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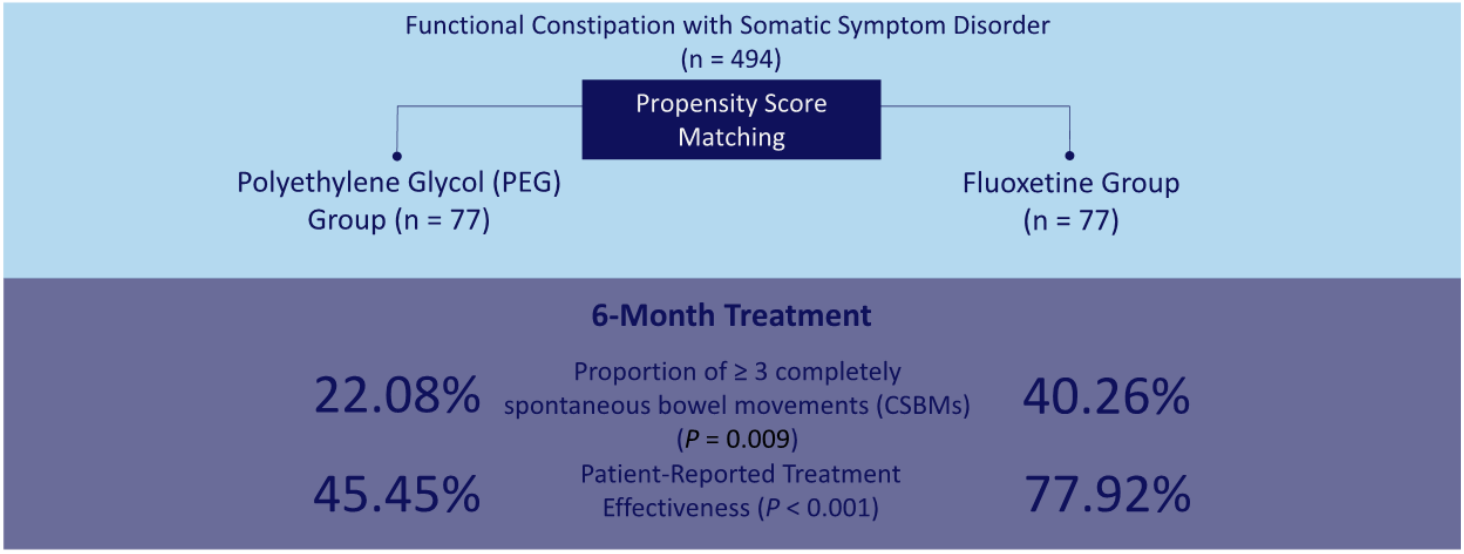

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Fluoxetine in functional constipation with somatic symptom disorder — Efficacy and safety from a propensity score-matched cohort study

Running title: Fluoxetine in Functional Constipation with Somatic Symptom Disorder

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Abstract

Introduction: Functional constipation (FC) is often accompanied by somatic symptom disorder (SSD), especially in refractory conditions. In such patients, constipation manifestations often appear to reflect heightened somatic symptoms rather than bowel dysfunction such as excessive preoccupation to defecation. We Therefore conducted a cohort study to evaluate the efficacy and safety of fluoxetine in patients with FC and comorbid SSD.

Methods: We conducted a cohort study involving 316 FC patients with somatic symptoms. Among them, 161 patients received fluoxetine, while 155 treated with polyethylene glycol (PEG). Using propensity scores, patients were matched into 77 pairs for comparative analysis. The primary outcome was proportion of achieving ≥ 3 completely spontaneous bowel movements (CSBMs) per week at six-month. Secondary outcomes included assessments of bowel symptom, mental Scale, treatment satisfaction. Safety was evaluated by adverse events.

Results: At six months, 40.26% of fluoxetine group achieved primary endpoint compared to 22.08% in PEG group (P = 0.009). Significant improvements were noted in secondary outcomes, including frequency of CSBMs, bowel symptom severity, GAD-9 score, and patient satisfaction. Key factors contributing to treatment effectiveness included baseline GAD-9 scores > 9 (OR=5.01; P < 0.01). Adverse events occurred in 16 cases (9.9%) of the fluoxetine group, with most being mild life-affecting.

Conclusion: Fluoxetine appears to be a safe and effective therapeutic option over a 6-month period for patients with FC and SSD, exerting dual benefits in alleviating both constipation and associated psychological symptoms.

