

Efficacy and Tolerability of Tianeptine Versus Escitalopram in Patients with Irritable Bowel Syndrome: A Hospital based, Randomized Comparative Study

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ABSTRACT

Introduction: Irritable bowel syndrome (IBS) is associated with a number of psychiatric co-morbidities and various antidepressants have been used in the treatment of this disorder. Few studies have been done to study the role of tianeptine; a selective serotonin reuptake enhancer in such patients. We aimed to study the effects of tianeptine in such patients and compare it with escitalopram.

Material and methods: Patients for the study were referral patients sent by gastroenterologist after diagnosing them with IBS. A total of fifty-one patients were included in our study. Cases (patients) were diagnosed using ROME III criteria for IBS. For the diagnosis of psychiatric co-morbidity, MINI International Neuropsychiatric Interview Schedule Plus (MINI PLUS) was used. To assess the response and tolerability of the drug tianeptine and compare it with escitalopram, Clinical Global Impression scale (CGI) was used and all the domains of the scale including illness severity (CGI-S), global improvement (CGI-I) and efficacy index or tolerability (E.I) were calculated.

Results: Mean age of patients in the tianeptine and escitalopram groups was 36.48 and 35.15 years respectively. Major psychiatric diagnosis seen was generalized anxiety disorder (40% vs 42.3%), depression (24% vs 26.9%) and somatisation (20% vs 15%). At baseline, CGI-S values were comparable in both the groups. Following treatment, lower values on the CGI-I index were seen in both the groups suggesting significant improvement. Comparing CGI-I and EI between the two groups, the results were statistically insignificant, although good response and tolerability was seen in patients in both groups.

Conclusion: Our study shows tianeptine to be equally efficacious as that of escitalopram with promising results in patients suffering from irritable bowel syndrome.

Keywords: Irritable Bowel Syndrome; Tianeptine; Escitalopram; Depression; Somatisation.

is multifactorial involving visceral hypersensitivity, disturbances of gut motility and secretion, autonomic nervous system dysfunction, dysregulation of the brain-gut axis, altered gut microbiota and inflammatory changes in the gut wall.^{7,8} The gut and the brain are highly integrated, and they communicate in a bidirectional fashion, largely through the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis. Patients with IBS have higher levels of depression, anxiety, and somatoform disorders than healthy persons or patients with organic disease.⁹ The neurotransmitters controlling the brain-gut axis are serotonin, norepinephrine, corticotrophin-releasing factor (CRF), opioids etc. that modify both sensation and motility in the gut.¹⁰ Of these mediators, serotonin is the best known.¹¹ The antidepressants commonly used in IBS (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) act by modulating serotonin levels. In patients with IBS, antidepressants are used three times more often than that of controls in the general population.¹² The prevailing view has been that depression results from abnormally low levels of monoamine neurotransmitter substances (e.g., serotonin, norepinephrine, dopamine) which is commonly known as the monoamine hypothesis.^{13,14} Thus, primarily pharmacotherapy for depression includes agents which are known to increase levels of the neurotransmitter serotonin, and nowadays selective serotonin reuptake inhibitors (SSRIs), such as escitalopram, paroxetine and sertraline are the most prescribed pharmacological treatments for this disorder.¹⁵ Recent research suggests that increasing the levels of monoamines provides only an indirect contribution to antidepressant actions.¹⁶ An alternative and well-established

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder manifesting as abdominal pain or discomfort, bloating, and abnormalities of stool frequency and consistency.¹ It is considered to be the most common functional gastrointestinal (GI) disorder^{2,3} with an estimated prevalence of 8-22% in general population.^{3,4,5} Irritable bowel syndrome is regarded as a major economic health burden associated with reduced health-related quality of life (HRQOL), diminished work productivity, and high cost.⁶ The pathophysiology of irritable bowel syndrome

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treatment for depression is tianeptine, an antidepressant which does not share pharmacological properties with tricyclic antidepressants (TCAs), monoamine oxidase inhibitor's (MAOI's) or SSRIs.¹⁷ Tianeptine is an antidepressant agent acting as a selective serotonin reuptake enhancer (SSRE).¹⁸ It has similar efficacy to TCAs and SSRIs for depression and anxiety, but lesser adverse effects than TCAs.¹⁹ Tianeptine has been shown to modulate glutamatergic transmission, and its effects on neuroplasticity have been extensively studied in the hippocampus and amygdala.²⁰ Tianeptine restores stress-induced reduction of dendritic arborization in hippocampal neurons. Moreover, tianeptine reverses stress-induced inhibition of long-term potentiation at excitatory synapses in the hippocampus and prefrontal cortex.¹⁹

We aimed to study the effects of tianeptine in patients presenting with irritable bowel syndrome having comorbid anxiety or depression and compare the efficacy and side-effect profile of tianeptine with escitalopram.

