mg, dosed 1 to 4 times a day for 3 to 24 weeks (13,17-22). A marked difference was observed in the studies on ketotifen as well, with doses ranging from 2 mg to 12 mg daily, dosed 2 times daily for 8 weeks (12,16). Further detailed information on the treatment substances, durations, doses, and frequencies is provided in Table 2.

Outcome measures

All study articles specified changes in GI symptoms as one of the main outcomes. Most frequently abdominal pain, changes in stool frequency or form, flatulence, bloating and meteorism were assessed using numerous different measurements and scales. Outcome measures in the included trials relevant to the research question are presented in Table 3.

Once relevant study data were extracted, the findings were collated and described according to the pooling strategy. Due to major differences in termed endpoints of the reported outcomes, the synthesis of results was organized by the three cardinal symptoms stated by the Rome IV criteria: abdominal pain (12-22), change in stool frequency (12,14,16-22), and change in stool form (12-14,16-21).

Efficacy on reducing abdominal pain

DSCG

Seven articles examined the efficacy of DSCG on abdominal pain reduction in 685 participants, of whom 36 were enrolled in cross-over trials (13,17-22). Two hundred and seventy-one of the participants were allocated to a control arm (25 no treatment, 246 elimination diet; placebo cross-over trials not taken into account), including 16 healthy participants. Abdominal pain reduction was measured with Visual Analogue Scales (VAS) evaluating pain severity (13,17,22) and various subjective symptom questionnaires (18-21). All six controlled trials of DSCG concluded a significant improvement in abdominal pain scores compared to the control groups (13,17-22). Relevant reported statistics are shown in Table 3. Stefanini *et al*. twice reported a significantly better efficacy of DSCG in skin prick test (SPT) positive patients in comparison with SPT-negative participants (19-20), whereas no control group was examined in their 1992 trial (20). All six studies were rated as high or critical overall risk of bias (13,17-20,22). Due to low certainty of evidence, GRADE was downgraded two to three steps.

Ketotifen

The efficacy of ketotifen on abdominal pain reduction was examined in 190 subjects participating in two trials (12,16), measured with a validated subgroup analysis (SGA) of Abdominal Pain in the study of Klooker *et al*. and a subjective symptom questionnaire with subscores summed up in a Total Symptom Score (TSS) in Wang *et al*.'s trial. Both trials concluded a significant improvement in pain scores ($p < 0.05$). Only in one study the randomization process raised some concerns (12), thus the level of evidence was judged to be moderate.

Ebastine and palmitoylethanolamide-polydatin

Ebastine (15) and palmitoylethanolamide-polydatin (14) showed beneficial results in 109 patients. In both active treatments, improvement in abdominal pain as an endpoint was superior compared to the improvement rates in the control groups. The efficacy of ebastine was measured by Wouters *et al*. with an assessment of the threshold for discomfort (15), whilst the results of palmitoylethanolamide-polydatin were evaluated by a symptom questionnaire (14).

At low risk of bias, the two study articles on ebastine and palmitoylethanolamide-polydatin delivered a high certainty of evidence. No steps in downgrading the evidence were applied, leading to a high GRADE.

A relative comparison between the four active compounds examined in the articles included could not be generated without serious concerns. Notable heterogeneity in the presented outcome measures, follow-up periods, and imprecise presentation of results are outlined in Table 3. However, data extracted from seven out of the 11 trials with abdominal pain reduction as one of the outcomes enabled calculation of the NNT (12-15,18-19,22). Figure 2 shows the quantitative efficacy, relatively by NNT of the four active treatments.