Keywords: Functional constipation. Fluoxetine. Somatic symptom disorder (SSD). Refractory

constipation.

Introduction

Functional constipation (FC) affects approximately 10% of the global population(1). The primary symptoms include infrequent bowel movements, straining, hard stools, a sensation of incomplete evacuation, etc.(2). Current therapeutic options comprise osmotic or stimulant laxatives, prosecretory agents, microbiota, and surgery(3). Nonetheless, almost 50% of patients respond inadequately to these measures, as known as refractory constipation(4). Our prior research indicates that patients with FC who exhibit prominent somatic symptoms experience greater constipation severity and diminished responsiveness to laxative(5), implying that this subgroup might benefit from specific treatment strategies.

Somatic symptom disorder (SSD) is characterized by distressing somatic symptoms accompanied by disproportionate cognitive, emotional, and behavioral responses, persisting for at least six months. Current data suggest that up to 33.8% of patients in tertiary hospital fulfil the diagnostic criteria for SSD, resulting in substantial proportion of cases remaining unrecognized(6). Moreover, somatic symptoms are significant predictors of gastrointestinal discomfort and are associated with reduced quality of life as well as functional impairment(7). In response, the Rome IV guidelines recommend the use of neuromodulators for disorders of gut-brain interactions(8). Accordingly, we aim to evaluate SSD-focused interventions to determine their potential capacity in constipation symptoms.

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been shown to alleviate symptoms of SSD when administered as antidepressant therapy. Notably, no significant therapeutic disparities have been reported among various antidepressants in this setting(9,10). Nevertheless, clinical evidence supporting the use of fluoxetine for FC comorbid with SSD remains limited. We therefore conducted a 6-month prospective study comparing the efficacy and safety of fluoxetine versus polyethylene glycol (PEG) in patients with refractory FC and comorbid SSD.

Methods

Study design

This prospective cohort study involved FC patients from Xijing Digestive Hospital, extended from

January 2020 to June 2024. Totally 316 patients were enrolled. FC was diagnosed according to the Rome IV criteria. Approval for the study was granted by the Medical Ethics Committee of the First Affiliated Hospital of the Air Force Military Medical University with the registration number XJLL-KY20222069.

Participants

All patients underwent semi-structured clinical interviews based on diagnostic criteria from DSM-5(6). The diagnostic criteria are as follows: A. One or more physical symptoms that are painful and/or cause significant disruption to daily life. B. Excessive thoughts, feelings, or behaviors related to physical symptoms or related health issues, manifested as at least one of the following: 1) excessive and persistent thoughts about the severity of symptoms, 2) persistent high anxiety about health or symptoms, and 3) excessive time and energy invested in these symptoms or health issues. C. Although any symptom may not persist, the state of symptoms is persistent (usually>6 months). SSD diagnosis required meeting A, at least one sub-criterion under B, and C. Interviews were conducted by professionals trained in DSM-5 classification, with all research assistants completing standardized training.

The inclusion criteria for the study are as follows: 1) individuals aged 18 to 70 years; 2) patients meeting Rome IV diagnostic criteria for FC, defined by at least two symptoms with at least six months: straining, lumpy or hard stools (Bristol Stool Scale types 1-2), incomplete evacuation, anorectal obstruction, need for manual maneuvers, or spontaneous bowel movements occurring less than three times per week; 3) refractory constipation, defined as the use of at least three medications for more than three months, with unsatisfactory outcomes; 4) patient meets the diagnostic criteria for SSD above; 5) patients who voluntarily provided informed consent prior to enrollment.

Exclusion criteria included: 1) women who are pregnant or lactating; 2) presence of cardiovascular conditions, organ dysfunction, immune disorders, or infections; 3) concurrent gastrointestinal organic conditions such as tuberculosis, polyps, Crohn's disease, tumors, etc.; 4) prior abdominal surgeries; 5) use of psychotropic medications; 6) diagnosis of hypothyroidism or Parkinson's disease.

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Intervention

Patients in fluoxetine group received fluoxetine orally with an initial dose of 20 mg/day. For patients not fully alleviated, dosage could be increased up to 60 mg/day. For patients who were unable to have a bowel movement for three consecutive days, or experiencing intolerable symptoms, PEG was available as rescue medication. Bowel movements occurring within 24 hours after the use of rescue medication were not counted as CSBM. In cases where patients experienced mild adverse effects such as dizziness, nausea, or tremors, the dosage was reduced. If there was no improvement even after dosage escalation, or serious adverse reactions occurred, the medication was discontinued. The control group took PEG (10g/day) as the main treatment strategy.

