A Randomised Double Blind Control Trial of Add-on Duloxetine on Symptom Severity and Quality of Life in Irritable Bowel Syndrome: Protocol of a Proof-of-Concept Study

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Abstract

Background: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), which has been approved in the United States and Europe for the treatment of the major depressive disorder, generalized anxiety disorder, peripheral neuropathy in patients with diabetes and fibromyalgia, but it has not been approved for the treatment of Irritable bowel syndrome. In an open-label study on the duloxetine impact on symptoms of irritable bowel syndrome, duloxetine resulted in significant improvement in the severity of pain, the severity of illness, quality of life, anxiety, and disability at work and life, but this study was conducted on small sample size. This study aims to investigate the effectiveness of duloxetine on symptom severity and quality of life in irritable bowel syndrome.

Methods: A total of 62 patients will be enrolled in the study and will be randomized into two groups (cases and control). Randomisation will be done using a computer generated random number table. Rome IV Criteria will be applied for diagnosis of Irritable bowel syndrome. Informed consent will be taken. Severity will be assessed by IBS severity scoring system. Screening for psychiatric disorders will be done following a clinical interview. Diagnosis will be confirmed as per ICD-10. Socio-demographic and clinical details of patients will be recorded on the semi-structured proforma. Specified rating scales (IBS-SSS, IBS-QOL) will be applied appropriately. The clinician can change the dosages as per the tolerability within the range. Control group shall receive treatment as usual only. Both the cases and controls will not be given any other psychotropic medications in addition to duloxetine during the study period. Both cases and controls shall be assessed on the start of the treatment and by 2nd, 4th and 8th week. Drug adverse effects and compliance to treatment will be evaluated every 2 weeks after starting the treatment. Data obtained will be analysed statistically with appropriate statistical tools.

The trial has been registered in the Clinical Trials Registry, India (CTRI/2023/04/051948).

Result: After the collection of data, statistical analysis will be done by using a computerized statistical program, Statistical Package for Social Sciences. Mean changes in the rating scale scores will be compared after each assessment and between the groups.

Conclusion: The findings will help to assess the efficacy of add-on duloxetine on symptom severity and quality of life in irritable bowel syndrome.
INTRODUCTION

Irritable bowel syndrome is one of the most common gastrointestinal dysfunctions affecting 5 to 20% of the world population. It causes significant impairment in the individuals' performance and incurs a lot of costs on the patient and the health system. The exact etiology for this syndrome is not clear, but such factors as gut-brain axis problems, disorders related to bowel movements, pain sensitivity, infections, neurotransmitters, genetic factors, and food allergies have been reported as the factors involved in this disorder. Serotonin is one of the most important neurotransmitters involved in this disease; 95% of the body's serotonin is found in the gastrointestinal tract, which is involved in the onset of peristaltic bowel movements, secretory reflexes, and visceral sensory perception. A total of 50 to 90% of patients with Irritable bowel syndrome have psychiatric disorders, such as mood disorders and anxiety, so the use of psychotropic drugs in many patients can help improve their symptoms.

Various treatments have been used so far for this syndrome, none of which has been able to completely improve the symptoms.

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), which has been approved in the United States and Europe for the treatment of the major depressive disorder, generalized anxiety disorder, peripheral neuropathy in patients with diabetes and fibromyalgia, but it has not been approved for the treatment of Irritable bowel syndrome. In an open-label study on the duloxetine impact on symptoms of Irritable bowel syndrome, duloxetine resulted in significant improvement in the severity of pain, the severity of illness, quality of life, anxiety, and disability at work and life, but this study was conducted on small sample size. Considering the high prevalence of Irritable bowel syndrome and its functional disorder associated with considerable costs for the individual and health system, paying attention to its treatment is crucially important. For this reason, the present study has investigated the effectiveness of duloxetine on the quality of life and symptoms of patients with Irritable bowel syndrome.

Hypothesis of the study

Patients with Irritable bowel syndrome will have higher rates of associated psychiatric disorders. Duloxetine will affect severity and quality of life in subjects with irritable bowel syndrome.

Aim

To study efficacy of add-on duloxetine with treatment as usual on severity and quality of life in subjects with Irritable bowel syndrome.

Objective

To compare the efficacy of add-on duloxetine with treatment as usual between groups receiving duloxetine (cases) and placebo (control) (Figure 1).

Null Hypothesis

There will be no significant difference in the symptom severity and quality of life of patients with Irritable bowel syndrome between the two groups.

Study Design

It is a proof-of-concept study with a randomized, double-blind, interventional design conducted at a tertiary care psychiatry centre. The institutional ethics committee has approved the protocol and the trial has been registered in the clinical trials registry India on 25/04/2023 (CTRI/2023/04/051948).