Table 2. — **Study characteristics**

Intervention	Study (year)	Duration, dose and frequency (Control)	Diagnostic criteria IBS and IBS subtype	Study design	Age [y] (Sex [M/F])	Sample size	Setting, country and data collection period
DSCG	Lobo, B. et al. (2017)	24 weeks, 200 mg, t.i.d. (No treatment)	Rome II, IBS-D	Randomized controlled trial (Pilot RCT)	IG: 42.5 ± 3.8 (11/7) CG: 37.4 ± 2.1 (17/8) HSG: 32.1 ± 2.3 (7/9)	Total: n = 59 G: n = 18 CG: n = 25 HSG: n = 16	Outpatient gastroenterology clinic of the Hospital Vall d'Hebron in Barcelona, Spain – 2007-2009
	Daryani, N. et al. (2008)	6 weeks followed by placebo for 6 weeks or vice versa, 50 mg, t.i.d. (Placebo)	Rome II, 50% IBS-D and 50% IBS-C	Randomized placebo-controlled double-blinded cross-over trial (RCT)	IG A & IG B: 40.3 ± 10.9 (A: 2/8 & B: 2/6) CG, HSG: NA	Total: n = 16 IG A: n = 10 & IG B: n = 6 CG, HSG: NA	Private gastrointestinal clinic in Tehran, Iran – 2007
	Leri, O. et al. (1997)	16 weeks, 250 mg, q.i.d. with unspecified exclusion diet (Exclusion diet without DSCG)	Clinical diagnosis, IBS-D	Randomized controlled trial (RCT)	Total: Male: 27.90 ± 8.56; female: 28.29 ± 8.47 (68/52) IG, CG, HSG: NA	Total: n = 66 IG: n = 36 CG: n = 30 HSG: NA	II Surgical clinic of University La Sapienza Rome, Italy – Not stated
	Stefanini, G.F. et al. (1995)	4 weeks, 1500 mg, q.1.d. (Elimination diet, permitted foods were rice, olive, oil, pears, salt, brown sugar, mineral water, lamb, turkey, lettuce, cooked carrots, sweet potatoes, and black tea)	Guidelines of the XIII International Congress of Gastroentero-logy, IBS-D	Randomized controlled trial (RCT)	IG A: 36.7 ± 12.6 (95/105) IG B: 37.6 ± 13.5 (90/119) CG, HSG: NA	Total: n = 409 IG A: n = 200 & IG B: n = 209 CG, HSG: NA	Fourteen study centers, Italy – Not stated
	Stefanini, G.F. et al. (1992)	8 weeks, 500 mg, t.i.d. (No control)	Clinical diagnosis, IBS-D	Cohort study (pre-experimental)	IG, CG, HSG: NA	Total = IG: n = 101 CG, HSG: NA	Polyclinic of the University of Bologna, Italy – Not stated
	Lunardi, C. et al. (1991)	8 weeks followed by placebo for 8 weeks or vice versa, 500 mg, q.i.d. (Placebo)	Clinical diagnosis, subtype not stated	Randomized placebo-controlled double-blind cross-over trial (RCT)	IG A & IG B: Mean 33.5 (2/18) CG, HSG: NA	Total: n = 20 IG A: n = 10 & IG B: n = 10 CG, HSG: NA	Polyclinic of the University of Verona, Italy – Not stated
	Paganelli, R. et al. (1990)	3 weeks, 250 mg, t.i.d. with elimination diet (Elimination diet, permitted foods were whole rice, flour, fresh salad, carrots, potatoes, all types of meat excluding chicken and veal, apples, pears, olive oil, salt, spring water, tea and sugar	Clinical diagnosis, subtype not stated	Randomized controlled trial (RCT)	IG: 39.43 ± 16.64 (1/6) CG: 33.86 ± 7.49 (2/5) HSG: NA	Total: n = 14 IG: n = 7 CG: n = 7 HSG: NA	University La Sapienza Rome, Italy – Not stated
Ebastine	Wouters, M. M. et al. (2016) - Part 2	12 weeks, 2 weeks follow-up, 20 mg, o.d. (Placebo)	Rome III, 47% IBS-D, 20% IBS-C, 17% IBS-M and 29% IBS-U	Randomized placebo-controlled double-blind proof-of-concept trial (RCT)	IG: HS mean: 28 (2/11) - NS mean: 43 (6/9) CG: HS mean: 27 (6/6) - NS mean: 35 (7/8) HSG: NA	Total: n = 55 IG: n = 28 (analysis n = 20) CG: n = 27 (analysis n = 24) HSG: NA	Outpatient clinic of the University Hospitals Leuven, Belgium – November 2009 - April 2012
Palmitoyl-ethanol-amide and poly-datin	Cremon, C. et al. (2017)	12 weeks, 200 mg/20 mg, b.i.d. (Placebo)	Rome III, 50% IBS-D, 19% IBS-C and 31% IBS-M	Randomized, placebo-controlled double-blind multicentered study (Pilot RCT)	IG: 37.0 ± 10.8 (11/18) CG: 40.4 ± 9.8 (14/11) HSG: 32.7 ± 13.0 (14/5)	Total: n = 54 IG: n = 29 CG: n = 25 HSG: n = 12	Five study centers in Bologna, Italy; Nantes, France; Barcelona, Spain; Tuzla, Bosnia and Herzegovina; Zagreb, Croatia – June 2010 - December 2012
Ketotifen	Wang, J. et al. (2020)	8 weeks, 1 mg, b.i.d. (Placebo)	Rome IV, IBS-D	Prospective randomized placebo-controlled study (RCT)	IG: 43.5 ± 11.6 (26/29) CG: 42.6 ± 10.3 (25/28) HSG: NA	Total: n = 108 IG: n = 55 CG: n = 53 HSG: NA	Outpatient clinic of the Zhejiang University School of Medicine, China – 2016-2018
	Klooker, T. K. et al. (2010)	8 weeks, 2 weeks follow up, 2 weeks 2 mg b.i.d., 2 weeks 4 mg b.i.d., 4 weeks 6 mg b.i.d. (Placebo)	Rome II, 37% IBS-D, 15% IBS-C and 48% IBS-A	Randomized placebo-controlled double-blind trial (RCT)	IG: HS: 34 ± 3 (5/10) - NS: 35 ± 3 (4/11) CG: HS: 34 ± 3 (3/12) - NS: 40 ± 3 (5/10) HSG: 30 ± 3 (7/15)	Total: n = 82 IG: n = 30 (HS = NS = 15) CG: n = 30 (HS = NS = 15) HSG: n = 22	Gastrointestinal motility unit of the Academic Medical Center Amsterdam, The Netherlands – January 2005 - December 2007

IBS = irritable bowel syndrome, IBS-D = diarrhea predominant IBS, IBS-C = constipation predominant IBS, IBS-M = mixed IBS, IBS-U = unclassifiable IBS, IBS-A = alternating IBS, DSCG = disodium cromoglicate, o.d. = once a day, b.i.d. = twice a day, t.i.d. = three times a day, q.i.d. = four times a day, RCT = randomized controlled trial, NA = not applicable, IG = intervention group; CG = control group; HSG = healthy subjects group; HS = hypersensitive; NS = normosensitive.

