INPLASY PROTOCOL

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Corresponding author:
Fei Ding

35371556889@qq.com

Author Affiliation:
Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

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Conflicts of interest:
None declared.

Efficacy and Safety of Secretagogues in Irritable Bowel Syndrome With Constipation and Functional Constipation: a Network Meta-analysis of RCTs in Adult Patients

Ding, F[1]; Meng, Y[2]; Liu, S[3].

Review question / Objective: **1) Population were adult participants who were diagnosed by FC or IBS-C through the Rome criteria. 2) Intervention were secretagogues or prokinetics in different dose. 3) Comparator were placebo or different kinds secretagogues or prokinetics. 4) Outcomes included efficacy outcomes and safety outcomes. efficacy outcome focus on CSBM in IBS-C and FC patients, abdominal pain in IBS-C. safety outcomes focus on adverse effect of any, diarrhear, and drop out.**
Information sources: **Datebase: PubMed, Cochrane Library, Embase, Web of Science, ClinicalTrials.gov Dead line: all up to July 13, 2021 no language and publication period limitation researched the references of included studies to identify eligible researches before the final analyse were doned, we re-run our searches we collected unpublished studies by ClinicalTrials.gov or email consultation.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 December 2021 and was last updated on 08 December 2021 (registration number INPLASY2021120044).

INTRODUCTION

Review question / Objective: **1) Population were adult participants who were diagnosed by FC or IBS-C through the Rome criteria. 2) Intervention were secretagogues or prokinetics in different dose. 3) Comparator were placebo or different kinds secretagogues or prokinetics. 4) Outcomes included efficacy outcomes and safety outcomes. efficacy outcome focus on CSBM in IBS-C and FC**

patients, abdominal pain in IBS-C. safety outcomes focus on adverse effect of any, diarrhear, and drop out.

Condition being studied: Irritable bowel syndrome with constipation (IBS-C): efficacy and safety of secretagogues functional constipation (FC): efficacy and safety of secretagogues.

METHODS

Search strategy: (Secretagogue or Serotonin Agents or Lubiprostone or Prucalopride or TD-5108 or elobixibat or Tenapanor or Tegaserod or Linaclotide or plecanatide or Secretagogue or Secretogogue or Secretagogue or Secretogogues or Agents, Serotonin or Drugs, Serotonergic or Serotonin Drugs or Serotonergic Drugs or Drugs, Serotonin or Serotonergic Agents or Agents, Serotonergic or Serotonin Effect or Effect, Serotonin or Serotoninergic Effect or Effect, Serotoninergic or Serotoninergic Effects or Effects, Serotoninergic or Serotonin Effects or Effects, Serotonin or promotility agent or Prosecretory agent or RU 0211 or 0211, RU or RU0211 or RU-0211 or Amitiza or SPI 0211 or 0211, SPI or SPI0211 or Lubiprostone or ASP-0456 or ASP0456 or Linzess or MD-1100 or Linaclotide Acetate or MD-1100 Acetate or Linaclotide or motegrity or resotran or resotrans or R 093877 or Resolor or R093877 or Prucalopride or TD5108 or velusetrag or A3309 or AZD1722 or RDX5791 or Zelnorm or Zelmac or SDZ HTF 919 or HTF 919 or SDZ HTF-919 or tegaserod maleate or SP-304 or Trulance) and (Constipation or Dyschezia or Colonic Inertia or Irritable Bowel Syndromes or Syndrome, Irritable Bowel or Syndromes, Irritable Bowel or Colon, Irritable or Irritable Colon or Colitis, Mucous or Colitides, Mucous or Mucous Colitides or Mucous Colitis).

Participant or population: Population were adult participants who were diagnosed by FC or IBS-C through the Rome criteria.

Intervention: Intervention were secretagogues or prokinetics in different dose.

Comparator: Comparison were placebo or different kinds secretagogues or prokinetics.

Study designs to be included: Only randomised trials to assess the effect of treatments would be included, while crossover studies, cohort and case–control studies and real-word studies would not.

Eligibility criteria: 1) Population were adult participants who were diagnosed by FC or IBS-C through the Rome criteria. 2) Intervention were secretagogues or prokinetics in different dose. 3) Comparator were placebo or different kinds secretagogues or prokinetics. 4) Outcomes included efficacy outcomes and safety outcomes. efficacy outcome focus on CSBM in IBS-C and FC patients, abdominal pain in IBS-C. safety outcomes focus on adverse effect of any, diarrhear, and drop out.

