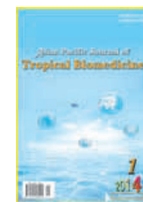


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# A preliminary evaluation of comparative effectiveness of riluzole in therapeutic regimen for irritable bowel syndrome

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## PEER REVIEW

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## Comments

This is a prudent study which meticulously evaluates the action of riluzole on brain–gut axis in abating visceral hypersensitivity, using valid clinical scales and adequate statistical measures. Results are encouraging and exciting and may act as a lead to future therapies.

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## ABSTRACT

**Objective:** To develop agents that are specifically effective in controlling the key disturbance of visceral hyperalgesia besides abating of associated multiple symptoms, and evaluate comparative effectiveness for IBS symptom relief for standard regimen (antispasmodic and probiotic) and add-on amitriptyline or riluzole regimens following two weeks administration.

**Methods:** 108 patients with visceral hypersensitivity accompanying IBS, divided into three groups were studied. First group received standard treatment (mebeverine 200 mg twice daily and probiotic 200 mg twice daily). Second group received add-on amitriptyline 25 mg before bedtime, while the third group got add-on riluzole 50 mg twice daily. Overall gastrointestinal symptom rating scale improving symptoms and hospital anxiety depression scale improving associated psychological morbidity were employed as measures at induction and at two-week follow-up period. Individual symptom scores were also examined to define the outcome profiles.

**Results:** Riluzole regimen resulted in significant reduction of overall gastrointestinal symptom rating scale score, not the other two regimens. Pain relief was seen with both riluzole and amitriptyline regimens significantly superior to standard treatment regimen, but riluzole effect appeared specific and independent anxiolytic effect. Amitriptyline caused relief in diarrhea and did not benefit in constipation point to non-specific remedial role in IBS.

**Conclusions:** Riluzole specifically relieves visceral hypersensitivity and is proved to be superior to current treatments in IBS patients. It appears a lead remedy based on glutamate transporter mechanisms in visceral hypersensitivity.

## KEYWORDS

Visceral pain, Riluzole, Glutamate transporter, Irritable bowel syndrome

## 1. Introduction

While irritable bowel syndrome (IBS) is common in the West, early studies suggest that the prevalence of IBS is low in developing countries. However, recent studies point out that there was increasing prevalence of IBS in newly developing Asian countries. Together with the changes with evolution of Asian countries such as westernization of the diet and increased psychosocial stress, it is proposed that **loss of internal protective effect, could**

give rise to a more uniform worldwide prevalence of IBS. IBS is one of the commonest gastrointestinal disorders. It is worrisome chronic disease of very productive life posing serious burden to medical care costs. The quality of life also suffers serious beating from IBS[1,2]. Varying systemic involvement of the gastrointestinal tract and both peripheral and central nervous system makes the syndrome difficult to be improved with single therapeutic agent[3,4]. Visceral hypersensitivity is highly prevalent in

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all functional bowel disorders with wider somatic referral of symptoms. Hypersensitivity at the level of the dorsal horn of the spinal cord is induced by peripheral inflammation or injury in the brain–gut axis. This process is mediated by mutual stimulation of N–methyl–d–aspartate receptors and neurokinin 1 receptors[5]. Tricyclic antidepressants (amitriptyline) have been used with variable success in control of IBS symptoms[6]. They cause sodium channel block in nociceptive neurons in an use–dependent manner. The antispasmodic compound mebeverine, a methoxybenzamine derivative is also widely used in IBS management[7]. It is thought to decrease motility and intraluminal bowel pressure via a direct effect on smooth muscle cells[8]. Probiotics also have shown some potential for global relief of IBS symptoms[9].

Neurotransmitter antagonist to reduce visceral hypersensitivity is an exciting new era for the treatment of functional gastrointestinal disorders[10]. The n–methyl d–aspartate (NMDA) receptor appears to be the most important molecular factor in the development of central sensitization at the spinal dorsal horn[11]. Changes in expression and glutamate uptake activity of spinal glutamate transporter are suspected to play a critical role in both induction and maintenance of hyperalgesic state by regulation of regional glutamate homeostasis. Human pharmacological studies have demonstrated that antagonism of the NMDA receptor preventing the development of central sensitisation within the oesophagus and ketamine may even reverse established visceral hypersensitivity[12]. Riluzole (a glutamate reuptake enhancer and NMDA receptor antagonist) was reported to attenuate hyperalgesia in neuropathic pain models at doses devoid of side effects, an action chiefly connected to the activation in glutamate reuptake[13]. The inclusion of riluzole in therapeutic regimen excluding amitriptyline is herein assessed for comparative effectiveness in relieving symptoms and improving quality of life in patients of IBS.