Endpoints were not very well described in four RCTs (10,16-17,20). Outcome measures were assessed by use of subjective scores, visual analogue scales, total symptom scores or questionnaires reporting global IBS symptoms; including abdominal pain, as well as changes in stool frequency and form. Studies that stated patients

were reporting improvement in all three IBS symptoms (total improvement rate), were thus included for all NNT comparisons, in Fig. 2-4.

Efficacy on reducing change in stool frequency

DSCG

Six articles examined the efficacy of DSCG on change in stool frequency in 626 participants, 46 of which were allocated to a control group (17-22). Change in stool frequency was measured using subjective IBS symptom questionnaires (18-21), VAS rating severity (17), and daily recording of bowel movements (22). Four of the controlled studies of DSCG concluded a significant improvement in change of stool frequency compared to the control groups (18-19,21-22). Relevant reported statistics are shown in Table 3. Although no control group was examined in the 1992 study of Stefanini *et al*., the study revealed a significantly better efficacy of DSCG in SPT-positive patients in comparison with SPT-negative participants. These results are partially in contrast with the more recent article of Daryani *et al*., where no significant difference between the treatment group and the control group was detected (17). Taking into account the high or critical overall risk of bias in five of the six included DSCG studies(17-20,22), GRADE was downgraded two to three steps as a result of very low certainty of evidence.

Ketotifen

Ketotifen's efficacy in improving stool frequency was examined in 190 IBS patients participating in two trials (12,16). This was measured with a validated 7-graded gastrointestinal symptom rating score (GSRS) in the study of Klooker *et al*. and a subjective symptom questionnaire with subscores summarized in a TSS in Wang *et al*.'s trial. Both trials concluded a significant improvement in stool frequency ($p < 0.05$), with low NNTs. Again, the randomization process of only one study raised some concerns (12) so the level of evidence was judged to be moderate.

Palmitoylethanolamide-polydatin

Palmitoylethanolamide-polydatin showed favorable results once more, after symptom assessment of 54 patients (14). Improvement in the change of stool frequency was superior in the IBS group compared to the improvement rate in the control group. The efficacy of the active compound was measured by evaluation of symptoms with a 4-graded questionnaire.

The study on palmitoylethanolamide-polydatin, for which the risk of bias was considered low, yielded a high certainty of evidence. No steps in reduction of evidence were applied, leading to a high GRADE.

Data extracted from four out of the nine trials with change in stool frequency as one of the outcomes enabled NNT calculation (12,18-19,22). Figure 3 presents the quantitative efficacy, relatively by NNT of the included studies.

Efficacy on reducing change in stool consistency

DSCG

Regarding the change in stool form, 6 trials studied the efficacy of DSCG in 671 participants, 55 of whom were allocated to a control group (13,17-21). Thirty-six patients were enrolled in cross-over designs and 16 healthy subjects were examined in the study of Lobo *et al*. Change in stool form was evaluated using subjective global IBS symptom questionnaires such as VAS rating severity (17), diary card scores (21), improvement in Bristol Stool Form Scale (BSFS) (13), and semiquantitative clinical scores (18-20). Four out of five controlled studies of DSCG concluded a significant improvement in change of stool consistency compared to the control groups (13,18-19,21). Relevant reported statistics are shown in Table 3. The study of Stefanini *et al*. (1992) did not include a healthy control group. This study also demonstrated significantly better efficacy of DSCG in SPT-positive patients compared with SPT-negative participants (20). In contrast, in the more recent cross-over study of Daryani *et al*. no significant difference was observed between the treatment group and the control group (17). Taking into account the high or critical overall risk of bias in five of the six included DSCG studies (17-20,22), GRADE was downgraded two to three steps as a result of very low certainty of evidence.

Ketotifen

The efficacy of ketotifen on reducing changes in stool consistency was examined additionally in 190 IBS-patients participating in two trials (12,16), measured with a validated 7-graded GSRS in the study of Klooker *et al*. and a subjective symptom questionnaire with subscores summed up in a TSS in Wang *et al*.'s trial. Both trials concluded a significant improvement in change of stool form as well ($p < 0.001$ and $p < 0.02$), with low NNTs. Moreover, the randomization process of only one study raised some concerns (12) so the level of evidence was also judged to be moderate.

Palmitoylethanolamide-polydatin

Palmitoylethanolamide-polydatin revealed beneficial results (14). Supported by a NNT of 5, improvement in change of stool form in IBS patients was superior compared to the improvement rate in the control group. The third endpoint of interest was measured by evaluating symptoms with a 4-graded questionnaire.

At low risk of bias, the article on palmitoylethanolamide-polydatin analogously delivered a high certainty of evidence. No steps in downgrading the evidence were applied, leading to a high GRADE.