MATERIAL AND METHODS

The present study was conducted in a tertiary care centre in the Post-graduate Department of Psychiatry in collaboration with Department of Gastroenterology over a period of one year from November 2015 to October 2016. Patients for the study were selected from outpatients visiting the Gastroenterology department. After complete history and physical examination, patients who were fulfilling the inclusion criteria were selected. Organic causes were ruled out by the Gastroenterologist after appropriate investigations wherever necessary. All the selected patients underwent a brief interview for socio-demographic details such as age, gender, employment, education, marital status and socioeconomic status. Inclusion criteria were patients >18 years of age who had received a diagnosis of IBS according to the Rome III diagnostic criteria. Patients with a history of organic disorder of the large and small bowel (e.g., inflammatory bowel disease), hepatic or renal disease, previous abdominal operation other than appendectomy, unstable thyroid disease and acute illness within the past 10 days were excluded. Alcoholics and pregnant females were also excluded. All enrolled patients provided written informed consent for the study. Patients who did not consent were excluded from the study. Patients were diagnosed using ROME III criteria for IBS. The Rome criteria are an international effort to characterize and classify functional GI disorders using a symptom-based classification system.²¹ For the diagnosis of psychiatric co-morbidity, we used MINI International Neuropsychiatric Interview Schedule Plus (MINI PLUS). The MINI PLUS is DSM-IV based diagnostic interview with high reliability and validity.^{22,23} The study was approved by the Institute ethical committee under reference number 102/ETH/GMC/ICMR.

Patients were either put on tianeptine 12.5mg twice a day or, escitalopram 10 mg once per day by a consultant psychiatrist. Medicines were procured from the hospital dispensary and dispensed by the pharmacist at the point of enrollment in the study and compliance was ensured by regular three weekly

follow ups. Patients were randomly allocated on 1:1 basis to receive either tianeptine or, escitalopram. A total of 51 patients consented for the study. To assess the response and tolerability of the drug tianeptine, we used Clinical Global Impression scale (CGI) and calculated all the domains of the scale including illness severity (CGI-S) which was applied at baseline to know the severity of illness, global improvement (CGI-I) at 4 weeks to assess improvement in the illness and tolerability (E.I) which is a composite measure of tolerability to the given drug and therapeutic efficacy. CGI-S is a 7 point scale where 1 means normal and 7 means extremely ill patient. CGI-I is also a 7 grade scale in which 1 means very much improved on treatment and 7 indicates very much worse. CGI-EI is a 16 point scale that combines therapeutic effect and side effects of a drug with lower scores in efficacy index indicating better drug effect. CGI is a validated and reliable scale to assess efficacy of a drug in any drug trial and is easy and quick to administer.²⁴ The same scale was administered to patients put on escitalopram. A total of twenty-six patients were present in escitalopram group and twenty-five were in tianeptine group.

CGI-S was calculated at baseline (day 0) in both the groups. Patients were seen on follow-up at 4 weeks and CGI-I as well as Efficacy Index (EI) was calculated. Patients were also asked about side-effects related to the drug. One patient in the tianeptine group was lost to follow-up. The primary outcome of the study was mean difference in CGI-I score between the two groups at day 28. Secondary outcomes included differences in efficacy index (EI) and side effect profile of the drugs. The treatment duration of 28 days was selected since the improvement in most of psychiatric illnesses occurs by this period and similar trial period was undertaken by other studies.

Data was entered into tables and analyzed for mean and standard deviation. Chi-square test was applied to find out the significance of different values. Fishers' exact test was applied where the data did not meet Cochran criteria. P-value of < 0.05 was taken as statistically significant.

RESULTS

A total of twenty-six patients were in escitalopram group and twenty-five in tianeptine group. One patient from the tianeptine group dropped to follow-up, the reasons of which could not be known. Mean age of patients in the tianeptine group was 36.48 ± 9.11 years and of those in the escitalopram group was 35.15 ± 8.95 years. The two groups were well balanced in terms of baseline and demographic characteristics and disease severity. Females outnumbered males in our study by a ratio of approximately 2:1 in both the groups. Most of our patients were from rural background in both the sub-groups. Majority belonged to socio-economic class II or, III as per Kuppuswamy's socio-economic status. [Table I]. Among the psychiatric diagnosis, generalized anxiety disorder was seen in about 40% of patients in tianeptine group and 42% of patients in escitalopram group followed by depression (24% vs 26.9%) and somatization (20% vs 15.4%), [Table II]. IBS-M and IBS-C formed the

