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Flupentixol/melitracen for epigastric pain syndrome in female patients with abnormal urinalysis and therapeutic insights into the brain–bladder axis

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The pathogenesis of abnormal urinalysis in female epigastric pain syndrome (EPS) is unclear. This study aimed to observe the effect of flupentixol/melitracen (FM) acting in central nervous system on urinalysis in female EPS. It is confirmed that abnormal urinalysis indicators may be related to somatization caused by abnormal brain-bladder axis. A total of 125 female patients with EPS were randomly assigned to the test and control groups. Patients in the control group ($n = 62$) received omeprazole for 4 weeks. On this basis, cases in the test group ($n = 63$) received FM. The changes of dyspepsia symptoms, somatization symptoms and urinalysis were observed at 0 and 4 weeks. In this clinical trial, the score of DSS, somatization symptoms and urinary inflammatory indicators could improve after received FM in female EPS patients with abnormal urinalysis indicators. These results suggest that the brain-bladder axis might contribute to the pathogenesis of EPS, combined with effective anti-somatization or anti-depression treatment is necessary in some female EPS patients with abnormal urinalysis. Further studies are needed to confirm about brain-gut-bladder axis in EPS pathogenesis. Clinical Trials.gov (number: ChiCTR2400079677).

Keywords Epigastric pain syndrome, Flupentixol/melitracen, The somatization symptoms, Urinalysis

Abbreviations

FD	Functional dyspepsia
EPS	Epigastric pain syndrome
PDS	Postprandial discomfort syndrome
QoL	Quality of life
DGBI	Brain-gut interaction disorder
DSS	Dyspepsia Symptoms Severity
PPIs	Proton pump inhibitor
SSRIs	Selective serotonin reuptake inhibitors
SNRIs	Serotonin noradrenalin reuptake inhibitors
FM	Flupentixol/melitracen
SF-NDI	The 10-item short form of the Nepean Dyspepsia Index
PSS-4	The 4-item Perceived Stress Scale
GAD-7	Generalized Anxiety Disorders-7
PHQ-8	Patient Healthy Questionnaire-8
PHQ-9	Patient Healthy Questionnaire-9
TCA	Tricyclic antidepressant
NE	Norepinephrine
5-HT	5-Hydroxytryptamine

Functional dyspepsia (FD) is one of the most common diseases of the upper digestive tract, it refers to a group of clinical syndromes with dyspepsia symptoms lasting for 6 months and without organic diseases. According to

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the Rome IV standard, FD is divided into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). These subgroups were established by the predominance of meal-related symptoms. PDS is manifested as postprandial fullness discomfort and early satiety while EPS is manifested as epigastric pain or burning sensation[1]. The global prevalence of FD is 10–30%, but there are differences in regional prevalence[2]. With the growth of the economy, changes in diet and lifestyle, the incidence of FD is increasing year by year, affecting the quality of life (QoL) of patients.

FD is a disease of gut-brain interaction disorder (DGBI). Its pathophysiology is multifactorial and closely related to psychological factors such as anxiety, depression, mental health, somatization and sleep disorders[3]. In the development of FD, the influence of mental disorders such as anxiety and depression has always been the focus of attention. Some studies have shown that somatization plays a key role in FD[4,5]. The reduction of abdominal pain symptoms in FGID patients did not directly improve the patient 's treatment satisfaction[6] while somatization symptoms can be used as an indicator of the QoL of FGID patients[7].

FD patients often have a series of digestive symptoms that cannot be explained by biochemical and structural abnormalities, such as dizziness, back pain, sleep disorders, and fatigue[7]. These symptoms are clinically called somatization symptoms[8,9]. Somatization is defined as a chronic mental disorder characterized by one or more frequently changing somatic symptoms involving multiple systems and organs of the body[10]. Somatization symptoms in FD patients often cause wrong understanding or excessive attention, which brings a greater economic burden to the society[11] and affects the severity and QoL of FD patients with dyspepsia[4,12]. In FD patients, somatization plays a more significant role in the severity of dyspepsia symptoms (DSS) than gastric sensitivity, anxiety and depression[5]. A 5-year follow-up study showed that somatization was an independent risk factor for impaired QoL in FD patients, while proximal gastric regulation, gastric emptying and Helicobacter pylori infection were not found as risk factors[4].

In addition, somatization can coexist with other emotional disorders, such as anxiety and depression[13]. The severity of gastrointestinal symptoms in FD patients may be partly attributed to health-related QoL and related psychological factors, which are even more important than gastrointestinal symptoms. Psychological factors interact with gastrointestinal symptoms and form a vicious circle. If insufficient attention is paid, the symptoms of the disease will be aggravated and more medical resources will be consumed[14].

Current treatments for FD include proton pump inhibitors (PPIs) prokinetics, eradication of Helicobacter pylori, and central neuromodulators[15]. These drugs can relieve the symptoms of some patients, while the symptoms of a considerable number of FD patients for several months did not achieve satisfactory results[16,17]. FD patients generally have emotional disorders such as somatization[18] and the effect of conventional drugs such as PPIs is not good, the addition of anti-anxiety and depression drugs may improve the symptoms of FD patients and improve the QoL[19]. Although some psychotropic drugs can effectively improve the gastrointestinal and somatization symptoms of FD patients, Meta-analysis showed that selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenalin reuptake inhibitors (SNRIs) and other drugs were ineffective in the treatment of FD, while FM was effective for EPS[20,21]. Therefore, it is necessary to conduct in-depth research on the somatization of FD patients, but the explanation for the symptoms of somatization is insufficient, and further research is needed.