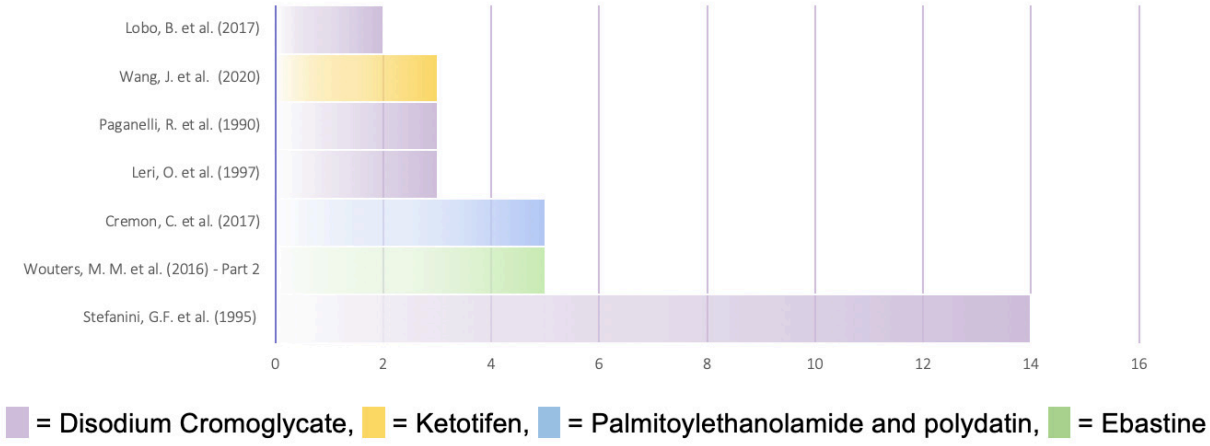

Figure 2. — Efficacy of mast cell directed therapies on reducing abdominal pain in IBS, by NNT.

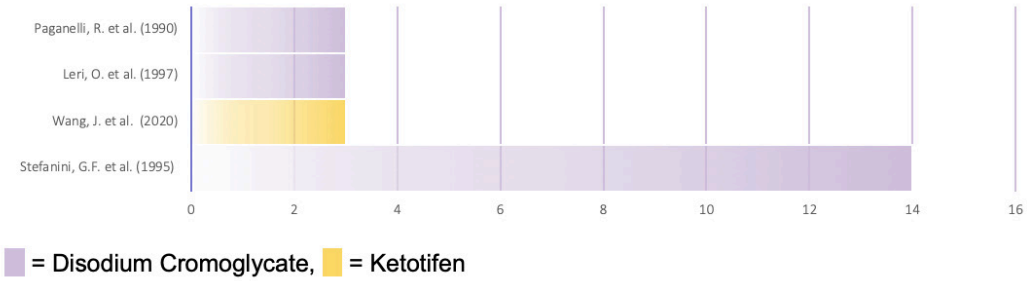

Figure 3. — Relative efficacy of mast cell directed therapies on reducing change in stool frequency in IBS, by NNT.

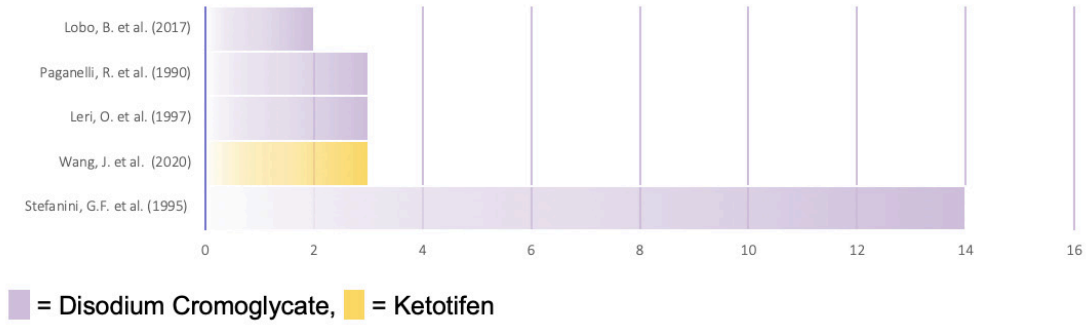

Figure 4. — Efficacy of mast cell directed therapies on reducing change in stool consistency in IBS, by NNT

Extracted data from five out of the nine trials with change in stool form as one of the outcomes enabled NNT calculation (12-13,18-19,22). Figure 4 shows the quantitative, relative efficacy by NNT of the included studies.

Adverse drug reactions

None of the studies reported serious side effects. Four studies on DSCG, ebastine, and palmitoylethanolamide-polydatin showed no significant difference in adverse events between treatment and placebo (13-15,17). Two articles provided side effects data, with a total of 29 of 85 patients (34%) allocated to ketotifen experiencing a mild adverse event (fatigue, dry mouth, dizziness), similar to the safety profile of placebo (12,16). The symptoms disappeared after continuing treatment for 1 week. Five publications included did not report presence or absence of side effects (18-22). These findings suggest safe profiles of all four examined active compounds.