Information sources: Datebase: PubMed, Cochrane Library, Embase, Web of Science, ClinicalTrials.gov Dead line: all up to July 13, 2021 no language and publication period limitation researched the references of included studies to identify eligible researches before the final analyse were doned, we re-run our searches we collected unpublished studies by ClinicalTrials.gov or email consultation.

Main outcome(s): Mean change from baseline of CSBM frequency in FC or IBS-C patients, a spontaneous bowel movement (SBM) is defined as a stool not induced by rescue medication, and a CSBM means an SBM associated with a sensation of complete evacuation.

Additional outcome(s): 1) +1 CSBM response failure rate: the proportion of FC or IBS-C patients in intention-to-treat(ITT) analysis who failed to have an increase of more than at least one weekly CSBM from baseline; 2) abdominal pain response failure rate: the proportion of IBS-C

patients in ITT analysis who failed to meet pre-set abdominal pain endpoint; 3) combined response failure rate: the proportion of IBS-C patients in ITT analysis who failed to meet pre-set global IBS-C symptom assessment endpoint.

Data management: Two researchers would remove duplicates through EndNote20, and then independently screen the titles and abstracts. Disagreements would be resolved by discussion or judged by the third researcher. Two researchers extract data independently. Two researchers extract items included basic information (author, publication year country and number of sites, diagnostic disease, sample size, age, drug, treatment period) and endpoints information (efficacy outcomes and safety outcomes, specific dose of intervention, baseline CSBM and type of endpoints definition) in Excel. Two researchers would extract binary data including event numbers and total numbers(ITT) and continual data including mean, standard deviation and total number. Missing data would be handled by contacting with study investigators or statistical conversion based on other data.

Quality assessment / Risk of bias analysis: Two researchers would remove duplicates through EndNote20, and then independently screen the titles and abstracts. Disagreements would be resolved by discussion or judged by the third researcher. Two researchers extract data independently. Two researchers extract items included basic information (author, publication year country and number of sites, diagnostic disease, sample size, age, drug, treatment period) and endpoints information (efficacy outcomes and safety outcomes, specific dose of intervention, baseline CSBM and type of endpoints definition) in Excel. Two researchers would extract binary data including event numbers and total numbers(ITT) and continual data including mean, standard deviation and total number. Missing data would be handled by contacting with study investigators or statistical conversion based on other data Revman 5.4 would be used to assess the risk of bias of included studies through the Cochrane Collaboration's tool, including randomisation, treatment allocation, blinding, incomplete outcome data and selective reporting. Disagreements would be resolved by discussion or judged by the third researcher. CINeMA would be applied as our quality evaluation method to assess the confidence of every result, including with-in study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence.

Strategy of data synthesis: Outcomes included efficacy outcomes and safety outcomes. The primary efficacy outcome is change from baseline of CSBM (complete spontaneous bowel movement) frequency in FC and IBS-C patients, while the second efficacy outcomes are +1 CSBM response failure rate in FC and IBS-C patients, abdominal pain response failure rate in IBS-C patients and combined response failure rate in IBS-C patients, as FDA recommended. The primary safety outcome was the proportion of FC or IBS-C patients who had at least 1 treatment-emergent adverse effect (TEAE), while the second safety outcomes are proportion of FC or IBS-C patients who experienced diarrhea adverse effect (AE), and proportion of FC or IBS-C patients who discontinued due to AE. We use the frequentist model to do the network meta-analysis through the command network in stata16 to pool MD (mean difference) for change from baseline of CSBM (complete spontaneous bowel movement) frequency in FC and IBS-C patients, and poor binary data by RR （relaive risk).

Subgroup analysis: we use meta-regression to explore the influence of covariates: baseline of CSBM frequency, proportion of female participants, diagnostic disease, mean ages, treatment period, definition of treatment endpoint baseline of CSBM frequency: in many diseases (e.g., hypertension), the change in continuous data may be related to baseline, but it is rarely explored in constipation relevant meta-analysis, here

we try to explore it proportion of female participants: Constipation mainly occurs in women, and most of the patients enrolled in constipation trials are women, but there are currently no clinical trials exploring differences in efficacy between women and men treatment period: A lot of patients complain that the effectiveness of the drug decreases over time, so we wanted to hace a further exploration definition of treatment endpoint: distictive end points may affect efficacy assessment.

Sensitivity analysis: None.

Language: Chinese.

Country(ies) involved: China.

Keywords: Systematic review; meta-analysis; Secretagogues; CSBM; IBS-C; FC.

Contributions of each author:

Author 1 - Fei Ding.
Email: 3537155689@qq.com
Author 2 - Ying-ying Meng.
Email: 1043512210@qq.com
Author 3 - Shi Liu.
Email: 1455019299@qq.com