The research team clinically observed that some FD female patients had abnormal urinalysis inflammatory indicators, which may be related to somatization. After Flupentixol/melitracen (FM) treatment, the urinalysis improved, and the abnormal urinalysis of male patients was rare. Hojo et al.[22] found that psychoactive drugs with both anti-anxiety and antidepressant effects can effectively alleviate EPS symptoms and somatization symptoms, while drugs with antidepressant effects alone are less effective. FM is a fixed combination of tricyclic antidepressant melitracen 10 mg and classical antipsychotic component flupentixol 0.5 mg, which can effectively improve the clinical symptoms and QoL of patients with refractory FD[19]. FM not only has anti-anxiety, anti-depression and activation effects at low doses, but also can effectively improve mental perception abnormalities due to the low doses of these two drugs and less side effects[23]. After FM treatment, the patient 's mental state was improved, gastrointestinal autonomic nerve dysfunction was regulated, and visceral hypersensitivity was reduced.

At present, there is no research on the correlation between somatization symptoms and urinalysis. Patients with functional bladder disease may have abnormal urinalysis, often accompanied by emotional disorders such as depression and anxiety. Emotional disorders may change the activity of the efferent or autonomic nervous system that regulates the gut itself and its microbial flora, and may eventually lead to the destruction of the dynamic balance in the bladder[24]. Such brain-bladder axis interactions may affect the permeability, inflammation, infectious etiology, and biological disorders of bladder disease[25]. Thus, investigating the association between urinalysis and brain-bladder axis-mediated somatization might enhance FD treatment strategies.

At present, the research for FD focused on gastrointestinal motility and gastrointestinal mucosal immunity[15]. The significance of abnormal urinalysis in FD female patients has not been studied in previous literature. Meta-analysis suggested that FM treatment was only effective for EPS, so we only selected EPS for study[20,21]. This study investigated the relationship between urinary occult blood, urinary leukocyte esterase, urinary leukocytes, urinary erythrocytes and somatization. In addition, the study explored the effects of DSS, anxiety, depression and QoL in female EPS patients.

Methods

Study population

This study initially screened 800 patients with epigastric pain syndrome (EPS) from the Department of Gastroenterology at the Affiliated Hospital of North Sichuan Medical College between May 2023 and February 2024. A total of 125 patients with EPS who had abnormal urinalysis and met the inclusion and exclusion criteria were selected. Eligible participants were randomly assigned in a 1:1 ratio using computer-generated

randomization, with 63 cases allocated to the test group and 62 to the control group. Patients in the test group received a combination of FM (1table once a day) and omeprazole (20 mg twice a day), while those in the control group received omeprazole alone. The treatment duration was 4 weeks for both groups. In the preliminary research, the sample size was calculated by the following formula: $n = (Z_{\alpha/2} + Z_{\beta})^2 \times [p_1 (1\text{-}p_1) + p_2 (1\text{-}p_2)]/(p_1\text{-}p_2)^2$. We found that 60% of female EPS patients with abnormal urinalysis improve with FM + PPIs, compared to 30% in patients with PPIs. The sample size was 57 patients per group calculated with a β error of 0.2 and an α error of 0.05. Assuming the loss rate of follow-up was 10%, 125 female EPS patients with abnormal urinalysis were selected.

Inclusion criteria: (1) Meeting the Rome IV criteria[26,27] : having one or more symptoms of epigastric pain, epigastric burning sensation, postprandial fullness, and early satiety, and there is no evidence of organic diseases that can explain the above symptoms; the above symptoms existed for at least 6 months, and at least two drugs were ineffective for 4 weeks[19,28] such as PPIs and eradication of Helicobacter pylor; (2) Laboratory examination (including blood routine, biochemistry, thyroid function, etc.), abdominal color Doppler ultrasound and gastroscopy were normal; (3) No sedative-hypnotics, antidepressants or anti-anxiety drugs have been used in the past 6 months; (4) Age ≥ 18 years old, education level of primary school and above, can use WeChat and other Internet tools and have certain reading comprehension and cognitive ability; (5) When collecting urine, avoid collecting urine during the menstrual period, correctly standardize the collection of midstream urine, and collect urine samples into sterile containers for timely inspection.

Exclusion criteria: (1) Organic (such as esophagitis, peptic ulcer), systemic, metabolic (such as hyperthyroidism, diabetes) and malignant tumors (esophageal cancer, gastric cancer) were found; (2) Patients without eradication of Helicobacter pylori or who use antibiotics before their first urine test; (3) Patients with a history of abdominal surgery; (4) History of allergic reactions to any drug used in the study; (5) Known mood disorders, or use of anti-anxiety drugs or antidepressants in the past 6 months; (6) Recent urinary tract infection or kidney disease; (7) Pregnant and lactating women; (8) Difficulty in completing follow-up or various factors affecting compliance.

Exit criteria: Patients did not cooperate for various reasons until the end of the follow-up period.

Data collection

The general data of the patients were collected, partial urinalysis data were collected, and the scores of Dyspepsia Symptoms Severity (DSS)[4] the 10-item short form of the Nepean Dyspepsia Index (SF-NDI)[29,30] Generalized Anxiety Disorders-7 (GAD-7)[31] Patient Healthy Questionnaire-8 (PHQ-8)[32] Patient Healthy Questionnaire-9 (PHQ-9)[33–35] before and after treatment were collected.