Discussion

The global aim of this systematic review was to determine the efficacy of mast cell directed therapies on the improvement of key gastrointestinal IBS symptoms: abdominal pain and changes in stool frequency or

Table 3. — **Synthesis of evidence**

Endpoint	Intervention	Study (year)	Result	Outcome measure	Follow-up t1	Level of Evidence
Abdominal pain	DSCG	Lobo, B. *et al.* (2017)	**DSCG > control**, NNT = 2	Proportion of patients reporting ≥ 50% improvement in pain severity (VAS 0 to 10)	24 weeks	GRADE: Low ••
		Daryani, N. *et al.* (2008)	**DSCG > control**, IG A: p < 0.01, IG B: p < 0.02	Reporting pain levels using VAS 0 to 9	6 weeks	
		Leri, O. *et al.* (1997)	**DSCG > control**, p < 0.01, NNT = 3	Semiquantitative subjective score (complete remission +++, significant improvement ++, partial remission +, worsening -)	16 weeks	
		Stefanini, G.F. *et al.* (1995)	**DSCG SPT+ > DSCG SPT- > control**, NNT = 14	Global assessment IBS symptoms reported by physician using 4-point score (0 to 3 for mild to severe)	4 weeks	
		Stefanini, G.F. *et al.* (1992)	**DSCG SPT+ > DSCG SPT-**, p < 0.05	Semiquantitative score (complete remission +++, significant improvement ++, partial remission +, no effect 0, worsening -)	8 weeks	
		Lunardi, C. *et al.* (1991)	**DSCG > control**, p < 0.003	Diary card scores, rating severity from 0 (none) to 2 (severe)	Every 2 weeks (8 x 8 weeks)	
		Paganelli, R. *et al.* (1990)	**DSCG & diet > diet**, NNT = 3	Daily recording abdominal pain, subjective assessment overall improvement on an analogue scale	3 weeks	
	Ebastine	Wouters, M. M. *et al.* (2016) - Part 2	**Ebastine > control**, NNT = 5	Threshold for discomfort [mmHg]	12 weeks	GRADE: High ••••
	Palmitoylethanolamide-polydatin	Cremon, C. *et al.* (2017)	**Palmitoylethanolamide-polydatin > control**, p < 0.05, NNT = 5	Symptom questionnaire, grades from 0 to 4 (Likert scale) to analyze both severity and frequency of abdominal pain	Every 4 weeks (12 weeks)	GRADE: High ••••
	Ketotifen	Wang, J. *et al.* (2020)	**Ketotifen > control**, p < 0.001, NNT = 3	Symptom questionnaire, TTS with grades from 0 to 4 for severity and from 0 to 6 for frequency of abdominal pain	8 weeks	GRADE: Moderate •••
		Klooker, T.K. *et al.* (2010)	**Ketotifen > control**, p < 0.02	Validated Subject's Global Assessment (SGA) of Abdominal Pain and Discomfort and SGA of Relief	Every week (8 weeks)	
Change in stool frequency	DSCG	Daryani, N. *et al.* (2008)	**DSCG = control**	Reporting main symptom severity using VAS 0 to 9	6 weeks	GRADE: Low ••
		Leri, O. *et al.* (1997)	**DSCG > control**, p < 0.01, NNT = 3	Semiquantitative subjective score (complete remission +++, significant improvement ++, partial remission +, worsening -)	16 weeks	
		Stefanini, G.F. *et al.* (1995)	**DSCG SPT+ > DSCG SPT- > control**, NNT = 14	Global assessment IBS symptoms reported by physician using 4-point score (0 to 3 for mild to severe)	4 weeks	
		Stefanini, G.F. *et al.* (1992)	**DSCG SPT+ > DSCG SPT-**, p < 0.05	Semiquantitative score (complete remission +++, significant improvement ++, partial remission +, no effect 0, worsening -)	8 weeks	
		Lunardi, C. *et al.* (1991)	**DSCG > control**, p < 0.003	Diary card scores, rating severity from 0 (none) to 2 (severe)	Every 2 weeks (8 x 8 weeks)	
		Paganelli, R. *et al.* (1990)	**DSCG & diet > diet**, NNT = 3	Daily recording number of bowel movements, subjective assessment overall improvement on an analogue scale	3 weeks	
	Palmitoylethanolamide-polydatin	Cremon, C. *et al.* (2017)	**Palmitoylethanolamide-polydatin > control**, p < 0.05, NNT = 5	Symptom questionnaire, grades from 0 to 4 (Likert scale) to analyze both severity and frequency of changing stool frequency	Every 4 weeks (12 weeks)	GRADE: High ••••
	Ketotifen	Wang, J. *et al.* (2020)	**Ketotifen > control**, p < 0.001, NNT = 3	Symptom questionnaire, TTS with grades from 0 to 4 for severity and from 0 to 6 for frequency of diarrhea	8 weeks	GRADE: Moderate •••
		Klooker, T.K. *et al.* (2010)	**Ketotifen > control**, p < 0.02	Validated Gastrointestinal Symptom Rating Scale (GSRS), 7-graded Likert scale	Every week (8 weeks)	
Change in stool form or consistency	DSCG	Lobo, B. *et al.* (2017)	**DSCG > control**, NNT = 2	Proportion of patients reporting ≥ 50% improvement in stool consistency (BSFS)	24 weeks	GRADE: Low ••
		Daryani, N. *et al.* (2008)	**DSCG = control**	Reporting main symptom severity using VAS 0 to 9	6 weeks	
		Leri, O. *et al.* (1997)	**DSCG > control**, p < 0.01, NNT = 3	Semiquantitative subjective score (complete remission +++, significant improvement ++, partial remission +, worsening -)	16 weeks	
		Stefanini, G.F. *et al.* (1995)	**DSCG SPT+ > DSCG SPT- > control**, NNT = 14	Global assessment IBS symptoms reported by physician using 4-point score (0 to 3 for mild to severe)	4 weeks	
		Stefanini, G.F. *et al.* (1992)	**DSCG SPT+ > DSCG SPT-**, p < 0.05	Semiquantitative score (complete remission +++, significant improvement ++, partial remission +, no effect 0, worsening -)	8 weeks	
		Lunardi, C. *et al.* (1991)	**DSCG > control**, p < 0.003	Diary card scores, rating severity from 0 (none) to 2 (severe)	Every 2 weeks (8 x 8 weeks)	
	Palmitoylethanolamide-polydatin	Cremon, C. *et al.* (2017)	**Palmitoylethanolamide-polydatin > control**, p < 0.05, NNT = 5	Symptom questionnaire, grades from 0 to 4 (Likert scale) to analyze both severity and frequency of changes in stool form	Every 4 weeks (12 weeks)	GRADE: High ••••
	Ketotifen	Wang, J. *et al.* (2020)	**Ketotifen > control**, p < 0.001, NNT = 3	Symptom questionnaire, TTS with grades from 0 to 4 for severity and from 0 to 6 for frequency of diarrhea	8 weeks	GRADE: Moderate •••
		Klooker, T.K. *et al.* (2010)	**Ketotifen > control**, p < 0.02	Validated Gastrointestinal Symptom Rating Scale (GSRS), 7-graded Likert scale	Every week (8 weeks)	

