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Research Article

A New Anxiolitic Approach With Passiflora Incarnata L., Herba In Patients With Irritable Bowel Syndrome And Comorbidy For Mild Anxiety Disorders: A Prospective, Observational, Real-Life Setting Study On 112 Patients.

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Abstract

Background: Irritable Bowel Syndrome (IBS) is a common disorder of gut-brain axis interaction associate with significant disease trouble. Visceral pain represents the cardinal symptom of patients with I.B.S. and has been attribuited to the malfunction of the brain-gut axis in the nervous system. A mood-modifier approach has been evaluated in multiple cinical trials on IBS. Our real life setting observational study aiming both to evaluate the activity of a new anxiolitic drug cointaning Passiflora Incarnata L., Herba on visceral pain sensation (abdominal pain) and on quality of stool. Adherence to treatment has also been evaluated in this setting of patients.
Methods: One hundred twelve (112) patients diagnosed with IBS according to Rome IV criteria and mild anxiety (Hamilton Anxiety Rating Scale between 8 – 14) have been enrolled in this prospective, real world, open clinical study. Every patient has been treated with two tablets daily (200 mg x 2) of a new drug (TRACTANA™) containing as active principle a dry extract of Passiflora Incarnata L., Herba. All the patients have been treated only with the test drug plus mediterranean diet. Two months after baseline evaluation (VAS for visceral pain and BFSF for stool formation) a second visit has been made to reasses visceral pain and stool formation and to evaluate adherence to treatment.
Results: After two months of treatment all the patients returned to the final control visit with a 100% of adherence to treatment. The medium score of BFSF statistically decreased from 4.88 to 4.29 ($p<0.006$) while visceral pain sensation median value at VAS also statistically decreased from 8.25 to 4.53 ($p<0.000$). All the patients reported an increase of their well being during the treatment period an no patient withdrawal the study during the treatment period. No patient developed adverse events to the study drug.
Conclusion: This real world study suggested that patients affected by IBS according to Rome IV criteria in comorbidity with mild anxiety disorders can improve both quality of stool and visceral pain sensation after two months of treatment with 2 tablets daily of a drug containing as active principle a dry extract of Passiflora Incarnata L., Herba. The adherence to treatment (100% of the patients returned to the final visit after two months), the improvement of well-being and the absence of adverse effects to the treatment seems to point out the role of Passiflora Incarnata L., Herba in the management of IBS patients with mild anxiety disorders.

Keywords : *Irritable Bowel Syndrome (I.B.S.), Mild Anxiety Disorders, Passiflora Incarnata L., Herba, Bristol Stool Form Scale (BSFS), Abdominal Pain.*

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INTRODUCTION

Irritable bowel syndrome (I.B.S.) can be considered as a common disorder of gut-brain interaction (DGBI)
(1) characterized by recurring symptoms of abdominal pain (visceral pain), bloating and altered bowel function in the absence of structural, inflammatory or biochemical abnormalities (2).
I.B.S. affects aproximately between 5 – 10% of the global population (3-4) and is more prevalent among females than in males also if this kind of prevalence rates vary considerably between countries and cultures (5).
Rome IV criteria define I.B.S. as "Recurrent abdominal pain on average at least 1 day/week in the last three months, associated with 2 or more of the following criterion fulfilled for the last three months with symptom onset at least 6 months prior to diagnosis (6):

1. Abdominal pain can increase related to defecation
2. Abdominal pain is associated with a change in frequency of stool
3. Abdominal pain is, associated with a change in form (appearance) of stool