	Escitalopram group (n= 26)	Tianeptine group (n=25)	p- value
Age (Mean) in years	35.15±8.95	36.48±9.11	0.603
Sex (Female/Male)	20/6	18/7	0.687
Marital status (Married/Unmarried)	19/7	18/7	0.931
Residence (Rural/ Urban)	18/8	17/8	0.924
Socio-economic status			
Class			
I	3	1	0.832
II	13	12	
III	8	10	
IV	2	2	
V	0	0	

Socio-economic status= Kuppuswamy's socio-economic classification used. Applying chi-square test, p-value was found to be statistically insignificant for all socio-demographic variables.

Table-1: Demographic and baseline characteristics of the study patients:

Psychiatric disorder	Escitalopram group (n=26)	Tianeptine group (n=25)	p-value
MDE	7(26.9%)	6(24%)	1.000
GAD	11(42.3%)	10(40%)	1.000
Somatisation	4(15.4%)	5(20%)	0.726
Mxd. anx.dep.	3(11.5%)	2(8%)	1.000
No	1(3.8%)	2(8%)	0.609

MDE= Major depressive episode, GAD= Generalized anxiety disorder, Mxd.anx.dep. = Mixed anxiety depression, No= No major psychiatric disorder. P-value was not significant for any of the psychiatric disorders among the two groups.

Table-2: Psychiatric co-morbidities in the groups:

Type of IBS	Escitalopram group (n=26)	Tianeptine group (n=25)	p-value
IBS(A)	9(34.6%)	11(44%)	0.689
IBS(C)	10(38.5%)	10(40%)	1.000
IBS(D)	4(15.4%)	2(8%)	0.668
IBS(U)	3(11.5%)	2(8%)	1.000

IBS= Irritable bowel syndrome, IBS (A) = Irritable bowel syndrome (alternating type), IBS (C) = Irritable bowel syndrome (constipation type), IBS (D) = Irritable bowel syndrome (diarrheal type), IBS (U) = Irritable bowel syndrome (unclassified type) as per ROME-III classification. P-value was not significant for any of the sub-types of IBS.

Table-3: Types of Irritable bowel syndrome present in the two groups:

Scale domain	Group	Mean	S.D.	SEM	p-value
CGI(S)	1	4.24	0.59	0.11	0.88
	2	4.27	0.77	0.15	
CGI(I)	1	2.33	0.70	0.14	0.26
	2	2.12	0.65	0.12	
EI	1	5.83	3.51	0.71	0.97
	2	5.81	3.22	0.63	

Group 1= escitalopram group. Group 2= tianeptine group. CGI(S) = Clinical global impression (severity score), CGI (I) = Clinical global impression (improvement score), EI = Efficacy index, S.D = Standard deviation, SEM= Standard error of mean. P-value was not significant for any of the domains of CGI scale.

Table-4: Comparison of efficacy and tolerability between the two groups:

Side-effects	Escitalopram (n=26)	Tianeptine (n=24)
Restlessness	17	08
Epigastric discomfort	12	10
Dry mouth	05	09
Constipation	04	08
Sedation	08	12
Insomnia	05	02

Table-5: Side-effect profile of the two groups

major sub-type of irritable bowel syndrome constituting in both the groups followed by IBS-D and IBS-U. [Table III]. At baseline, mean severity score (CGI-S) was 4.24 in the escitalopram group and 4.27 in the tianeptine group indicating that on an average the patients were moderately ill in both the groups. At 4 weeks, mean improvement score (CGI-I) was 2.33 in the escitalopram group and 2.12 in the tianeptine group indicating significant improvement in both the arms. Comparing the efficacy index between the two

groups, it was 5.83 in the escitalopram group and 5.81 in the tianeptine group signifying moderate improvement with few side effects not interfering with patient's functioning. In the severity index, improvement index and efficacy index, p-value was statistically insignificant showing the two drugs to be equally effective and tolerated by patients. [Table IV]. Among the side-effects, patients on escitalopram had epigastric discomfort and restlessness as the most commonly reported ones while patients on tianeptine reported sedation and dry mouth as common side-effects. [Table V].