Data collection

Various data was collected including demographic information, CSBM, SBM, feelings of incomplete evacuation, bloating, defecation time, BSFS, disease duration, Patient Health Questionnaire-9 (PHQ-9) for depression, Patient Health Questionnaire-15 (PHQ-15) for somatic symptoms, Generalized Anxiety Disorder-7 (GAD-7) for anxiety, Kessner Constipation Scoring System (KESS), Patient Assessment of Constipation Quality of Life (PAC-QOL), Bristol Stool Form Scale (BSFS), etc. Treatment effectiveness was assessed using the question "Over the past week, have you experienced adequate relief from your constipation symptoms?" with responses of 'yes' or 'no'(11).

Outcome

The primary endpoint was the proportion of participants achieving ≥3 CSBMs per week to the end of 6-month. Secondary outcomes included the change from baseline in mean CSBMs per week, mean score for straining during defecation, PAC-QOL, KESS, PHQ-9, PHQ-15, GAD-7, BSFS (3-5), and effective rate collected at the initiation of treatment and 1, 3, and 6 months afterwards. The outcomes were primarily monitored via telephone follow-ups.

Safety assessments

Safety assessments were conducted at each visit, employing non-leading questions to elicit or

identify treatment-emergent adverse events (AEs) and serious adverse events (SAEs) and their relationship to the study treatment. The main AEs associated with fluoxetine included headache, nausea, diarrhea, dry mouth, decreased appetite, fatigue or drowsiness. Additional safety assessments encompassed physical examinations, vital signs measurements, and standard clinical laboratory tests.

Statistical analysis

Statistical analyses were generated using R (version 4.4.1). Continuous variables were presented as means±standard deviation (SD), while categorical variables are described in frequency and percentage. The χ^2 test or Fisher's exact test was employed for comparing categorical variables across subgroups. For comparisons of continuous variables, we utilized Student's *t*-test, Mann-Whitney *U* test, or one-way ANOVA, as appropriate. A $P<0.05$ was seen as statistical significance. Propensity score matching (PSM) was employed to minimize confounding and ensure comparability between groups. Multivariate logistic regression was used to identify independent risk factors associated with effectiveness of fluoxetine treatment. In managing missing data within this cohort study, consideration was given to the potential exclusion of incomplete datasets. Missing data due to loss to follow-up were handled using multiple imputation under the missing at random (MAR) assumption.

Results

Baseline characteristics

The cohort comprised 494 patients with FC and comorbid SSD (Fig. 1). Of these, 316 (72%) met eligibility criteria: 155 received PEG, and 161 received fluoxetine. Before matching, the fluoxetine group demonstrated a higher rates of >3 SBMs/week (58.8% vs. 32.9%, $P=0.001$), incomplete evacuation (29% vs. 14.8%, $P=0.02$) versus PEG. PAC-QOL scores were also higher with fluoxetine (62.6±22.5 vs. 52.9±21.9, $P=0.001$). Conversely, PEG had more BSFS type 1-2 stools (37.3% vs. 24.8%, $P=0.001$). After 1:1 PSM (77 matched pairs), baseline characteristics showed no significant differences ($P>0.05$, Table 2).

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Outcomes

Fluoxetine demonstrated significantly higher response rates for the primary endpoint (≥3 CSBMs/week: 40.26% [31/77] vs. 22.08% [17/77], *P*=0.009; Table 2) and superior efficacy across most secondary outcomes. Key stool parameters (mean change/week: CSBMs 1.93±1.79 vs. 1.02±1.46, SBMs 2.28±1.52 vs. 1.16±1.76, both *P*<0.001; endpoint CSBMs 2.97±1.83 vs. 2.02±1.67, *P*<0.001) and stool consistency (68.83% [53/77] vs. 42.86% [33/77], *P*<0.001) significantly improved versus PEG. Straining scores showed greater reduction (-1.68±1.23 vs. -1.22±1.51, *P*=0.038) and lower endpoint values (1.63±1.29 vs. 2.30±1.34, *P*=0.002). The overall response rate was higher with fluoxetine (67.53% [52/77] vs. 32.47% [25/77], *P*<0.001). Psychological outcomes revealed greater improvement with fluoxetine in KESS (-8.28±5.89 vs. -5.05±5.95, *P*<0.001) and GAD-7 scores (-5.17±6.02 vs. -2.50±4.96, *P*=0.035), while no intergroup differences were observed for PAC-QOL, PHQ-9 (both *P*=0.522), or PHQ-15 changes (*P*=0.812).