Outcome measurements

DSS

DSS was used to evaluate the severity of 8 dyspepsia symptoms in FD patients in the past 2 weeks, including epigastric pain, epigastric burning sensation, postprandial fullness, early satiety, abdominal distension, nausea, vomiting, and belching[4]. The specific scores of each item are as follows: 0 indicates no symptom, 1 is slight attention to symptoms, 2 is conscious symptoms, but does not affect life and work, 3 significantly affects life and work, and the total score is 0–24 points. The higher the score, the more severe the dyspepsia symptoms.

SF-NDI

The scale for evaluating the impact of disease on the QoL of FD patients in the past two weeks[29,30] is divided into five subscales. The impact of disease on the QoL of FD patients is measured from five aspects: tension/anxiety, interference with daily activities, eating/drinking water, cognition/control, and work/learning. The score of each subscale is in the range of 2–10 points. Each subscale has 2 items, a total of 10 items. The score of each item is 0–5 points, and the total score is 0–50 points. The higher the total score, the greater the impact of the disease on the QoL of patients.

GAD-7

GAD-7 is a self-rating scale developed according to the 7-item criteria of the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)[31]. It is used to investigate the number of days in which patients have been troubled by each item in the past 2 weeks. It includes 7 items, each item has a score of 0–3 points, and the total score is 0–21 points. It can be divided into no anxiety (0–4 points), mild anxiety (5–9 points), moderate anxiety (10–14 points), and severe anxiety (15–21 points). Patients with a total score of ≥ 10 points considered to have anxiety.

PHQ-8

PHQ-8 was used to assess the severity of somatization symptoms in patients[32] including 8 items. The degree of influence of each item in the past 4 weeks was investigated. The scores of each item ranged from 0 to 2 points, with a total score of 0–16 points. It can be divided into no somatization symptoms (0–4 points), mild somatization symptoms (5–9 points), moderate somatization symptoms (10–14 points), and severe somatization symptoms (15 points and above).

PHQ-9

A total of 9 items were used to assess the patient's depressive state[33–35]. The number of days that the patient was troubled by each item in the past 2 weeks was investigated. The scores of each item ranged from 0–3 points. The total score was 0–21 points, which could be divided into no depression (0–4 points), mild depression

(5–9 points), moderate depression (10–14 points), moderate to severe depression (15–19 points), and severe depression (20–27 points). Patients with a total score ≥ 10 were considered to have clinical depression.

Urinalysis
Random urine samples were taken from all patients. The clinical laboratory of the Affiliated Hospital of North Sichuan Medical College used the FUS-2000 automatic urine dry chemistry analyzer and chemical test strips produced by Changchun Dirui Co., Ltd.for automatic sampling and analysis.

Evaluation of effective rate of urinalysis
The outcomes were classified based on improvement in urinary indicators: abnormal urinary indicators completely normal was defined as a cure; the reduction of abnormal urinary indicators was regarded as improvement; no change or aggravation of abnormal urinary indicators was considered ineffective. The Total effective rate = (Cured cases + Improved cases)/Total cases × 100%.

Evaluation of effective rate of dyspepsia symptoms
The total score reduction rate of symptoms (DSS) [(total score of symptoms before treatment-total score of symptoms after treatment)/total score of symptoms after treatment × 100%] was calculated. The clinical symptoms of patients completely disappeared or basically disappeared, and the total score reduction rate of symptoms > 75% was markedly effective. The clinical symptoms of the patients were relieved, and the total symptom score reduction rate of 50–75% was effective. The clinical symptoms of the patients were not relieved, and the total symptom score reduction rate < 50% was invalid. The total effective rate = (Effective cases + Markedly effective cases)/Total cases × 100%.

Statistical analysis
All data were analyzed by SPSS 25.0 software. The non-normal quantitative data were expressed as Median (IQR), and comparisons before and after treatment were conducted using the paired Wilcoxon rank-sum test. The Mann-Whitney U test was used to compare the data. The count data were expressed as n (%), and the χ^2 test was used to compare the groups. Spearman rank correlation coefficient test was used for correlation analysis. Multivariate analysis of dyspepsia symptoms and improvement of urinalysis was performed by multivariate ordered Logistic regression. All statistical tests were two-tailed tests, and the results were $P < 0.05$, which was significant.

Ethical approval
This prospective, randomized clinical trial was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College and registered at Clinical Trials.gov (number: ChiCTR2400079677). Written informed consent to participate was obtained from all participating patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

Result
Comparison of two groups of general data
One patient in the control group and one patient in the test group were lost in follow-up; treatment was discontinued in two patients in the control group, and in three patients in the test group. Ultimately, 60 and 60 patients were included in the analysis in the control and test groups, respectively (Fig. 1). In the test group, 60 cases were female, with an average age of (51.65 ± 7.77) years. In the control group, 60 cases were female, with an average age of (47.22 ± 10.30) years. Urinary specific gravity, urinary nitrite, urinary ketone body and urinary protein were negative in all patients before and after treatment. There was no significant difference in general data between the two groups ($P > 0.05$).