## 2. Materials and methods

### 2.1. Patients

After prior approval of institutional ethics committee, IBS patients aged 18 years or older with symptoms that fulfilled the Rome II criteria[14] for IBS for at least 6 months were included in the study. History, physical examinations

(including sigmoidoscopy/colonoscopy), routine and special laboratory investigations were recorded. Patients were excluded if they were lactose intolerant or had any other significant medical condition requiring concurrent therapy. Cases with psychiatric disorder or substance abuse within the previous 2 years, pregnant or breast–feeding women and those using hormonal contraception were also excluded. All included cases were advised to observe week long drug free period prior to inclusion in the study.

### 2.2. Study design

Strictly in sequence, cases entering the study were prescribed A, B or C therapy regimens. Regimen A: mebeverine 200 mg twice daily and probiotic 200 mg twice daily; Regimen B: Regimen A+amitriptyline 25 mg before bedtime; Regimen C: Regimen A+riluzole 50 mg twice daily.

### 2.3. Clinical scales

Standard gastrointestinal symptom rating scale (GSRS)[15] was used as measure. Concurrent psychological morbidity was assessed using hospital anxiety depression scale (HADS) [16]. The scores were compared at induction and at 2 weeks of compliant adherence to the prescribed therapy. Non–compliance with the prescribed regimen was thoroughly enquired and cases with more than one occasion of missing medicine were excluded.

### 2.4. Statistical methods

Overall variance of outcomes relating different symptoms in the compared regimens was examined using Kruskal–Wallis ANOVA test[17]. Chi square statistic was employed to evaluate relative outcomes of symptom relief in the compared treatment groups. *P* value less than 0.05 was considered significant. Interrelation among different symptoms was analysed using Spearman's correlation coefficient (*Q*)[18]. SPSS version 17 software was used.

## 3. Results

Table 1 summarizes GSRS scores prevalent among the overall studied sample of IBS patients. Pain was constantly present in all cases. Indigestion also occurred in majority,

**Table 1**

Overall profile of GSRS scores.

	Number of cases	GSRS score			Std. deviation	Variance	Mean	
		Range	Min.	Max.			Statistic	Std. error
Reflux	55	5	1	6	1.292	1.669	3.67	0.174
Pain	108	8	1	9	2.278	5.189	4.77	0.219
Indigestion	63	10	1	11	2.537	6.437	5.83	0.320
Diarrhoea	71	6	2	8	1.647	2.714	4.17	0.196
Constipation	19	6	2	8	1.968	3.871	4.74	0.451

**Table 2**

Overall profile of HADS scores.

	No. of cases		HADS Score			Std. deviation	Variance	Mean	
	Total	HADS $\geq$ 8	Range	Min.	Max.			Statistic	Std. error
Anxiety	108	53	18	0	18	5.482	30.055	8.40	0.528
Depression	108	46	19	0	19	5.148	26.502	7.61	0.495

the score varied quite. Diarrhoea and constipation were prevalent next in order and their magnitude had less variance. Reflux occurred in nearly half of the cases with clearly narrow variation of magnitude.

Table 2 summarizes HADS scores among the studied sample of IBS cases in general. Nearly half the cases suffered anxiety and slightly less had depression while a third (29) had significant presence of both the symptoms. It appears that these psychiatric co-morbidities have far varied contributions among IBS patients.

Overall improvement in particular symptoms following various treatment regimens was assessed for variance. Pain and diarrhea scores as well as overall GSRS scores significantly differed among the treatment groups. Significant differences were seen in outcomes of studied three regimens in respect to pain relief, diarrhea and overall GSRS scores. (Table 3 and Figure 1)

**Table 3**

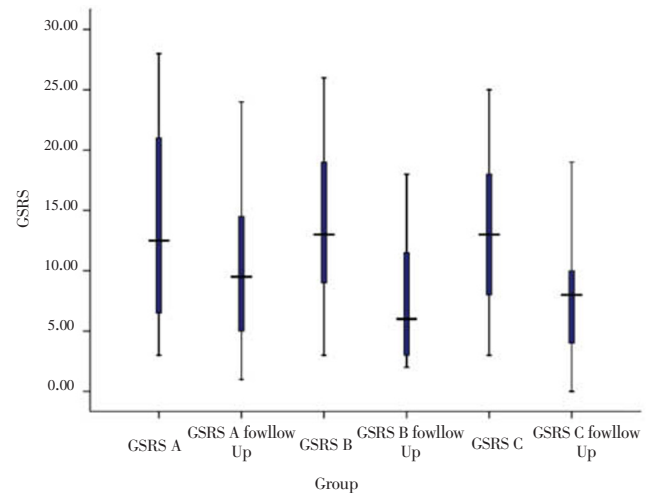
Post-treatment changes in symptom scores in various groups (Kruskal-Wallis ANOVA test).