Comparative analysis over time

The CSBMs for fluoxetine and PEG groups were as follows (Fig. 2): At month 0, fluoxetine was 1.04±0.82 and PEG 1.00±0.75. By month 1, fluoxetine increased to 1.44±0.68, while PEG reached 1.22±0.92. At month 3, fluoxetine recorded 1.71±0.90, and PEG was 1.41±1.20. By month 6, the mean frequency of CSBMs in the fluoxetine group had increased significantly to 2.97 ± 1.83, surpassing that of the PEG group (2.02 ± 1.67), with fluoxetine showing greater improvements over time(*P*<0.05).

The effective rates for PEG and fluoxetine were assessed at months 0, 1, 3, and 6 (Fig. 2). Both groups started at 0%, with month 1 showing 33.1% for PEG and 32.7% for fluoxetine. By month 3, PEG increased to 37.9%, and fluoxetine to 57.0% (*P*<0.05). At month 6, PEG reached 45.3%, while fluoxetine increased to 77.9%. Significant differences were noted between groups (*P*<0.05), with fluoxetine showing progressive improvement over time.

Logistic analysis of fluoxetine therapeutic effectiveness

In a multivariate analysis of all patients treated with fluoxetine (n=161), factors associated with the efficacy of fluoxetine treatment were included in a logistic regression model. A GAD-7 ≥ 9 (OR 5.01;

95% CI, 1.44-17.50; *P*<0.01), a PHQ-9 ≥ 9 (OR 0.31; 95% CI, 0.09-1.01; *P*<0.05) emerged as significant predictors of fluoxetine treatment efficacy (Table 3).

Adverse events

Adverse events were reported in 17 recipients of PEG (10.9%) and 16 of fluoxetine (9.9%). Treatment was discontinued owing to severe events in three PEG and four fluoxetine patients (symptoms resolved post-cessation). Predominant events were nausea/diarrhea in PEG and sleep disturbances/headaches in fluoxetine. No deaths or significant intergroup differences in adverse events occurred (Table 4).

Discussion

This prospective study assessed the efficacy and safety of fluoxetine in patients with refractory FC comorbid SSD. Of the 316 eligible participants, PSM generated 77 patients in both fluoxetine and PEG groups. At six months, 40.26% of fluoxetine group achieved primary endpoint of ≥3 CSBMs/week, compared with 22.08% in PEG group (*P* = 0.009). The overall response rate was 77.9% with fluoxetine versus 45.3% with PEG. Fluoxetine also produced greater improvements in secondary outcomes, including SBMs, stool consistency, defecation time, and anxiety. Multivariate regression analysis identified PHQ-9 and GAD-7 scores as independent predictors of treatment efficacy. AE occurred in 9.9% of fluoxetine group and 10.9% of PEG group (*P* > 0.05). These findings indicates that fluoxetine is a safe and effective option for patients with FC and SSD.

In our previous cohort, 36.7% patients exhibited refractory to standard therapies(5), consistent with prior investigations(4). Refractory constipation is typically defined as a lack of response to standard interventions, including lifestyle modification, dietary fiber, osmotic laxatives (PEG), stimulant laxatives (bisacodyl), prokinetic agents (prucalopride), and biofeedback therapy(12–14). Recent research has increasingly focused on neuromodulation-based therapies, including electroacupuncture(14), sacral nerve stimulation(15) and vibrating capsules(12).

Although the mechanism remain poorly characterized, FC is closely associated with psychosocial factors, parental influences, and early-life stressful events, suggesting potential new intervention targets(16,17). Our previous study showed that the incidences of depression, anxiety, and somatic

symptoms in FC were 58.8%, 56.8%, and 78.3%, respectively(5). In refractory constipation, these proportions were higher: anxiety (80.2%), depression (72.8%), and somatic symptoms (86.3%). Similar rates of anxiety (21.3%) and depression (30.3%) have been reported in FC(18). Additionally, individuals with psychological disorders are more likely to report gastrointestinal dysfunctions, with constipation rates ranging from 20% to 37%(19). In this study, FC patients exhibited pretreatment scores on the GAD-7 (9.37 ± 6.62), PHQ-9 (9.32 ± 4.52), and PHQ-15 (8.56 ± 5.91), all significantly higher than population norms.