Rome IV I.B.S. subtypes criteria are: IBS –C (more than one-fourth (25%) of bowel movements with Bristol Stool Types 1 – 2 and less than one-fourth (25%) with Types 6 - 7; IBS-D (more than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 6-7 and less than one-fourth (25%) with Types 1-2; IBS-M (more than one fourth (25%) of bowel movements with Bristol Stool Scale Types 1-2 and more than one- fourth (25%) with types 6-7; IBS-U (Patients meet diagnostic criteria for IBS but their bowel habits cannot be accurately categorized in any of the above subtypes) (6).
The term Functional Gastrointestinal Disorders (FGIDs) to which previously I.B.S. belonged, has recently been changed in the Rome IV criteria in the term Disorders of Gut-Brain Interaction (DGBI) to point out the central role of the Central Nervous System (CNS) in controlling functional gastrointestinal disorders (6).
The association between I.B.S. and anxiety/depressive disorders is high considering that people with I.B.S. have a threefold higher risk of anxiety and depression than healthy controls (1).
One meta-analysis shows a prevalence of anxiety disorders in 39% of patients affected by I.B.S. and of depressive disorders in 29% while the prevalence of co-occuring of both disorders was present in 23% (7).
Animal models and clinical studies in humans suggests a bidirectional link between gastrointestinal symptoms and psychological comorbidity that could be mediated by various mechanisms such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, immune activation and genetic habit (1).
The most important physiological link between I.B.S. and anxiety/depression disorders is obviously the gut- brain axis, the bidirectional, neurohumoral communication pathway that connects the gut and the brain through interaction between the autonomic nervous system, the HPA axis and the microbiome (1).
Genetic predisposition has been identified for anxiety, mood disorders and IBS (1).
A genome-wide analysis of more than 250.000 people affected by IBS pointed out shared genetic risk factors across these conditions (1)
The impact of IBS on daily activities is high: an high rates of abstenteism has been demostrated in IBS patients when confronted with no IBS patients (average of 13.4 days of work or school per year compared with 4.9 days for those without IBS) and , conversely, a low rates of presenteism (87% reported reduced productivity at work in the past week resulting in nearly 14 hours per week of lost productivity due to IBS) (8).
Multiple factors affect the development of physical symptoms in this co-occurring conditions: IBS pathophysiolosy involves visceral hypersensivity, disordered motility and modified immune, mucosal and microbial integrity and these actions could be triggered and perpetuated by psychological factors (9).
Anxiety related to gastrointestinal symptoms can be a key driver of gastrointestinal symptoms severity and can impaired quality of life in IBS (10).
As a results a treatment of anxiety disorders in patients in comorbidity with IBS can improve gastrointestinal symptoms such as abdominal pain and stool formation.
Benzodiazepines (BDZs) are effective to control anxiety disorders and are commonly used for IBS patients too as both type of pathologies often co-exist; these drugs are GABA A receptor enhancer and inhibit neural activity in the central nervous system (CNS) (11).
A lot of clinical studies have been performed by using BDZs in IBS with controversial results in patient with IBS alone leading to consider these drugs for IBS patients in comorbidity for anxiety disorders (11, 12)
Since it is safe to use these drugs for short-time for anxiety disorders because of long-term use cognitive impairment and other adverse mental and physical effects (11) we have performed a pilot, real world setting prospective assessment evaluating the effectiveness of a new OTC drug containing as active principle 200 mg of Passiflora Incarnata L., Herba dry extract according to EMA monography and marketed in 14 European countries in patients (TRACTANA®) affected by IBS (Rome IV criteria) in comorbidity for mild anxiety disorders (Hamilton Anxiety Rating Scale 8 – 14) (13) to control gastrointestinal symptoms related to I.B.S. such as abdominal pain and stool formation.

METHODS

We performed a real world setting evaluation on 112 outpatients 18 years or older (medium age 39.86 - SD 11.668) with a primary care diagnosis of IBS of any subtypes (IBS with costipation – IBS-C =34 patients; IBS with diarrhoea – IBS-D = 66 patients; IBS with mixed bowel habits = 12 patients; IBS unclassified- IBS-U = 0) and Mild Anxiety HAMA (13) enrolled between 2022 and 2024 according to Roma IV classification for IBS as DGPI (1).

All the patients collected an informed consent and the study was conducted in accordance with the Ethical statement of Helsinki Declaration.