The correlation between urinalysis and DSS, SF-NDI, GAD-7, PHQ-8, PHQ-9 in the two groups before treatment
Before treatment, urinary erythrocytes were correlated with SF-NDI and PHQ-8 ($P < 0.05$), and urinary erythrocytes are negatively correlated with SF-NDI and positively correlated with PHQ-8. There was no significant correlation between urinary occult blood, urinary leukocyte esterase, urinary erythrocytes, urinary erythrocytes and DSS, SF-NDI, GAD-7, PHQ-8, PHQ-9 (Table 1).

The correlation between urinalysis and DSS, SF-NDI, GAD-7, PHQ-8 and PHQ-9 in the two groups after treatment
After treatment, there was a positive correlation between urinary occult blood and PHQ-8 in the experimental group ($P<0.05$), and no correlations were found between urinary leukocyte esterase, urinary erythrocytes, urinary erythrocytes and DSS, SF-NDI, GAD-7, PHQ-8, PHQ-9 ($P>0.05$) (Table 2). After treatment, in the control group, urinary leukocyte esterase, urinary erythrocytes, urinary erythrocytes were correlated with PHQ-8 ($P<0.05$), and urinary occult blood, urinary leukocyte esterase, urinary erythrocytes, urinary erythrocytes were not correlated with DSS, SF-NDI, GAD-7, PHQ-9 ($P>0.0\ 5$) (Table 2).

The scores of DSS, SF-NDI, GAD-7, PHQ-8 and PHQ-9 were compared between the two groups before and after treatment
There was no significant difference in the scores of DSS, SF-NDI, GAD-7, PHQ-8 and PHQ-9 between the two groups before treatment ($P > 0.05$). Post-treatment comparisons showed a statistically significant difference in

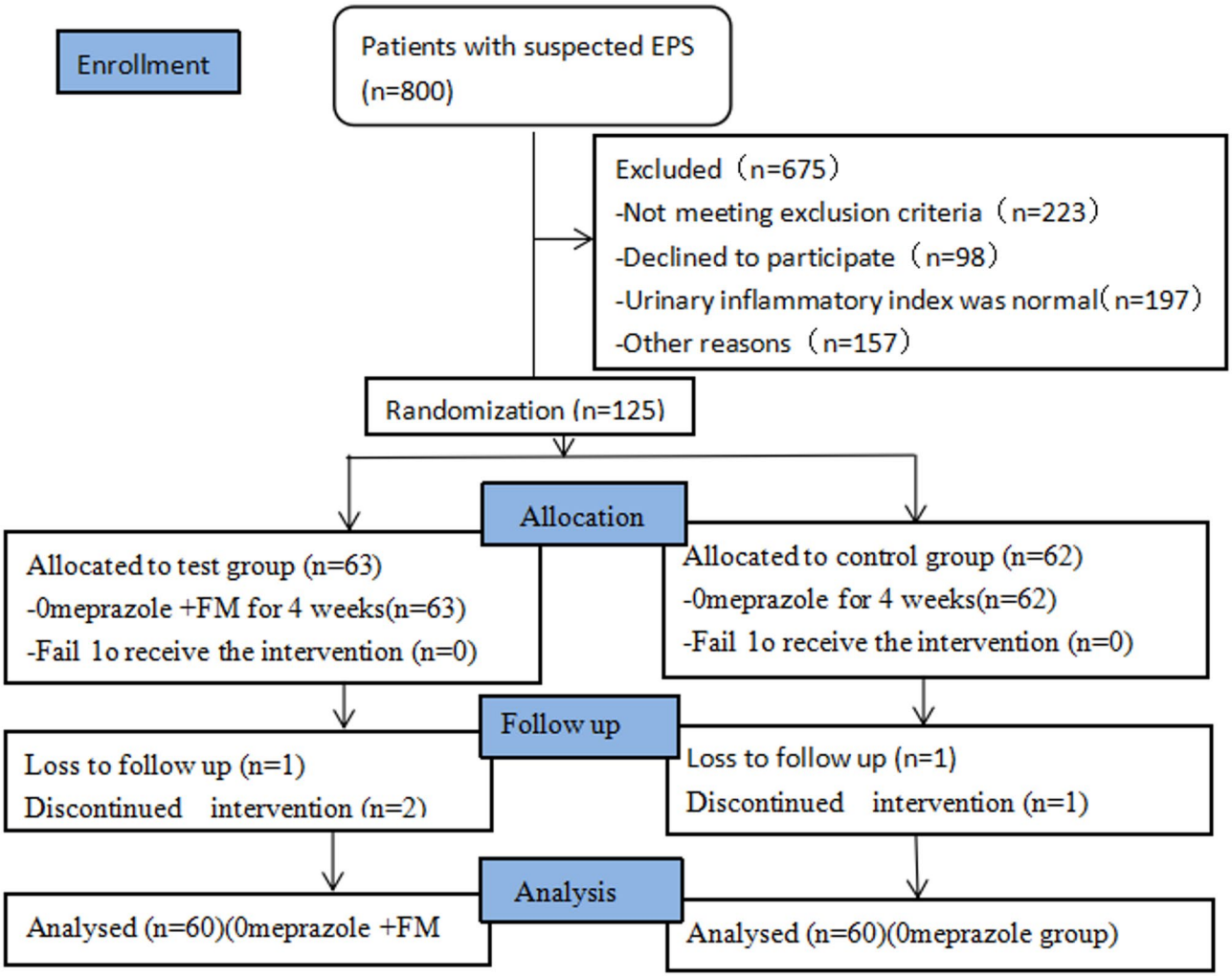

Fig. 1. Workflow of randomization and treatment procedures of enrolled patients. *FM* flupentixol/melitracen.