Based on DSM-5, several features render the FC patients in our cohort closer to SSD as a psychiatric disorder rather than a gastrointestinal dysfunction, including defecatory discomfort, excessive preoccupation with defecation, lack of response to laxatives, and repeated medical consultations with insufficient outcomes(6). Similarly, somatic cough syndrome has supplanted psychogenic cough(20). Our prior study indicated that 44.4% of FC patients had comorbid somatic symptoms(5), which is comparable to the prevalence of SSD among Chinese outpatients (40.2%)(6). Additionally, FC accompanied by somatic symptoms was associated with more severe clinical manifestations and poorer treatment responses, suggesting a heterogeneous subgroup.

Fluoxetine, an SSRI, has been proposed as a therapeutic option for SSD due to its modulation of serotonin (5-HT) signaling(9,21–23). Therefore, the primary outcome of this study was the proportion of achieving ≥3 CSBMs per week at six months, which better reflected excessive preoccupation with defecation, a feature of SSD. CSBM has also been widely used in studies on refractory constipation(12,14). At six months, 40.26% of fluoxetine group achieved primary endpoint compared to 22.08% in PEG group (P=0.009). Regression analysis indicated that fluoxetine response was independently associated with anxiety, which is more closely related to SSD. Because SSRIs have a relatively delayed onset of action, larger clinical trials of at least 12 weeks' duration are generally recommended(24). Consistent with this, our study showed that although patients reported subjective improvement at 12 weeks, the increase in CSBMs frequency was not yet significant; the most pronounced benefits emerged only after 24 weeks.

While fluoxetine has mixed results in irritable bowel syndrome with constipation (IBS-C), its application in FC comorbid SSD may reflect a different pathophysiologic pathway and therapeutic rationale. IBS-C, a prototypical disorder of brain-gut interaction, is characterised by visceral hypersensitivity and abdominal pain(25). One randomized controlled trial showed that fluoxetine

significantly outperformed placebo in relieving abdominal pain and bloating and in increasing stool frequency in patients with IBS-C(26); however, subsequent investigations produced conflicting findings(8,27–30). Accordingly, the 2022 American Gastroenterological Association (AGA) guideline conditionally recommends against SSRIs because of their limited ability to reduce abdominal pain and visceral sensitivity(31). Although emerging evidence suggests that FC and IBS-C may represent different stages of the same disease spectrum(32,33), FC patients with comorbid SSD constitute a heterogeneous subgroup whose clinical profile is more closely aligned with psychiatric disorders. Consistent with this perspective, the present study demonstrated that fluoxetine significantly improved SSD-related outcomes, including CSBM frequency, in patients with FC.

This study introduced a novel therapeutic perspective: the use of fluoxetine in a specific subgroup of FC patients characterized by comorbid SSD. Being frequently marked by refractory constipation, these patients are currently advised for colectomy with controversial effectiveness(34). In the present study, fluoxetine was effective in 77.9% of FC patients with SSD, compared with 45.5% in PEG group, a first-line laxative that softens stools to increase bowel movement(35). These findings suggested that, in the management of FC, patients with comorbid SSD may derive benefit from fluoxetine, potentially avoiding surgery and reducing symptom burden.

This study has several limitations. First, as a single-center study, the proportion of refractory constipation may exhibit selection bias. Second, condition constraints limited the fully structured interviews and SSD assessments during follow-up. thirdly, the pathogenesis of FC with SSD remains incompletely understood. Finally, as a cohort study, this study lack of blinding may introduce reporting bias. We minimized selection bias through prospective design (n=316) and PSM, with cross-validation using quantitative indicators such as CSBM, PHQ-9, GAD-7, and PAC-QOL. We also plan to conduct RCT studies in the future to further validate our findings.

Conclusions

Fluoxetine, a safe and effective SSRI, can significantly increase CSBM frequency in patients with refractory FC and comorbid SSD, providing dual benefits by relieving constipation and concomitant psychological symptoms.

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Abbreviations

Adverse event, AE; American Gastroenterological Association, AGA; Bristol Stool Form Scale, BSFS; Complete spontaneous bowel movement, CSBM; Functional constipation, FC; Functional gastrointestinal disorders, FGID; Functional magnetic resonance imaging, fMRI; Generalized Anxiety Disorder-7, GAD-7; IBS with constipation, IBS-C; Irritable bowel syndrome, IBS; Knowles-Eccersley-Scott Symptom, KESS; Patient Assessment of Constipation Quality of Life, PAC-QOL; Patient Health Questionnaire-15, PHQ-15; Patient Health Questionnaire-9, PHQ-9; Polyethylene glycol, PEG; Propensity score matching, PSM; Somatic symptom disorder, SSD; Selective serotonin reuptake inhibitor, SSRI; Serious adverse event, SAE; Spontaneous bowel movements, SBM; Standard deviation, SD; Tricyclic antidepressant, TCA; γ-aminobutyric acid, GABA.