Study Setting and Population

The study will be conducted at the Department of Psychiatry, King George Medical University, Lucknow, India. Symptomatic patients attending Medical Gastroenterology OPD diagnosed with Irritable bowel syndrome using ROME IV Criteria.
will be recruited, if they fulfill the following selection criteria. The patient selection criteria are mentioned in Table 1.

**Sampling Technique and Randomization**

Purposive sampling with random allocation of participants by computer-generated random table method using www.random.org was done. There will be double blinding as the participants as well as investigators will not be aware of the allocation.

**Sample Size Calculation**

G*Power version 3.1.9 was used to do a sample size calculation. Repeated Measure ANOVA (between factors) will be used as statistical tests and accordingly effect size f of 0.3 is kept with a power of 0.8. There will be 2 groups and the assessment will be done on 4 points. The required sample size was 62 for the entire study (31 in each group). Considering an attrition rate of about 10%, the expected number of participants to be enrolled is 69.

**Description of Tools**

*Semistructured Sociodemographic and Clinical Proforma UHID*

Name
Age
Gender
Address
Domicile
Education
Occupation
Contact Details
Family Income
No Of Family Members
Type Of Family
Sociodemographic Status
Developmental Milestones
Past History Of Psychiatric Illness
Family History Of Psychiatric Illness
Substance Use
Menstrual History
Chief Complaints
Duration Of Symptoms
Course
Diagnosis
Treatment Taken
Source Of Referral
Comorbidities

**Rome IV Criteria**

A self-report integrated questionnaire for diagnosis of all functional gastrointestinal disorders in adults (Rome IV diagnostic Criteria), including alarm symptoms or red flags to alert clinicians to consider testing for alternative medical disorders.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Drop out criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of IBS as per ROME IV Criteria</td>
<td>Patients having medical illness requiring priority management</td>
<td>Subject withdrawing consent</td>
</tr>
<tr>
<td>Patient not receiving psychotropic medication for at least 2 weeks (5 weeks for fluoxetine)</td>
<td>Patients with pre-existing gastrointestinal disorders other than functional gastrointestinal syndromes, patients with history of gastrointestinal surgery or abnormal upper and lower gastrointestinal endoscopy</td>
<td>Any serious side effect, intolerability or worsening of symptoms</td>
</tr>
<tr>
<td>Age: 18 to 60 years</td>
<td>Patients having chronic medical illness, like chronic kidney disease and diabetes mellitus</td>
<td>The subject fails to come for follow up visit +/- 3 days of the scheduled visit</td>
</tr>
<tr>
<td>Written informed consent from Patient.</td>
<td>Patients with any diagnosable psychiatric disorders as per ICD-10 and having active suicidal ideas</td>
<td>Missing more than 20% of dosages by pill count/self-report</td>
</tr>
<tr>
<td></td>
<td>Substance use disorders except nicotine in the last 6 months</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Inclusion, exclusion, and dropout criteria for study participants
Irritable Bowel Syndrome Severity Scoring System\textsuperscript{8}

- The IBS-SSS is a 5-question survey that asks the severity of abdominal pain, frequency of abdominal pain, severity of abdominal distention, dissatisfaction with bowel habits, and interference with quality of life over the past 10 days.
- Subjects respond to each question on a 100-point visual analogue scale.
- Scores on the IBS-SSS can range from 0 to 500 with higher scores indicating more severe symptoms.
- Subjects can be categorized as having mild (75–175), moderate (175–300), or severe (>300) IBS.
- A decrease of 50 points is associated with a clinically meaningful improvement.

Irritable Bowel Syndrome-Quality Of Life Measure (IBS-QOL)\textsuperscript{9}

- The IBS-QOL is a self-report quality-of-life measure specific to irritable bowel syndrome (IBS) that can be used to assess the impact of IBS and its treatment. The IBS-QOL was developed using a needs based model. The IBS-QOL consists of 34 items, each with a five-point response scale. The individual responses to the 34 items are summed and averaged for a total score and then transformed to a 0 to 100 scale for ease of interpretation with higher scores indicating better IBS specific quality of life.
- The transformation formula used for the IBS-QOL total and scale scores is \[ \frac{\text{Sum of the items - lowest possible score}}{\text{Possible raw score range}} \times 100 \]

UKU Side Effect Rating Scale\textsuperscript{10}

The UKU side effects questionnaire has been adapted from a study done by O. Lingjzerde (1987) and it contains categorical rating scales in a Likert form (ranging from 0-1-2-3) under subdivisions—Psychic, Neurologic, Autonomic, and others.