Variables	DSS($n=120$)	SF-NDI($n=120$)	GAD-7($n=120$)	PHQ-8($n=120$)	PHQ-9($n=120$)
Urinary occult blood					
r value	− 0.063	− 0.102	− 0.078	0.140	− 0.061
P value	0.496	0.270	0.400	0.128	0.507
Urinary leukocyte esterase					
r value	− 0.076	− 0.046	− 0.111	0.028	− 0.017
P value	0.048	0.621	0.226	0.759	0.858
Urinary leukocyte					
r value	0.037	0.018	− 0.085	0.057	0.038
P value	0.690	0.842	0.355	0.538	0.680
Urinary erythrocyte					
r value	− 0.115	− 0.200	− 0.144	0.216	0.005
P value	0.211	0.029	0.116	0.018	0.959

Table 1. The correlation between urinary occult blood, urinary leukocyte esterase, urinary leukocyte, urinary erythrocyte and DSS, SF-NDI, GAD-7, PHQ-8, PHQ-9 before treatment.

Variables	DSS($n=60$)	SF-NDI($n=60$)	GAD-7($n=60$)	PHQ-8($n=60$)	PHQ-9($n=60$)
The test group after treatment					
Urinary occult blood					
r value	0.051	0.121	0.163	0.321	0.126
P value	0.701	0.356	0.214	0.012	0.338
Urinary leukocyte esterase					
r value	0.027	0.032	0.037	0.025	0.026
P value	0.837	0.808	0.781	0.852	0.841
Urinary leukocyte					
r value	0.018	0.015	0.097	0.063	0.044
P value	0.889	0.908	0.460	0.631	0.741
Urinary erythrocyte					
r value	0.004	0.144	0.084	0.009	0.014
P value	0.976	0.272	0.523	0.948	0.915
The control group after treatment					
Urinary occult blood					
r value	0.041	0.016	0.181	0.066	0.104
P value	0.757	0.901	0.165	0.616	0.428
Urinary leukocyte esterase					
r value	0.149	0.122	0.128	0.279	0.136
P value	0.257	0.355	0.330	0.031	0.299
Urinary leukocyte					
r value	0.241	0.228	0.185	0.453	0.230
P value	0.063	0.080	0.157	<0.001	0.076
Urinary erythrocyte					
r value	0.164	0.096	0.080	0.322	0.159
P value	0.210	0.464	0.544	0.012	0.226

Table 2. The correlation between urinary occult blood, urinary leukocyte esterase, urinary leukocyte, urinary erythrocyte and DSS, SF-NDI, GAD-7, PHQ-8, PHQ-9 after treatment.

DSS scores between the two groups ($P<0.05$), while no significant differences were found in SF-NDI, GAD-7, PHQ-8, or PHQ-9 scores ($P>0.05$). Significant improvements in DSS, SF-NDI, GAD-7, PHQ-8, and PHQ-9 scores were observed after treatment in both the test and control groups ($P<0.05$) (Fig. 2A and B).

Comparison of two groups of urinalysis before and after treatment

No significant differences were observed in urinary leukocyte esterase, urinary leukocytes and urinary erythrocytes between the two groups before treatment ($P>0.05$). After treatment, there were significant differences in urinary leukocyte esterase, urinary leukocytes and urinary erythrocytes between the two groups ($P<0.05$). No significant differences were observed in urinary leukocyte esterase, urinary erythrocytes and urinary erythrocytes before and after treatment in the test group ($P<0.05$). There was no statistically significant difference ($P>0.05$) in urinary leukocyte esterase, urinary leukocytes and urinary erythrocytes before and after treatment in the control group (Fig. 2C).

Comparison of detection of abnormal inflammatory indicators of urine before and after treatment

There was no significant difference in the detection rate of urinary occult blood, urinary leukocyte esterase, urinary erythrocytes and urinary erythrocytes between the two groups before treatment ($P>0.05$). After treatment, the detection rates of urinary occult blood, urinary leukocyte esterase, urinary erythrocytes and urinary erythrocytes in the test group were lower than those in the control group, and the differences were statistically significant ($P<0.05$) (Table 3).

Comparison of the improvement of dyspepsia symptoms and urinalysis between the two groups after treatment

After treatment, there were significant differences in the improvement of dyspepsia symptoms and urinalysis between the two groups ($P<0.05$) (Table 4).

Multivariate regression analysis of dyspepsia symptoms and changes of urinalysis in the two groups

Multivariate ordered logistic regression analysis showed that urinary erythrocytes, DSS, SF-NDI, urinalysis changes, and groups differences were statistically significant (all $P<0.05$). There were no statistically significant in urinary occult blood, GAD-7, PHQ-8 and PHQ-9 (all $P>0.05$) (Table 5).