Declaration

Ethics approval and consent to participate

Approval for the study was granted by the Medical Ethics Committee of the First Affiliated Hospital of the Air Force Military Medical University, with the registration number XJLL-KY20222069. Permissions for using the questionnaires and clinical data were conducted with informed consent from all participants. All patient data were kept strictly confidential, in accordance with the ethical guidelines of the Helsinki Declaration.

Consent for publication

Not Applicable

Availability of data and material

The datasets generated and analyzed during the current study are not publicly available as the data are being used in next study but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The funding body had no role in the design of the study and collection, analysis, interpretation of data or preparation of the manuscript.

Authors' contributions

BY and ZZ were involved in designing the study and drafting the manuscript. XF and XJ participated in the data collection and follow-up. QH contributed to the manuscript's development and the analysis of data. XL assisted in drafting and revising the manuscript. WF is responsible for all psychological assessments and reviews. QZ participated in the study design and provided final approval for the version to be published. All authors have agreed to be accountable for all aspects of the manuscript, ensuring accuracy and integrity.

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Figures & Tables

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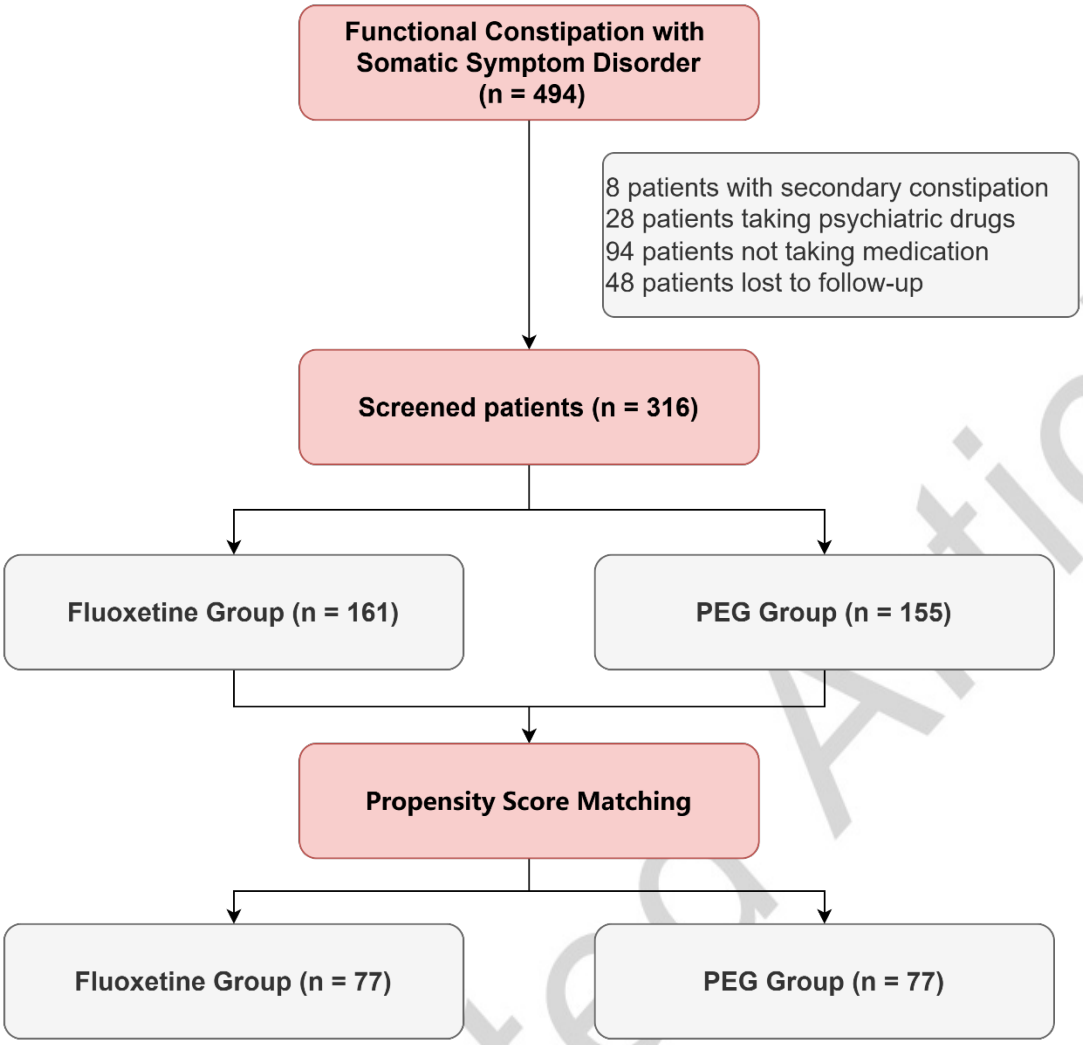