All the enrolled patients were treated with a basic mediterranean diet and with a GABAergic drug (TRACTANA®) containing as active principle a dry extract of Passiflora Incarnata L., Herba (200 mg tablet – BID) for two months as only treatment medicine for IBS.

A diagnosis of IBS according to Rome IV criteria (6) and of mild anxiety according to Hamilton Anxiety Rating Scale (13) has been done at baseline (M0) for all the enrolled patients.

A VAS scale for abdominal pain (0 = no pain – 10 = severe pain) and a BRISTOL STOOL FORM SCALE (BSFS) was also collected for every patients at M0.

After 2 months of treatment all the patients were reassessed for abdominal pain (VAS) and for stool formation (BSFS).

The aim of the study was to determine whether administration of a dry extract of Passiflora Incarnata L., Herba treatment alone was effective in control gastrointestinal symptoms of IBS such as abdominal pain and quality of stool formation between M0 and M2 (after two months of treatment).

All the statistical analysis were performed by a per-protocol set: treated patients that had no major protocol violation and who were able to be evaluated for the primary endpoints after two months meet the minimum protocol requirements.

VAS for abdominal pain and BSFS for stool formation were espressed as means +/- SD and analyzed using the Student's two tailed paired T-test.

P values < 0.05 between M0 and M2 were considered to be stastically significant.

All the analysis were performed by using a computer based SPSS program (version 13.0).

The compliance of the patients to treatment as number of patients losting during the 2 months trial because of unefficacy of the study drug or adverse effect were also evaluated at the end of the study period.

RESULTS

A total of 112 outpatients with IBS diagnosed by Rome IV criteria have been enrolled in the real world observational study and a total of 112 patients completed the study (100% of patient's compliance to the treatment)

Demographic and baseline characteristics were reported in table 1

Table 1. Patient demographic characteristic (number of patients 112)

	Minimum	Maximum	Medium Value	DS
Age (years +/- DS)	19	64	39.86	11.668
Gender (male/female)	male = 11	female = 101		
IBS D (Rome IV criteria) =	number of cases 66			
IBS C (Rome IV criteria) =	number of cases 34			
IBS M (Rome IV criteria) =	number of cases 12			
IBS U (Rome IV criteria) =	number of cases 0			

Changes in IBS abdomnial pain scores were reported in table 2 and in fig 1

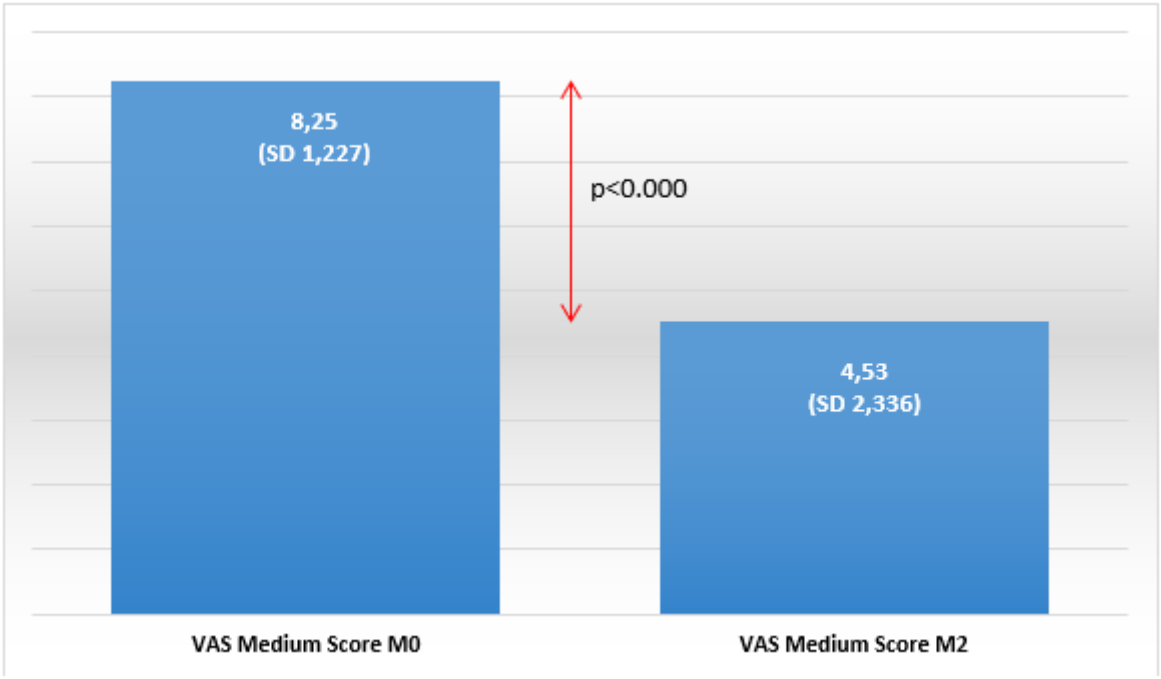
Abdominal pain has been detected by a Visual Analogue Scale (V.A.S.) (0 -10) by the investigator at the beginning of the trial (M0) and after 2 months (M2)