DSCG = disodium cromoglycate ('cromolyn' and 'SCG' also used in studies), QoL = quality of life, ARR = absolute risk reduction, NNT = number needed to treat, SPT = skin prick test, VAS = visual analogue scale, BSFS = Bristol stool form scale

consistency. Mast cells play a central pathophysiological role in IBS, partly established by the release of histamine, although not well defined. Treatment with mast cell stabilisers may offer a reasonably safe and promising option for the management of patients with IBS (6). Limited evidence suggests a significant overall improvement in the key symptoms after treatment with DSCG, ebastine, ketotifen or palmitoylethanolamide-polydatin compared to control groups. Out of 1.384 articles retrieved, 11 eligible trials were included, with varying study designs: RCTs, two of which cross-over trials, and one cohort study. Patients' endpoints were examined in 943 subjects by the clinical effect of the substances. This review highlights that mast cell stabilizing therapies have a lot of potential in treating IBS symptoms.

The present review has some noteworthy strengths. First, a comprehensive set of search terms was composed and applied in three databases for searching relevant studies. Second, the performed systematic search prevented overlooking relevant trials. Third, two groups of independent reviewers performed screening, risk of bias assessment, and data extraction blinded.

The results of our review are affected by several factors, including methodological issues and differences between bias in the scarce number of relevant studies. Furthermore, there was a large heterogeneity in dose, duration, and frequency of administration of the active substances, in quality of evidence, outcome measures, and IBS diagnosis in the included trials. Moreover, even if studies were randomized and controlled, blinding was an issue. Especially trials on DSCG were often judged to be at high risk of bias and low to moderate GRADE, resulting in low levels of evidence. Other therapies were examined in higher quality designs, yet thoroughly restricted in quantity of subjects. There was no search for gray literature and additional databases could have been consulted.

Despite therapeutic evidence in multiple articles on the effect of antihistamines (e.g., mesalazine) on IBS symptoms (23), the lack of recent insight into the relative efficacy of promising mast cell directed therapies implied a critical gap in literature. In addition, it should be emphasized that one of the active substances addressed in the review is not considered a mast cell directed therapy strictu sensu, but rather as an antihistamine compound. Nonetheless, various scientific articles state ebastine may be implemented as a mast cell blocker (24).

Prospects for future research

Hence, it should be noted that there is an extensive need for additional high-quality evidence to allow for robust conclusions to be drawn and to present adequate therapeutic options in the relief of life-altering symptoms in IBS patients. Future research should focus on the relative efficacy of mast cell directed therapies compared with current clinical strategies to improve symptoms in IBS patients diagnosed by Rome IV criteria. Additionally, patient satisfaction and QoL should be considered to investigate outcomes and results in the long-term. Finally, some level of standardization of dose, duration, and frequency of drug administration may be necessary for comparative efficacy and safety assessments. Robust scientific trial designs to examine these interventions could be large high quality randomized, placebo-controlled, double blind, multicentered studies or cross-over designs with short-term measurements and long follow up periods.