Fig. 1 Study Flowchart.

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Table 1 Baseline characteristics between fluoxetine and PEG groups before and after propensity score matching

	before matching			**after matching**		
Characteristic	PEG (n=155)	Fluoxetine (n=161)	*P* value	PEG (n=77)	Fluoxetine (n=77)	*P* value
Gender, female (%)	105 (67.4)	121 (75.2)	0.144	52 (67.5)	53 (68.8)	0.863
Time since onset (%)			0.424			0.813
0-18 months	33 (21.3)	43 (26.7)		17 (21.3)	17 (26.7)	
18 months - 5 years	30 (19.4)	37 (23.0)		18 (19.4)	19 (23.0)	
5-10 years	47 (30.3)	45 (28.0)		16 (20.8)	21 (27.3)	
More than 10 years	45 (29.1)	36 (22.3)		26 (33.8)	20 (26.6)	
CSBM/week	1.39 ± 1.32	1.49 ± 1.24	0.457	0.99 ± 0.75	1.04 ± 0.82	0.732
SBM/week	2.66 ± 1.73	3.57 ± 1.95	< 0.05*	2.42 ± 0.99	2.46 ± 1.04	0.813
SBM >3 times/week (%)	51 (32.9)	94 (58.8)	0.001*	32 (41.6)	36 (46.8)	0.786
Always failed defecation (%)	25 (17.6)	30 (20.7)	0.670	20 (26.0)	16 (20.8)	0.715
Always incomplete evacuation (%)	21 (14.8)	42 (29.0)	0.020	21 (27.3)	19 (24.7)	0.866

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Straining during defecation (%)	66 (46.5)	77 (48.3)	0.520	44 (57.1)	36 (46.8)	0.447
Stool consistency abnormal (%)	53 (37.3)	36 (24.8)	< 0.001*	21 (27.3)	24 (31.2)	0.776
KESS (mean ± SD)	18.38 ± 5.28	18.78 ± 5.16	0.509	19.10 ± 5.76	18.70 ± 5.28	0.720
PAC-QOL (mean ± SD)	52.9 ± 21.9	62.6 ± 22.5	< 0.001*	57.71 ± 23.3	56.57 ± 23.9	0.760

Table 2 Constipation-related primary and secondary outcome after 6 months treatment

	PEG (n=77)	**Fluoxetine (n=77)**	***P* value**
Change from baseline in mean CSBMs per week	1.02 ± 1.46	1.93 ± 1.79	<0.001*
Participants with ≥3 CSBMs per week, n (%)	17 (22.08)	31 (40.26)	0.009*
Change in mean SBMs per week	1.16 ± 1.76	2.28 ± 1.52	<0.001*
Change in mean score for straining	-1.22 ± 1.51	-1.68 ± 1.23	0.038*
Change in PAC-QOL score	-3.94 ± 6.21	-2.96 ± 7.12	0.522
Change in KESS score	-5.05 ± 5.95	-8.28 ± 5.89	<0.001*
Change in PHQ-9 score	-3.94 ± 6.21	-2.96 ± 7.12	0.522
Change in PHQ-15 score	-3.41 ± 4.46	-3.12 ± 6.04	0.812
Change in GAD-7 score	-2.50 ± 4.96	-5.17 ± 6.02	0.035*
Effective rate, n (%)	35 (45.45)	60 (77.92)	<0.001*
Mean SBMs/week	3.57 ± 2.03	4.73 ± 1.60	<0.001*
Mean CSBMs/week	2.02 ± 1.67	2.97 ± 1.83	<0.001*
Stool consistency (BSFS=3-5)	33(42.86)	53 (68.83)	< 0.001*