Table 2. Changes in abdominal pain between M0 and M2.

M0		M2
112	Number of patients	112
8.25	V.A.S. medium score	4.53
4 - 10	V.A.S range value	1 - 9
1.227	V.A.S. Standard Deviation (SD)	2.336

Student's two tailed paired T-Test (95% confidence interval) of V.A.S. medium score value between M0 and M2: p<0.000

Figure 1. Changes in VAS scores for abdominal pain between M0 and M2.



Changes in BSFS were reported in table 3 and in fig 2

BSFS is a validated scale to classify the STOOL FORMATION; it is a 7 point scale used extensively in clinical practice for stool form measurement .BSFS is an ordinal scale of stool types ranging from the hardest type (Type 1) to the softest (Type 7) (14).

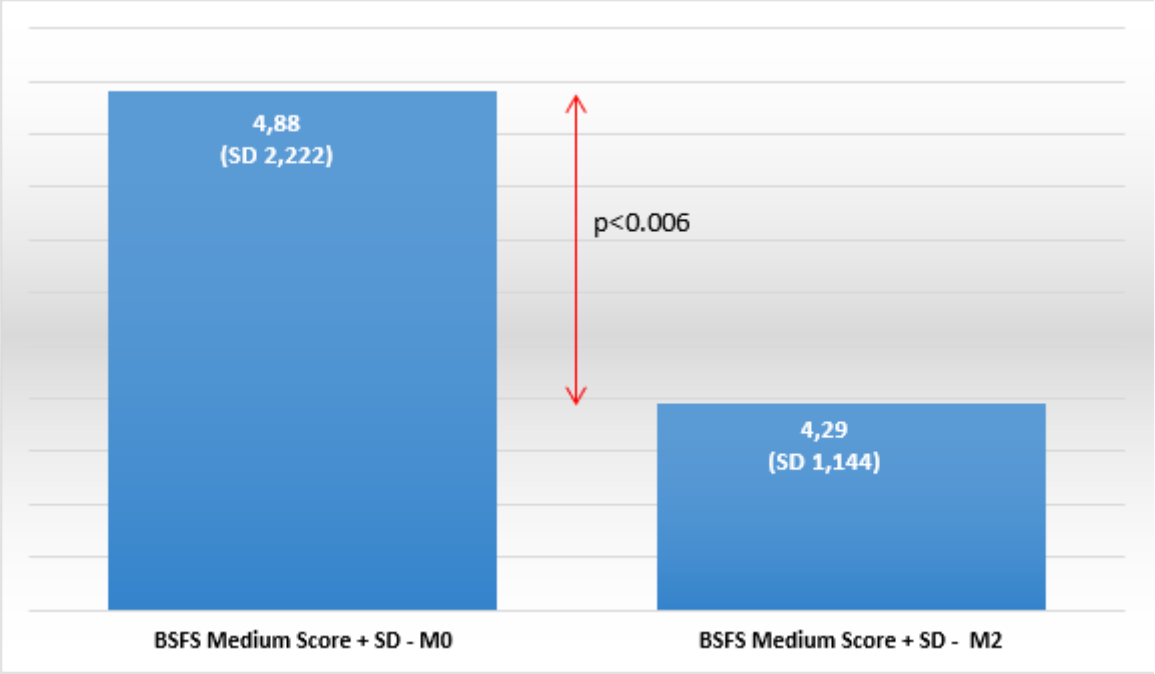
BRISTOL STOOL FORM SCALE (BSFS) (14)
Type 1 Separate, hard lumps, like nuts (hard to pass)
Type 2 Sausage-shaped but lumpy
Type 3 Like a sausage but with cracks on its surface
Type 4 Like a sausage or snake, smooth and soft
Type 5 Soft bloobs with clear cut edges (passed easily) Type 6 Fluffy pieces with ragged edges, a mushi stoll Type 7 Watery, no solid piece (entirely liquid)
Types 1 and 2 are considered to be abnormally hard stools indicating costipation while type 6 and 7 are considered abnoramly loose/liquid stools indicating diarrhoea.
Types 3, 4 and 5 are generally considered the most "normal" stool form and Type 4 represents the gold standard stool formation (14).
Stool consistency is a central component in the description of bowel habit and it is determined by stool water content.
Liquid stools are always related to the rapid intestinal transit that limits gastrointestinal water absorption while harder stool belong to slow intestinal transit with larger amount of water absorption (14).