Author contributions

Daan Coppens*: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); Methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal)

Max Kips*: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); Methodology (equal); validation (equal); writing – original draft (equal); writing - review and editing (equal)

Thomas Stiévenard*: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); Methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal)

Caro Mertens*: Conceptualization (supportive); data curation (equal); formal analysis (equal); investigation (supportive); methodology (supportive), validation (equal); writing - review and editing (supportive), supervision (supportive)

Heiko De Schepper: Conceptualization (lead); formal analysis (equal); investigation (supportive); supervision (lead)

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Conflict of interest statement

No conflict of interest.

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Addenda

Eligibility criteria

The eligibility criteria are built on the defined keywords using the PICOST method. Inclusion and exclusion criteria are formulated via this framework.

Supplementary Table 1. — **Eligibility criteria within the PICOST framework**

PICOST	Definition	Eligibility criteria	
		Inclusion criteria	Exclusion criteria
P:	*Patients, Persons of interest, Problem, Population*	IBS diagnosed	No specific diagnose of IBS (e.g. IBD, fibromyalgia, microscopic colitis, functional dyspepsia, Crohn's disease and ulcerous colitis) No animal models, in vitro
I:	*Intervention, Indicator*	Mast cell directed therapy	No mast cell directed therapy (e.g. mesalazine, cognitive behavioral therapy, electroacupuncture)
C:	*Comparison, Control*	Placebo, no treatment or control (other intervention)	NA
O:	*Outcome*	NA	NA
S:	*Study design*	Randomized controlled trials (RCT) > cohort studies > case control studies	No reviews, case reports No academic English
T:	*Timing*	NA	NA

Databases and search queries

PubMed

PubMed is an online bibliographic database since 1996. PubMed contains citation information and abstracts of articles published in biomedical and scientific journals only. Medline, MEDLINE is the U.S. National Library of Medicine (Indexes since 1966), is the biggest component of PubMed and provides about 80% of the content.

Following systematic search provides 668 results.

Supplementary Table 2. — **Query box for PubMed**

((IBS[Title/Abstract]) OR ("Irritable bowel syndrome*"[Title/Abstract]) OR ("Irritable bowel syndrome"[MESH]) OR ("visceral hypersensitiv*"[Title/Abstract])) AND ((MC[Title/Abstract]) OR ("mast cell*"[Title/Abstract]) OR ("mast cell* degranulati* stabilizer*"[Title/Abstract]) OR ("mast cell* stabilizer*"[Title/Abstract]) OR ("mast cell* stabiliz* compound*"[Title/Abstract]) OR (Mast cell [MESH]) OR ("Mast Cell Stabilizers"[Mesh]) OR ("Mast Cells/therapy"[Mesh]) OR ("Histamine Antagonists"[Mesh]) OR (Antihistamin* [Title/Abstract]) OR ("Histamin* Antagonist*" [Title/Abstract]) OR (ketotifen [Title/Abstract]) OR (cromogl* [Title/Abstract]) OR (loratadin* [Title/Abstract]) OR (desloratadin* [Title/Abstract]) OR (olopatadin* [Title/Abstract]) OR (rupatadin* [Title/Abstract]) OR (mepolizumab [Title/Abstract]) OR (omalizumab [Title/Abstract]) OR (pemirolast [Title/Abstract]) OR (nedocromil [Title/Abstract]) OR (azelastin* [Title/Abstract]) OR (tranilasat [Title/Abstract]) OR (palmitoylethanolamide [Title/Abstract]) OR (GW876008 [Title/Abstract]) OR (DNK333 [Title/Abstract]) OR (FUT*175 [Title/Abstract]) OR (mesalazin* [Title/Abstract]) OR (acrivastin* [Title/Abstract]) OR (cetirizin* [Title/Abstract]) OR (ebastin* [Title/Abstract]) OR (fexofenadin* [Title/Abstract]) OR (levocetirizin* [Title/Abstract]) OR (mizalastin* [Title/Abstract]) OR ("cromolyn sodium" [Title/Abstract]) OR ("olopatadine hydrochloride" [Title/Abstract]) OR (Mesalamine [Title/Abstract]) OR (Futhan [Title/Abstract]) OR ("Nafam*stat mesilate" [Title/Abstract]) OR (ketotifen [Mesh]) OR ("cromolyn sodium"[Mesh]) OR (loratadine [Mesh]) OR ("olopatadine hydrochloride" [Mesh]) OR (omalizumab [Mesh]) OR (nedocromil [Mesh]) OR (Mesalamine [Mesh]) OR (cetirizine [Mesh]))

Web of Science

Web of Knowledge – Web of Science is managed by Thomson Reuters. It is a multipurpose database and provides additional features like citation reports, impact factors and rankings of the journals in their domain of expertise.

Following types of literature are indexed: scholarly books, peer reviewed journals, original research articles, reviews, editorials, chronologies, abstracts, as well as other items. Disciplines included in this index are agriculture, biological sciences, engineering, medical and life sciences, physical and chemical sciences, anthropology, law, library sciences, architecture, dance, music, film, and theater. Seven citation databases encompasses coverage of the above disciplines.

Following systematic search provides 607 results.