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Straining score	2.30 ± 1.34	1.63 ± 1.29	0.002*

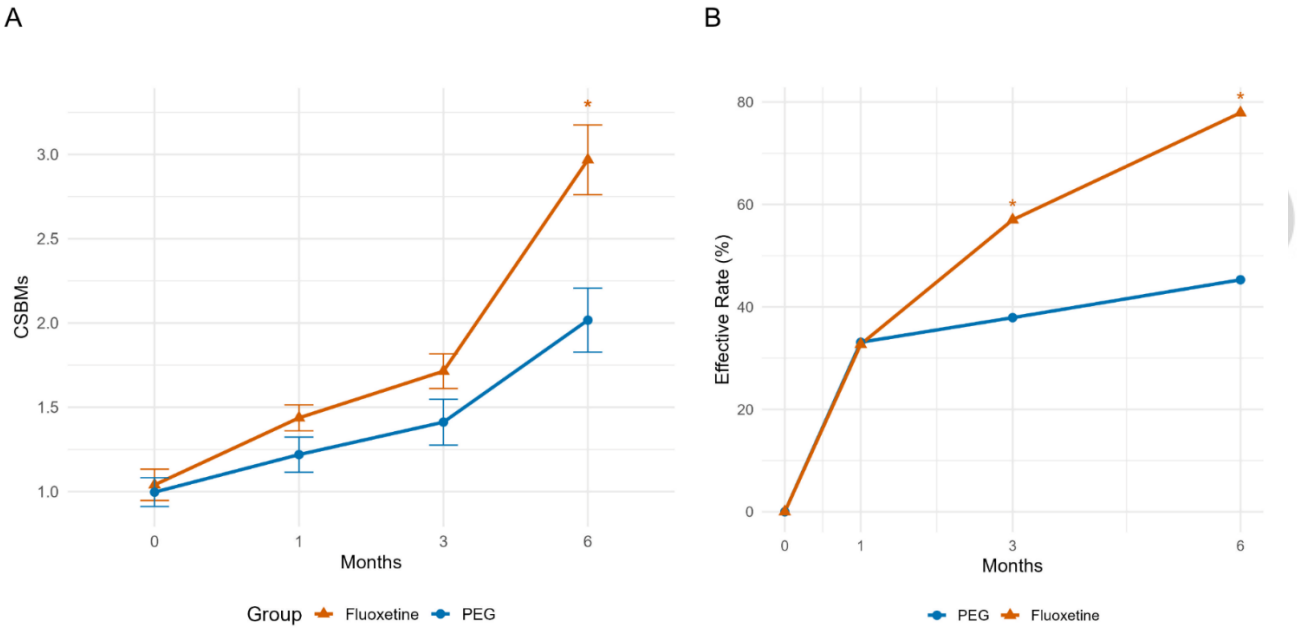

Fig. 2 Comparative changes of complete spontaneous bowel movements (CSBMs, A) and effective rate (%, B) per week between PEG and fluoxetine groups over 6-month period

Table 3 Logistic regression model to identify factors independently associated with effective of fluoxetine treatment

Variables	**OR (95% CI)**	***P* value**
Gender	0.51 (0.16-1.63)	0.25
Age	1.00 (0.97-1.04)	0.89
Onset of Symptoms	1.11 (0.744-1.67)	0.60
Bowel Movement Frequency	0.96 (0.49-1.87)	0.91
Incomplete Evacuation	0.67 (0.32-1.40)	0.29
Time Spent on Defecation	0.86 (0.47-1.59)	0.63
Straining During Defecation	0.98 (0.50-1.92)	0.60

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Bristol Stool Form Scale	1.29 (0.97-2.09)	0.31
PHQ-9	0.31 (0.09-1.01)	<0.05*
PHQ-15	1.09 (0.42-2.85)	0.86
GAD-7	5.01 (1.44-17.50)	<0.01*
KESS	1.02 (0.81-1.89)	0.88
PAC-QOL	1.01 (0.99-1.05)	0.24

Table 4 Adverse events (AE) leading to discontinuation (safety population)

Adverse event	**PEG (n=155)**	**Fluoxetine (n=161)**
Patients with at least 1 AE	17 (10.9%)	16 (9.9%)
Patients with at least 1 AE leading to discontinuation	3 (1.9%)	4 (2.5%)
Mild or moderate adverse events		
Nausea	4	3
Diarrhea	3	1
Abdominal distension	2	0
Flatulence	3	1
Sleep disorder	0	4
Headache	2	3