Table 3. Changes in BSFS between M0 and M2.

M0		**M2**
112	number of patients	112
4.88	BSFS score medium value	4.29
1 -7	BSFS score range value	2 - 7
2.222	BSFS score SD	1.144

Student's two tailed paired T-Test (95% confidence interval) of BSFS medium score value between M0 and M2: p<0.006

Figure 2. Changes in BFSF between M0 and M2 + SD.



No patients during the trial and at the end of the study (M2) withdrawal from this real world setting study and no one refers adverse events to the treatment test so that the compliance of the patients to the study treatment was judged good from the Investigator (112 IBS patients have been enrolled in this study and 112 IBS patients returned after 2 months to the control visit).

DISCUSSION

According to Rome IV criteria abdominal pain and stool formation are critical in diagnosis of IBS and changes in bowel movements define different subtypes (6).

Usually, the abdominal pain is related to defecation or it's once is associated with a different intestinal habits that can be further exhacerbated by stressful life events therefore changes in the severity of abdominal pain are considered a reliable measure of treatment outcome (15, 16, 17).

In this real word setting evaluation we have determined the effectiveness of a 2 months treatment with a new drug containing as active principle 200 mg of a dry extract of Passiflora Incarnata L., Herba (TRACTANA®) 2 tabs daily in controlling abdominal pain by using a 0 – 10 VAS points scale.

Considering that the drug has beed administered as "unique drug treatment" together with a stantardized mediterranean diet for every patient it was surprising to point out that the pain score have been statistically reduced from M0 to M2 (from 8.25 to 4.53) without any gastrointestinal drug specific treatment.

Recently GABA receptors have been identified within the gastrointestinal system and it has been shown that among various GABAergic drugs some of them influence gastrointestinal stress related diseases (18).

So that it was not surprising that a GABAergic drug, such as a dry extract of Passiflora Incarnata L., Herba, could be useful not only in management of anxiety in IBS patients but also in controlling symptoms such as abdominal pain: the GABA B presinapic receptor antagonism of this drug with the re-uptake inhibition of the GABA from synaptic space demostrated activity could explain the evidence pointed out in our clinical real world setting study on outpatients affected by IBS (18).