Supplementary Table 3.— **Query box for Web of Science**

((TI=(IBS) OR AB=(IBS)) OR (TI=("Irritable bowel syndrome*") OR AB=("Irritable bowel syndrome*")) OR (TI=("visceral hypersensitiv*") OR AB=("visceral hypersensitiv*"))) AND ((TI=(MC) OR AB=(MC)) OR (TI=("mast cell*") OR AB=("mast cell*")) OR (TI=("mast cell* degranulati* stabilizer*") OR AB=("mast cell* degranulati* stabilizer*")) OR (TI=("mast cell* stabilizer*") OR AB=("mast cell* stabilizer*")) OR (TI=("mast cell* stabiliz* compound*") OR AB=("mast cell* stabiliz* compound*")) OR (TI=(Antihistamin*) OR AB=(Antihistamin*)) OR (TI=("Histamin* Antagonist*") OR AB=("Histamin* Antagonist*")) OR (TI=(ketotifen) OR AB=(ketotifen)) OR (TI=(cromogl*) OR AB=(cromogl*)) OR (TI=(loratadin*) OR AB=(loratadin*)) OR (TI=(desloratadin*) OR AB=(desloratadin*)) OR (TI=(olopatadin*) OR AB=(opolatadin*)) OR (TI=(rupatadin*) OR AB=(rupatadin*)) OR (TI=(mepolizumab) OR AB=(mepolizumab*)) OR (TI=(omalizumab) OR AB=(omalizumab)) OR (TI=(pemirolast) OR AB=(pemirolast)) OR (TI=(nedocromil) OR AB=(nedocromil)) OR (TI=(azelastin*) OR AB=(azelastin*)) OR (TI=(tranilasat) OR AB=(tranilasat)) OR (TI=(palmitoylethanolamide) OR AB=(palmitoylethanolamide)) OR (TI=(GW876008) OR AB=(GW876008)) OR (TI=(DNK333) OR AB=(DNK333)) OR (TI=(FUT*175) OR AB=(FUT*175)) OR (TI=(mesalazin*) OR AB=(mesalazin*)) OR (TI=(acrivastin*) OR AB=(acrivastin*)) OR (TI=(cetirizin*) OR AB=(cetirizin*)) OR (TI=(ebastin*) OR AB=(ebastin*)) OR (TI=(fexofenadin*) OR AB=(fexofenadin*)) OR (TI=(levocetirizin*) OR AB=(levocetirizin*)) OR (TI=(mizalastin*) OR AB=(mizalastin*)) OR (TI=("cromolyn sodium") OR AB=("cromolyn sodium")) OR (TI=("olopatadine hydrochloride") OR AB=("olopatadine hydrochloride")) OR (TI=(Mesalamine) OR AB=(Mesalamine)) OR (TI=(Futhan) OR AB=(futhan)) OR (TI=("nafam*stat mesilate") OR AB=("nafam*stat mesilate")))

Scopus

Scopus is Elsevier's abstract and citation database launched in 2004. Scopus covers articles and peer-reviewed journals in top-level subject fields: life sciences, social sciences, physical sciences and health sciences. It covers three types of sources: book series, journals, and trade journals.

Following systematic search provides 109 results.

Supplementary Table 4. — **Query box for Scopus**

((IBS[Title/Abstract]) OR ("Irritable bowel syndrome*"[Title/Abstract]) OR ("visceral hypersensitiv*"[Title/Abstract])) AND ((MC[Title/Abstract]) OR ("mast cell*"[Title/Abstract]) OR ("mast cell* degranulati* stabilizer*"[Title/Abstract]) OR ("mast cell* stabilizer*"[Title/Abstract]) OR ("mast cell* stabiliz* compound*"[Title/Abstract]) OR (Antihistamin* [Title/Abstract]) OR ("Histamin* Antagonist*" [Title/Abstract]) OR (ketotifen [Title/Abstract]) OR (cromogl* [Title/Abstract]) OR (loratadin* [Title/Abstract]) OR (desloratadin* [Title/Abstract]) OR (olopatadin* [Title/Abstract]) OR (rupatadin* [Title/Abstract]) OR (mepolizumab [Title/Abstract]) OR (omalizumab [Title/Abstract]) OR (pemirolast [Title/Abstract]) OR (nedocromil [Title/Abstract]) OR (azelastin* [Title/Abstract]) OR (tranilasat [Title/Abstract]) OR (palmitoylethanolamide [Title/Abstract]) OR (GW876008 [Title/Abstract]) OR (DNK333 [Title/Abstract]) OR (FUT*175 [Title/Abstract]) OR (mesalazin* [Title/Abstract]) OR (acrivastin* [Title/Abstract]) OR (cetirizin* [Title/Abstract]) OR (ebastin* [Title/Abstract]) OR (fexofenadin* [Title/Abstract]) OR (levocetirizin* [Title/Abstract]) OR (mizalastin* [Title/Abstract]) OR ("cromolyn sodium" [Title/Abstract]) OR ("olopatadine hydrochloride" [Title/Abstract]) OR (Mesalamine [Title/Abstract]) OR (Futhan [Title/Abstract]) OR ("Nafam*stat mesilate" [Title/Abstract]))