	Treatment groups	ANOVA analysis			
		A	B	C	P value
Reflux	> Median	4	4	5	0.894
	$\leq$ Median	13	14	15	
Pain	> Median	7	20	24	0.000
	$\leq$ Median	25	15	17	
Indigestion	> Median	7	6	6	0.903
	$\leq$ Median	13	14	17	
Diarrhoea	> Median	4	14	15	0.009
	$\leq$ Median	15	10	13	
Constipation	> Median	1	1	0	0.763
	$\leq$ Median	6	4	7	
GSRS total	> Median	8	16	19	0.000
	$\leq$ Median	24	19	22	

**Table 4**

Distribution of symptom severity among various treatment groups (comparison of before and after treatment).

		Treatment groups								
		A			B			C		
		Pre	Post	P	Pre	Post	P	Pre	Post	P
Reflux	> Median	6	5	1	4	3	1	5	3	0.6948
	$\leq$ Median	11	12		14	15		15	17	
Pain	> Median	10	14	0.4390	13	5	0.0539	19	9	0.0352
	$\leq$ Median	22	18		22	30		22	32	
Indigestion	> Median	11	11	1	6	6	1	8	15	1
	$\leq$ Median	9	9		14	14		15	16	
Diarrhoea	> Median	5	4	1	12	4	0.0305	11	6	0.2448
	$\leq$ Median	14	15		12	20		17	22	
Constipation	> Median	3	2	1	3	3	1	3	3	1
	$\leq$ Median	4	5		2	2		4	4	
GSRS total	> Median	15	16	1	17	11	0.2223	20	9	0.0201
	$\leq$ Median	17	16		18	24		21	32	

**Figure 1.** Box-plots of overall GSRS scores pre and post treatment with median marks in various study groups.

Reflux symptoms were not improved significantly by any of the regimens, yet the outcomes were numerically better with riluzole. Both amitriptyline ( $P=0.0539$ ) and riluzole ( $P=0.0352$ ) regimens gave significant pain relief wherein outcomes with riluzole had superior level of statistical significance. Overall GSRS scores improved significantly solely in the riluzole treatment group ( $P=0.0201$ ). As a contrast, only amitriptyline regimen caused significant relief in diarrhea ( $P=0.0305$ ) and did not benefit in constipation. Riluzole did insignificantly reduce diarrhea better than the standard regimen A (Table 4).

Pain is significantly associated with degree of anxiety ( $P<0.0001$ ). Riluzole as well as amitriptyline regimens simultaneously relieved pain and anxiety. Another symptom diarrhea, also correlated to anxiety ( $P<0.0001$ ),