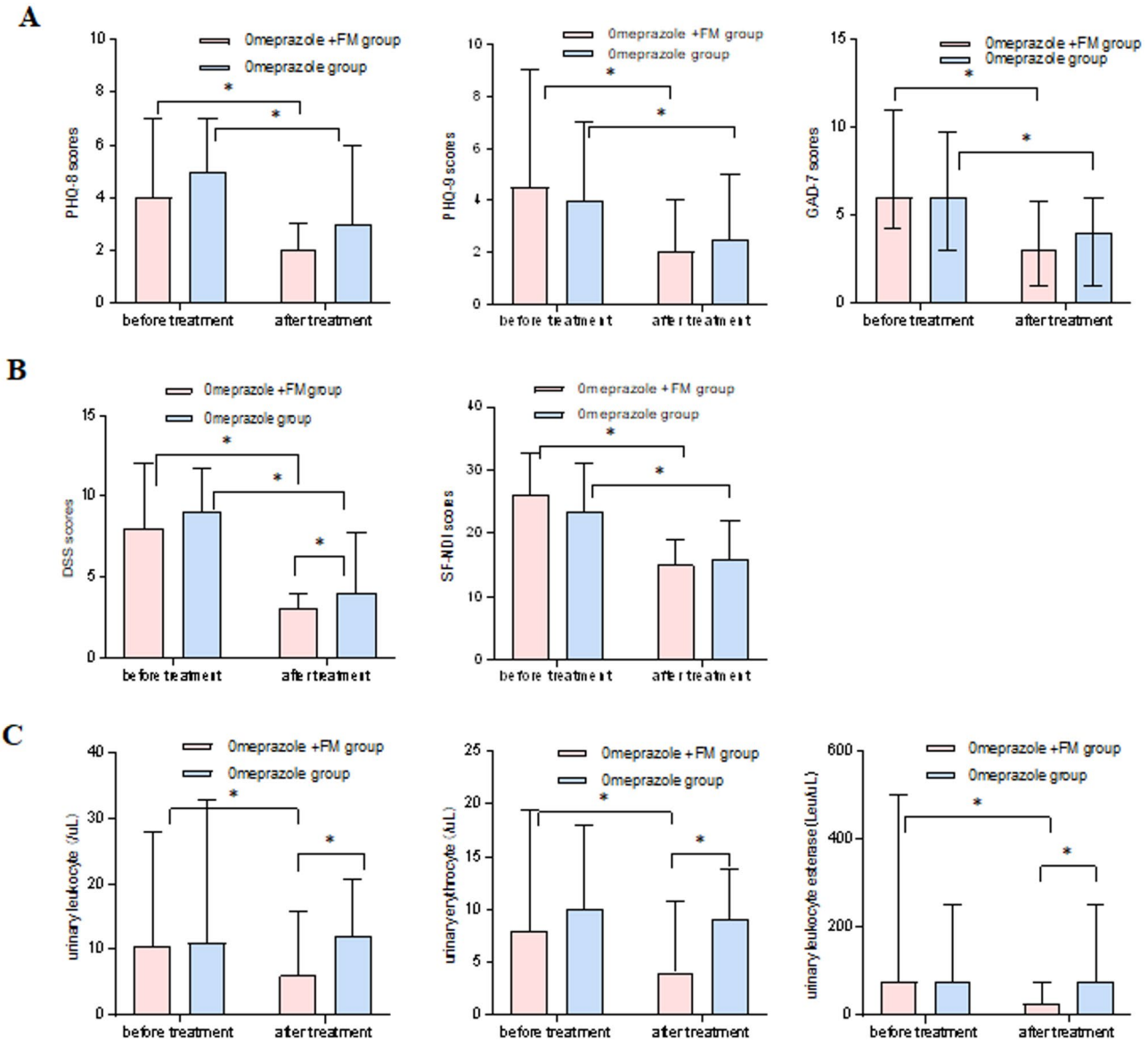

Fig. 2. Treatment outcomes of patients with EPS receiving 4-week 0meprazole + FM or 0meprazole treatment. **A** PHQ-8: Patient Health Questionnaire-8 Somatization Scale, PHQ-9: Patient Health Questionnaire-9Depression Scale, GAD-7: Generalized Anxiety Disorder-7 **B** DSS: Dyspepsia Symptoms Severity, SF-NDI: The 10-item short form of the Nepean Dyspepsia Index **C** Urinary leukocyte count, Urinary erythrocyte count, and Urinary leukocyte esterase. *EPS* epigastric pain syndrome, *FM* flupentixol/melitracen; $^{*}P < 0.05$.

Similarly, multivariate ordered logistic regression analysis revealed that urinary leukocytes, urinary erythrocytes, dyspeptic symptoms, clinical efficacy and group differences were statistically significant (all $P < 0.05$). There were no statistically significant in urinary occult blood, DSS, SF-NDI, GAD-7, PHQ-8, and PHQ-9 (all $P > 0.05$) (Table 6).

Discussion

The results of correlation analysis showed for the first time that urinary erythrocytes were associated with somatization and QoL in female patients with EPS before treatment. After treatment, the correlation between urinary erythrocytes and somatization/quality of life disappeared in the experimental group. In contrast, the control group maintained significant correlations between urinary leukocyte esterase, leukocytes, erythrocytes, and somatization symptoms, with higher correlation coefficients and more pronounced differences. The correlation analysis suggests that certain urinalysis are associated with somatization symptoms, indicating that FM can effectively improve somatization symptoms related to urinalysis.