DISCUSSION

IBS is reported more frequently in women than men, female-male odd ratio being 2:1 and seems to be more common in the ages between 20 and 40.²⁵ Similar pattern was seen in our patients. In case of IBS, 50%-90% of those seeking treatment have been found to also have comorbid lifetime psychiatric disorders, especially depressive and anxiety disorders.²⁶

It has been studied that IBS patients have abnormal personality with higher anxiety-depression scores.^{27,28,29} In both groups of patients in our study, generalized anxiety disorder (GAD) was the most common psychiatric comorbidity followed by depression (MDE) which is consistent with other studies done in patients with IBS.^{30,31} Somatization disorder was the next common diagnosis seen in our study which is in accordance with the rates seen in other studies where the prevalence rates of somatization disorder is between 15% to 48% among IBS patients.^{32,33,34,35}

A number of studies have been done to study the role of antidepressants in IBS. Antidepressants and psychotherapy has been found to show significant improvement over the usual treatments used in IBS patients in terms of health related quality of life assessments.³⁶ Most commonly used antidepressants in the treatment of IBS are tricyclic antidepressants (TCA's) like desipramine and amitriptyline and selective serotonin reuptake inhibitors (SSRIs). There are some studies to support the use of SSRIs in improving global symptoms of IBS^{36,37} while some others find the use of SSRIs to be of no benefit in treatment of IBS.^{38,39} Very few studies in literature have shown the role of tianeptine in IBS. Tianeptine is used mainly as antidepressant and its efficacy is comparable with that of SSRIs.^{40,41,42} Tianeptine is a selective serotonin reuptake enhancer but, exhibits its antidepressant effects through a variety of mechanisms. It does not affect noradrenaline and dopamine reuptake; serotonergic, noradrenergic, dopaminergic or cholinergic receptors. However, it has been found to significantly decrease blood serotonin level with simultaneous increase of blood dopamine and platelet serotonin concentration. Tianeptine elicits inhibitory effect on the function of hypothalamic-pituitary-adrenal axis that controls reactions to stress.^{43,44,45}

Tianeptine is an efficacious μ -opioid receptor (MOR) and δ -opioid receptor (DOR) agonist, which could explain its effectiveness in treating symptoms of IBS especially abdominal pain associated with IBS.⁴⁶ In a study done in about one hundred patients of irritable bowel syndrome over a period of eight weeks, significant improvement was seen

in all psycho-somatic symptoms after putting the patients on tianeptine.⁴⁷ Keeping in view all the above, we analyzed the effectiveness of tianeptine in patients suffering from irritable bowel syndrome and compare it with escitalopram.

In our patients, tianeptine was seen to be equally efficacious as that of escitalopram in treating the core symptoms of IBS and also the associated psychiatric co-morbidity. Patients showed improvement both subjectively and objectively as assessed by clinical global impression (improvement index) scale. This index of the scale measures the global improvement in the patient from the time of commencement of study. Lower values of the index on follow up as seen in our study suggest good to marked clinical improvement. Although, we followed the patients for a shorter duration of time, positive response was seen in almost all patients.

Various studies have shown that although the bowel frequency improved with SSRI's, patients do not improve much in pain component. Tianeptine on the other hand has been found to relieve abdominal pain. In our study, patients put on tianeptine did well in terms of post-prandial discomfort and belching as compared to patients put on escitalopram. Similar effects of tianeptine have been observed in other studies also.⁴⁰ Among patients put on tianeptine, drowsiness was the most common side-effect noted while patients put on escitalopram reported gastric irritation as a common complaint. Assessing the therapeutic benefits as well as side-effects of the two drugs using the efficacy index, the results were comparable, proving tianeptine to be equally effective and tolerable as that of escitalopram for treating IBS. Although, the side-effect profile of the two drugs was different, none scored over the other in terms of improvement shown by patients and tolerability. Our patients put on tianeptine complained of restlessness less often as compared to escitalopram group, possibly due to the stronger anxiolytic effect of tianeptine. Although, constipation was seen more frequently in patients taking tianeptine, this side-effect itself was beneficial in diarrheal sub-type of IBS. Keeping in view all the above advantages, tianeptine can be a good therapeutic option for patients suffering from IBS. No patient discontinued either of the two medicines due to tolerability issues, thus, giving us a promising new option for treating irritable bowel syndrome.

Limitations

We had a small sample size; a larger one would give us better idea about tianeptine and its comparison with escitalopram. Also, the study was done in a single hospital and to generalize the findings, sample had to be taken from other hospitals. Longitudinal studies with longer duration of follow up could be done as follow-up of four weeks is quite short for patients of irritable bowel syndrome.

CONCLUSION

Patients with IBS have associated psychiatric co-morbidities which warrant proper treatment. Our study showed tianeptine to be equally efficacious as escitalopram in treating IBS patients, thus advocating the use of this drug as an emerging pharmacological agent for treating this chronic disabling disorder.

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