**Table 5**  
Spearman's correlation ( $\rho$ ) between symptoms with one-another (values indicate  $P$ )

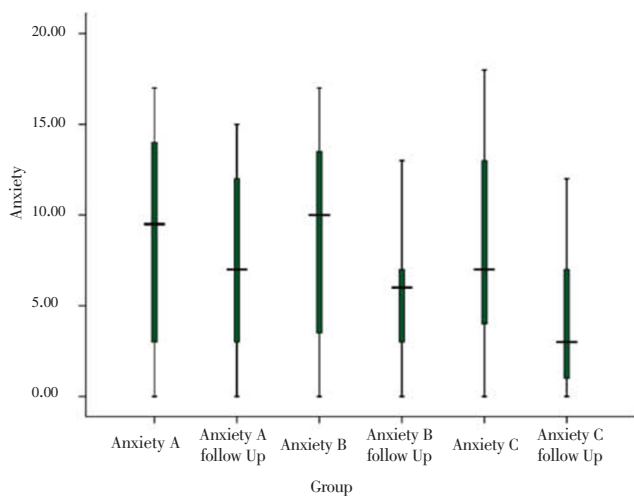
			Reflux	Pain	Indgs	Diarr	Const	GSRS	Anx	Depress
Spearman's rho ( $\rho$ )	Reflux	Correlation Coefficient	1.000	-0.090	-0.250	0.032	-0.047	0.025	-0.040	0.149
		Sig. (2-tailed)		0.512	0.098	0.872	0.896	0.854	0.771	0.278
	Pain	Correlation Coefficient	-0.090	1.000	0.190	0.668**	0.034	0.730**	0.650**	-0.124
		Sig. (2-tailed)	0.512		0.136	0.000	0.890	0.000	0.000	0.200
	Indigestion	Correlation Coefficient	-0.250	0.190	1.000	0.274	0.149	0.766**	0.197	0.261*
		Sig. (2-tailed)	0.098	0.136		0.143	0.596	0.000	0.121	0.039
	Diarrhoea	Correlation Coefficient	0.032	0.668**	0.274	1.000		0.667**	0.540**	-0.085
		Sig. (2-tailed)	0.872	0.000	0.143			0.000	0.000	0.480
	Constipation	Correlation Coefficient	-0.047	0.034	0.149		1.000	0.849**	0.156	0.915**
		Sig. (2-tailed)	0.896	0.890	0.596			0.000	0.523	0.000
	GSRS	Correlation Coefficient	0.025	0.730**	0.766**	0.667**	0.849**	1.000	0.510**	0.184
		Sig. (2-tailed)	0.854	0.000	0.000	0.000	0.000		0.000	0.056
	Anxiety	Correlation Coefficient	-0.040	0.650**	0.197	0.540**	0.156	0.510**	1.000	0.018
		Sig. (2-tailed)	0.771	0.000	0.121	0.000	0.523	0.000		0.854
	Depression	Correlation Coefficient	0.149	-0.124	0.261*	-0.085	0.915**	0.184	0.018	1.000
		Sig. (2-tailed)	0.278	0.200	0.039	0.480	0.000	0.056	0.854	

\*\* Correlation is significant at the 0.01 level (2-tailed).  
\* Correlation is significant at the 0.05 level (2-tailed).

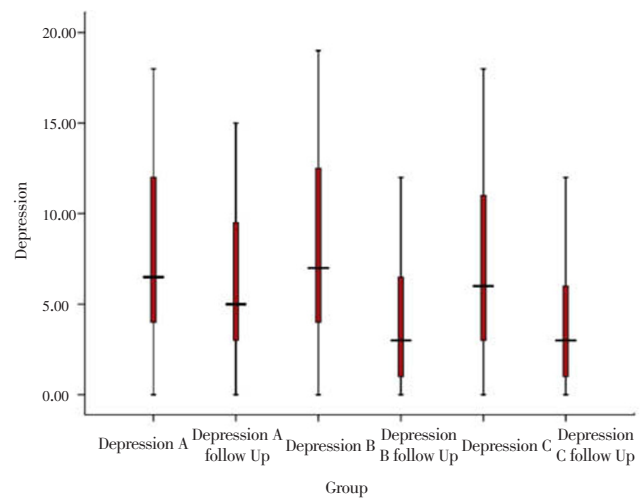
**Table 6**  
Pain relief with respect to basal anxiety scores with different treatment regimens.

		Pre-treatment anxiety score								
		Standard group (A)		$P$	Amitriptyline group (B)		$P$	Riluzole group (C)		$P$
		Above median	Below median	value	Above median	Below median	value	Above median	Below median	value
Post-treatment	Above median	9	3	0.0695	5	2	0.2075	7	2	0.0283
pain relief	Below median	7	13		11	17		11	21	

but significant improvement of diarrhea was seen selectively with amitriptyline ( $P=0.003$ ), not so much with riluzole. Despite correlation of depression to constipation ( $P<0.0001$ ), amitriptyline did not relieve constipation significantly (Table 5, Figure 2 and 3).



**Figure 2.** Box-plots of anxiety scores pre and post treatment with median marks in various compared groups.



**Figure 3.** Box-plots of depression scores pre and post treatment with median marks in various compared groups.

Table 6 shows that higher pain relief appears to occur more frequently in cases with higher anxiety scores and those with lesser anxiety frequently continued to get inferior pain relief. Such difference is significant both in standard therapy ( $P=0.0695$ ) and riluzole regimen ( $P=0.0283$ ) but not in amitriptyline regimen ( $P=0.2075$ ). This would suggest that the pain relieving effect of riluzole is more

specific and less dependent on anxiolytic mechanism.