The presence of leukocytes in urine may suggest a potential urinary tract infection (UTI), as urinary leukocyte esterase—a serine protease derived from neutrophils—serves as a marker for inflammatory activity. However, the significant improvement in anxiety and depression symptoms observed in this patient cohort argues against

Time and groups	Urinary occult blood	Urinary leukocyte esterase	Urinary leukocyte	Urinary erythrocyte
Before treatment				
Test group($n=60$)	25 (41.7)	42 (70.0)	30 (50.0)	23 (38.3)
Control group($n=60$)	26 (43.3)	38 (63.3)	33 (55.0)	28 (46.7)
χ^2value	0.034	0.600	0.301	0.853
P value	0.853	0.439	0.583	0.356
After treatment				
Test group($n=60$)	12 (20.0)	25 (41.7)	24 (40.0)	15 (25.0)
Control group($n=60$)	22 (36.7)	39 (65.0)	35 (58.3)	26 (43.3)
χ^2value	4.104	6.563	4.034	4.483
P value	0.043	0.010	0.045	0.034

Table 3. The detection rates of urinary occult blood, urinary leukocyte esterase, urinary leukocyte and urinary erythrocyte between the two groups before and after treatment [n (%)].

Groups	*N*	Markedly effective	Effective	Ineffective	Total effective rate (%)
Comparison of the effect of the improvement of dyspepsia symptoms					
Test group	60	39 (65.0)	4 (6.7)	17 (28.3)	71.7*
Control group	60	23 (38.3)	1 (1.7)	36 (60.0)	40.0
Comparison of the effect of improvement of urinalysis					
Test group	60	24 (40.0)	16 (26.7)	20 (33.3)	66.7*
Control group	60	5 (8.3)	15 (25.0)	40 (66.7)	33.3

Table 4. Comparison of the effect of the improvement of dyspepsia symptoms and Urinalysis between the two groups [n (%)]. Compared with the control group, **P*<0.05.

Variables	β	SE	Wald	*P* value	OR (95%CI)
Urinary leukocyte esterase	0.000	0.002	0.058	0.810	1.000 (0.997–1.003)
Urinary leukocyte	0.012	0.007	2.983	0.084	1.012 (0.998–1.025)
Urinary erythrocyte	− 0.024	0.012	4.237	0.040	0.976 (0.955–0.999)
DSS	− 0.183	0.073	6.321	0.012	0.833 (0.723–0.961)
SF-NDI	0.119	0.046	6.821	0.009	1.126 (1.030–1.231)
GAD7	− 0.159	0.089	3.228	0.072	0.853 (0.717–1.014)
PHQ8	0.030	0.111	0.072	0.788	1.030 (0.829–1.279)
PHQ9	− 0.055	0.119	0.215	0.643	0.946 (0.750–1.195)
Changes of urinalysis					
Cure	0.941	0.622	2.288	0.130	2.563 (0.757–8.680)
Improvement	1.264	0.579	4.771	0.029	3.540 (1.139–11.012)
Ineffective[a]	–	–	–	–	–
Group					
Control group	1.812	0.532	11.621	0.001	6.123 (2.160–17.357)
Test group[a]	–	–	–	–	–

Table 5. Ordered logistic regression analysis of the influencing factors of dyspepsia symptoms improvement. [a] Represents the reference group; SE, standard error; β, Standardized regression coefficient.

an infectious etiology, distinguishing these findings from typical UTI presentations (manuscript under review). Regarding hematuria, the detection of urinary erythrocytes warrants clinical vigilance for glomerular pathology. In the present study, abnormalities in urinary erythrocytes demonstrated further improvement during follow-up. Phase-contrast microscopic analysis of erythrocyte morphology revealed a predominance of isomorphic (uniform) red blood cells, consistent with non-glomerular (i.e., lower urinary tract) hematuria.

The results of this study also showed that there were differences in the scores of DSS, SF-NDI, GAD-7, PHQ-8 and PHQ-9 between the two groups before treatment, however, these differences were not statistically significant. After 4 weeks of treatment, the scores of dyspepsia symptoms, QoL, anxiety, depression and somatization symptoms of the two treatment schemes were improved, and the difference was statistically significant. The improvement of dyspepsia symptoms in the test group was the most obvious, and the difference was statistically

Variables	β	SE	Wald	*P* value	OR(95%CI)
Urinary leukocyte esterase	− 0.001	0.001	0.272	0.602	0.999 (0.997–1.002)
Urinary leukocyte	0.014	0.007	4.085	0.043	1.014 (1–1.027)
Urinary erythrocyte	− 0.025	0.010	5.866	0.015	0.975 (0.955–0.995)
DSS	0.016	0.060	0.075	0.784	1.016 (0.905–1.142)
SF-NDI	0.034	0.037	0.820	0.365	1.035 (0.962–1.113)
GAD7	− 0.107	0.075	2.006	0.157	0.899 (0.776–1.042)
PHQ8	0.049	0.096	0.263	0.608	1.050 (0.870–1.269)
PHQ9	− 0.071	0.099	0.525	0.469	0.931 (0.767–1.130)
Clinical efficacy					
Markedly effective	1.020	0.471	4.688	0.030	2.773 (1.102–6.980)
Effective	0.296	1.074	0.076	0.783	1.344 (0.164–11.034)
Ineffective[a]	–	–	–	–	–
Groups					
Test group	1.731	0.455	14.488	0.000	5.646 (2.316–13.777)
Control group[a]	–	–	–	–	–

Table 6. Ordered logistic regression analysis of the influencing factors of the improvement of urinalysis. [a]Rpresents the reference group; SE, standard error; β, Standardized regression coefficient.

significant compared with the control group, indicating that the two treatment schemes had therapeutic effects, but the effect was the best after combined with FM treatment. Compared with conventional drugs, the adverse symptoms of dyspepsia in EPS patients were greatly improved after FM treatment, and the symptoms of anxiety, depression and somatization were also significantly alleviated, and the QoL was improved.