Procedure

Patients attending Medical Gastroenterology OPD, KGMU, on specified days of a week will be screened on selection criteria. On any specified day, the first 2 patients fulfilling the selection criteria will be included after taking informed consent. Those who cannot be evaluated on the same day, for any reason, will be evaluated on a mutually convenient day. Rome IV Criteria\textsuperscript{7} will be applied for diagnosis of irritable bowel syndrome. Informed consent will be taken. Randomisation will be done using a computer generated random number table.\textsuperscript{5} Severity will be assessed by IBS severity scoring system. Screening for psychiatric disorders will be done by a clinical interview. Diagnosis will be confirmed as per ICD-10.\textsuperscript{11} Socio-demographic and clinical details of patients will be recorded on the semi-structured proforma. Specified rating scales (IBS-SSS, IBS-QOL) will be applied appropriately.\textsuperscript{8,9} The clinician can change the dosages as per the tolerability within the range. Control group shall receive treatment as usual only. Both the cases and controls will not be given any other psychotropic medications in addition to duloxetine during the study period. Both cases and controls shall be assessed on the start of the treatment and by 2\textsuperscript{nd}, 4\textsuperscript{th} and 8\textsuperscript{th} week. Drug adverse effects and compliance to treatment were evaluated every 2 weeks after starting the treatment. Data obtained will be analysed statistically with appropriate statistical tools.

Data Collection

Assessments using appropriate scales will be done at 3 stages during the study.
- Baseline assessment at the time of recruitment will be done. The following will be applied
  - Rome IV Criteria for diagnosing functional gastrointestinal syndrome
  - Irritable bowel syndrome severity scoring system (IBS-SSS)
  - Irritable bowel syndrome Quality of Life Instrument (IBS-QOL)
  - The patient will be assessed for comorbid psychiatric illness clinically. (Using The International Classification of Diseases (ICD-10), Classification of Mental and Behavioural Disorders for diagnosis in patients)

2\textsuperscript{nd} Assessment

At the end of 2 weeks. The following will be applied
- IBS-SSS
- IBS-QOL
Role of Duloxetine in Irritable Bowel Syndrome

- The patient will be assessed for comorbid psychiatric illness clinically. (Using ICD-10, Classification of Mental and Behavioural Disorders for diagnosis in patients)
- The patient will be assessed for comorbid psychiatric illness clinically. (Using ICD-10, Classification of Mental and Behavioural Disorders for diagnosis in patients)
- The UKU Side effect rating scale for assessing side effects of add-on psychotropic drug.

3rd Assessment

At the end of 4 weeks. The following will be applied
- IBS-SSS
- IBS-QOL
- The patient will be assessed for comorbid psychiatric illness clinically. (Using ICD-10, Classification of Mental and Behavioural Disorders for diagnosis in patients)
- The UKU Side effect rating scale for assessing side effects of add-on psychotropic drug.

4th Assessment

At the end of 4 weeks. The following will be applied
- IBS-SSS
- IBS-QOL
- The patient will be assessed for comorbid psychiatric illness clinically. (Using ICD-10, Classification of Mental and Behavioural Disorders for diagnosis in patients)
- The UKU Side effect rating scale for assessing side effects of add-on psychotropic drug.

Study Outcomes

The primary outcome will be measured by the change in scores of IBS-SSS, IBS-QOL from baseline to 2th, 4th and 8th weeks between the two groups. The number of patients reporting adverse events in each group following treatment will be the secondary outcome measure.

Result

After the collection of data, statistical analysis will be done by using a computerized statistical program, Statistical Package for Social Sciences (SPSS). The data will be checked for normality. The mean and standard deviation of various clinical and sociodemographic variables between the two groups will be compared by using the appropriate parametric (student’s t-test)/non-parametric test (Mann Whitney U test). Changes in scores of various scales pre- and post-intervention in between and among the groups (cases vs control) will be done using a two-way repeated measure analysis of one-way variance (ANOVA) test. The correlational analysis will be done between the outcome (change in IBS severity and baseline symptom severity) with socio-demographic (age) and clinical variables (age of onset of illness, duration of illness, type of IBS: IBS-C, IBS-D, IBS-M, IBS-U and associated comorbidities).

Discussion

Several population and clinical research have been performed, but knowledge remains sparse and psychiatric comorbidity prevalence varies from study to study. Socio-demographic and clinical correlations have been explored, but little knowledge about the Indian population is available. In an open-label study on the duloxetine impact on symptoms of irritable bowel syndrome, duloxetine resulted in significant improvement in the severity of pain, the severity of illness, quality of life, anxiety, and disability at work and life, but this study was conducted on small sample size. Through this proof-of-concept study, we can assess the efficacy of duloxetine as an add on treatment in patients of Irritable bowel syndrome and its This could lead to early mitigation of IBS symptoms, decreased associated psychiatric comorbidities, early attainment of functioning and better quality of life. This could aid in formulating new treatment recommendations for irritable bowel syndrome.

Conclusion

The results of this study will help understand the efficacy of duloxetine as an add on treatment in patients of irritable bowel syndrome. This might help in managing symptoms effectively and help improve the quality of life of patients suffering from IBS. This may further lead to less disease burden and better level of functioning of such patients.

References

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