#### 4. Discussion

Understanding of pain and its receptors is based on studies of somatic sensory system which leaves much regarding unique features of visceral pain<sup>[19]</sup>. Visceral pain therefore is managed rather poorly and drugs relieving somatic pain inflict adverse visceral effects. Pathophysiology of chronic visceral pain is beginning to be understood with focus on alterations in the peripheral and central nervous system. A number of receptors, neurotransmitters, cytokines and second messenger systems in the neurons are implicated in visceral hypersensitivity. NMDA receptors are found in the peripheral nervous system as well as central terminal of affected neurons and play important role in regulating release of nociceptive neurotransmitters<sup>[20]</sup>. Since visceral hypersensitivity in IBS typically exhibits spontaneous periods of flare and remissions, clinical evaluation of candidate remedies is difficult. It therefore becomes relevant to study results as function of subgroups based on clinical symptoms, with tendency to benefit with particular therapeutic approach.

Modulation of visceral nociceptive pathway can occur at peripheral, spinal and supraspinal sites<sup>[21]</sup>. Therefore compounds which hit several targets should offer superior therapeutic option. Glutamate is the major excitatory neurotransmitter and mediates visceral nociceptive neurotransmission and hypersensitivity. Removal of extracellular glutamate is predominantly mediated by glial glutamate transporter-1. The pharmacological approach to up-regulate glutamate transporter-1 with ceftriaxone has been successful in mitigating visceral nociception<sup>[22]</sup>. Riluzole is a positive regulator of glutamate transporter activity and has shown to attenuate neuropathic pain behaviors, indicating that changes in expression and uptake activity of spinal glutamate transporters may play a critical role in induction and maintenance of neuropathic pain<sup>[23]</sup>. This makes it a lead to explore development of specific therapy for visceral hypersensitivity in IBS<sup>[24]</sup>.

Most significant finding of the study is that adopting the standard CSRS score, both riluzole and amitriptyline regimens, not the standard regimen, resulted in significant improvement. Riluzole regimen distinctly renders significant relief of pain symptoms suffered by IBS cases, at least comparable to those given amitriptyline medication. The relief of anxiety does not appear to significantly contribute to pain relief produced by riluzole, which makes it more specific medication for IBS than the antidepressants. Anti-diarrheal benefit of amitriptyline may be consequent to anti-cholinergic effects. Amitriptyline does not relieve constipation despite association of constipation to depression. Both

these findings make amitriptyline as nonspecific drug for treating IBS. The development of visceral hyperalgesia involves alterations at transcriptional level caused by variety of stresses including some hazardous to very survival of the neurons. Riluzole and other benzothiazoles protect against transcriptional impact and adverse molecular networks following neuronal stress<sup>[25]</sup>. Suitability of riluzole for symptom relief as well as potential for prevention of neurodegenerative consequences associating visceral hypersensitivity do provide a new class of specific therapeutic agent for treating irritable bowel syndrome.

#### Conflict of interest statement

We declare that we have no conflict of interest.

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#### Comments

##### *Background*

The last decade has seen a tremendous surge of interest in the study of the augmented visceral sensitivity of the gut in several disease states. For further advance of this discipline, novel diagnostic tests and treatments are necessary but these await a clearer understanding of the mechanisms and pathophysiology of visceral sensation, with particular emphasis on effects of medications on antinociception. Riluzole is one such excellent candidate which needs to be evaluated.

##### *Research frontiers*

A prerequisite for correction of visceral hypersensitivity in IBS is a more thorough understanding of the transmitters or mediators involved in visceral hypersensitivity and the development of novel, selective approaches to target those transmitters. Preclinical data on role of riluzole in IBS is encouraging and clinical studies on this front are welcome.

##### *Related reports*

CSRS and HADS are valid and effective measures to evaluate their respective parameters. Statistical measures used here are appropriate and adequate.

##### *Innovations and breakthroughs*

Very few studies regarding role of riluzole are published. Little data, whatever available, is mostly pre-clinical



only. This study is a commendable effort to evaluate the encouraging results obtained in preclinical studies in a clinical form. More such studies targeting brain–gut axis should be encouraged.

### Applications

Riluzole is not only glutamate reuptake enhancer but also NMDA receptor antagonist. It can act in many ways in the central axis to counter the visceral pain. This study can be used as a reference study and studies of this type need to be encouraged on a larger patient population to get better inference for riluzole.

### Peer review

This is a prudent study which meticulously evaluates the action of riluzole on brain–gut axis in abating visceral hypersensitivity, using valid clinical scales and adequate statistical measures. Results are encouraging and exciting, and may act as a lead to future therapies.

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