This study also found that EPS female patients often accompanied by abnormal urinalysis when PPIs treatment was ineffective, which was different from asymptomatic bacteriuria, with longer duration and repeated no remission. Furthermore, the study suggested that urinalysis were significantly correlated with somatization symptoms. Compared with conventional drug treatments, the combination with FM therapy resulted in a significant reduction in urinary occult blood, urinary leukocyte esterase, urinary leukocytes, and urinary erythrocytes in EPS patients.These findings suggest that changes in urinalysis may serve as potential indicators for therapeutic response to FM augmentation in female EPS patients refractory to PPI therapy, and could provide predictive value for FM treatment outcomes in EPS patients with abnormal urinalysis results.

The multivariate ordered logistic regression analysis indicated that the improvement of dyspeptic symptoms and the changes in urinalysis parameters were significantly associated with the urinary erythrocyte and leukocyte counts. Notably, the independent association of urinary erythrocytes was stronger. There were no significant associations with psychological scales. The urinary erythrocytes and leukocytes may affect gastrointestinal function through cross-systemic inflammatory responses, involving the mechanisms of neurogenic regulatory pathways. These findings emphasized the necessity of integrated, multisystem approaches for the evaluation and management of EPS, which merits further investigation.

Flupentixol, as an antipsychotic drug, directly acts on dopamine D1 and D2 receptors on the presynaptic membrane and increases dopamine concentration in the synaptic cleft[36,37]. Melitracen, as a TCA, can increase the concentration of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) in the synaptic cleft[23]. In a randomized clinical trial, FM has been shown to relieve anxiety and depression symptoms of chronic physical diseases within 2 weeks[38] but also the remission rate of gastrointestinal symptoms is 86.73%, and the incidence of adverse reactions is low[39]. In this study, the combination of low-dose FM with PPIs therapy improved both gastrointestinal symptoms and mood disorders in EPS patients, which is consistent with previous research findings.

Mahjani et al.[40] found that a significant correlation between clinical anxiety and lower urinary tract symptoms. Patients with depression or emotional disorders are also more likely to have lower urinary tract symptoms, lower urinary tract symptoms can also cause central nervous inflammation and emotional disorders. Treatment of emotional disorders can effectively improve potential inflammation in the bladder and brain[41]. The proposed mechanisms may collectively explain the clinical remission of somatic manifestations and normalization of urinary parameters in female EPS patients, who received FM-integrated treatment as demonstrated in our cohort.

This study proposes that the therapeutic efficacy of FM in managing EPS induced somatization symptoms and abnormal urinalysis may be mediated through a potential connection between the gut–brain axis and gut–bladder axis. The gut microbiota and its metabolites have been demonstrated to play a significant role in modulating the nervous system. Notably, emerging research has revealed a 60% similarity between the urinary microbiome and gut microbiome[42]. Mental disorders such as anxiety and depression may alter gut motility and affect the efferent nerves of the gut microbiota or the activity of the autonomic nervous system, leading to abnormal brain-gut interactions and comorbid conditions like FD[43]. Furthermore, impaired intestinal barrier function can result in systemic translocation of gut microbes and their metabolites, potentially triggering neuroinflammation and bladder inflammation[44].

There are some deficiencies in this study. Firstly, because the follow-up subjects may have different understandings of some contents of FD-related scales, there may be some bias in the process of scale information collection, which may affect the accuracy. Whether it has an impact on the correlation between abnormal urinary inflammation indicators and anxiety and depression needs further study. Secondly, this study did not include patients with effective conventional drug treatment and abnormal urinalysis. In the future, more patients can be included to further analyze the clinical application value of abnormal urinalysis. In addition, the pre-experiment of this study found that the proportion of abnormal urinalysis in male EPS patients was less, so the sample size of this experiment was female. And the abnormal urinalysis were also related to living habits, personal hygiene, especially sexual life, which was not included in two groups. In the future, these indicators can be included to further study the value of abnormal urinalysis for somatization and QoL. Finally, the sample size of this study was limited, which is not a double blind randomized controlled trial. Future multicenter, large-scale, double-blind, randomized controlled trials are warranted to validate these findings.

Conclusion

In this study, the urinalysis of EPS patients were correlated with somatization symptoms, but not with anxiety and depression. The urinalysis could be significantly improved after combined with FM treatment. Compared to the PPIs control group, the combination therapy with FM significantly alleviated dyspepsia symptom severity, anxiety, depression, and somatization symptoms in EPS patients, while also improving quality of life. Furthermore, post-treatment urinalysis demonstrated more pronounced improvement. These findings suggest that the brain–bladder axis might contribute to the pathogenesis of EPS in female patients. Patients with poor efficacy of PPIs in the treatment of female EPS may be accompanied by abnormal urinalysis, and combined with effective anti-somatization/depression treatment is necessary. These results need to be confirmed by further research in the future.

Data availability

This published article contains all of the data generated during the course of this study.

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Author contributions

G.H, F.P. were involved in the design and conception. F.P., Y.X.L. and Y.R.L. collected the data and wrote the article. F.P., Y.X.L., Y.R.L. and X.W. analyzed the data; All authors critically revised the article for important intellectual content. G.H. and G.Y. critically revised and approved the final manuscript. Guarantor of article. Guobin & He.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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