Tractana®, a new OTC drug registered in 14 European Country according to EMA monography for mild anxiety disorders and for sleep disorders, has been shown a direct preclinical activity on CNS and expecially on GABAergic system by enhancing GABA trasmission via a reuptake inhibition of GABA B presinaptic receptors: this atypical mechanism of action, expecially when confronted with Benzodiazepines (GABAergic activity via GABA A post synaptic agonist effect), make the drug considered as the first GABARIs, (Gamma Ammino Butyrric Acid Reaptake Inhibitors) allowing to the drug a "physiological activity in increasing GABA trasmission without dependance, tolerance and daytime residual effects (18).

Considering the central role of the GUT-BRAIN AXIS in which the BRAIN was controlled by Benzodiazepines Receptors, GABA receptors and Psychological conditions that involves a NEURAL PATHWAY (5-HT, EPINEPHRINE, NOREPINEPHRINE, ACETYLCHOLINE, GABA) that control an ENDOCRINE PATHWAY (CHOLECYSTOKININ) and an IMMUNE PATHWAY (Increasing Proinflammatory Mediators such as IL-1, IL-6, TNF alpha, INF Gamma and decreasing Antiinflammatory Mediators such as IL-10) with a peripherial modulation on GABA receptors,

GUT and Enteric Nervous System (12) it seems reasonable that Benzodiazepines and the new GABARIs drug (Passiflora Incarnata L., Herba) could directly control IBS not only by an anxiolytic effects but also with perypheral direct activity on endocrine system and local immunomodulation as demostrated in a review of Salari P et Al (12) and in other trials (18, 24–26).

Also the results obtained by the test drug cointaining as active principle a dry extract of Passiflora Incarnata L., Herba on stool formation (a stastically significant reduction – $p<0.006$) from M0 to M2 in the BSFS (M0 = 4.88 and M2 = 4.29) with an improvement of gastro-intestinal motility seems to be related to both activity on the CNS and at Peripheral level of the drug. Obviously, this real word setting evaluation has a lot of methodologcal bias such as the the uncontrolled design, the non randomization of the patients, the open, un-blind design, the abscence of a medium-time evaluation (1 month), the absence of a long term follow-up of the patients and the short term treatment making this observation only “pilot” needing to be confirmed in double-blind, controlled clinical trials.

From the other side the high sample size of this real world setting evaluation together with the use of validated diagnostic criteria to include patients (Rome IV criteria) and to evaluate the primary end points such as VAS for abdominal pain and BSFS for stool formation seems to indicate “ a central role” of the GABARIs drug, such as Passiflora Incarnata L., Herba, in the management of I.B.S. without side effects and with a better compliance (no one patient withdrawal from the study). These results encourage to plan further controlled, double-blind clinical trials aimed to confirm our preliminary but interesting results in terms of efficacy and safety on I.B.S. not only in comorbidity with anxiety but also in I.B.S. without psychiatric co-morbidity.

CONCLUSIONS

In this large uncontrolled, real world setting clinical evaluation the Investigators use well-validated instruments to assess I.B.S. and mild Anxiety disorders and to point out drug effectiveness on the primary end-points (V.A.S. for gastrontestinal abdominal pain and BFSF for Stool Formation). A new drug containing as active principle a dry extract of Passiflora Incarnata L., Herba that has demostrated a GABAergic activity via an antagonist effect on GABA–B pre synaptic receptors (GABA reuptake Inhibitors) has shown to significant control abdominal pain and stool formation over a period of two months.

It is also important to point out the high compliance of the patients to this kind of treatment (no one patients of the 112 enrolled withdrawal the study) and the absence of adverse effects making this treatment, expecially if confronted with Benzodiazepines, safe and effective for patients affected by I.B.S. in co-morbidity with anxiety disorders, If this results will be confirmed in larger, double-blind controlled clinical trials we could underlined the role of the GABA control in the pathogenesis of I.B.S. and the role of this new class of drug (GABARIs) in the management of I.B.S. in co-morbidity with anxiety disorders.

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