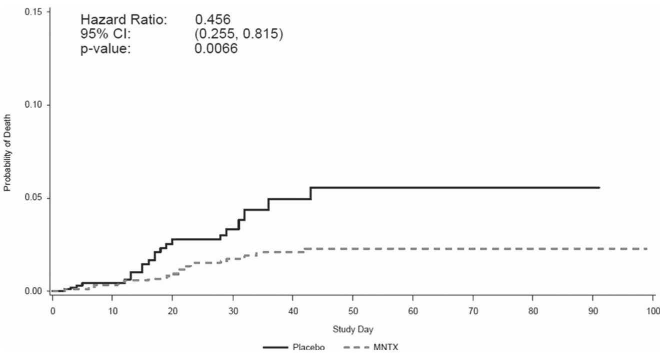
Methods: This analysis assessed all-cause mortality in patients enrolled in Phase 2 and Phase 3 PBO-controlled trials of MNTX for the treatment of opioid-induced constipation (advanced illness and noncancer pain patients) and postoperative ileus. The probability of death was calculated using the Cox proportional-hazards model, with a 2-sided test and significance level of 0.05, to compare the time to death for patients treated with MNTX versus PBO. Baseline cardiovascular risk factors were also assessed.
Results: Overall, 3,491 patients were treated with either MNTX (n=2,413) or PBO (n=1,078). Demographic characteristics were comparable in the MNTX (33.9% ≥60 years of age, 54.7% female, 38.9% with BMI ≥30) and PBO groups (38.7% ≥ 60 years of age, 54.5% female, 36.5% with BMI ≥30). Cardiovascular history and risk factors across all patients in the analysis included: hypertension (MNTX: 44.3%, PBO: 45.5%), hyperlipidemia/hypercholesterolemia (26.2%, 23.5%), diabetes (22.3%, 23.9%), angina (11.2%, 13.2%), myocardial infarction (13.2%, 13.1%), and stroke (11.3%, 12.2%). Some subjects had multiple risk factors. There were 25 deaths (rate=13.7 events per 100 person-years of exposure) in the MNTX group and 21 deaths (rate=31.4 events per 100 person-years of exposure) in the PBO group. The hazard ratio for risk of death in the MNTX group relative to the PBO group was 0.46 (p=0.007), corresponding to a relative reduction in risk of death of 54%.
Conclusion: In a pooled analysis of all-cause mortality in PBO-controlled trials of MNTX, a lower risk of mortality was observed in MNTX-treated patients.
Kaplan-Meier Curve of All-Cause Mortality in Placebo-Controlled Studies with Methylnaltrexone.
Disclosure - Lynn Webster: Consultant for AstraZeneca, Covidien Mallinckrodt, Nektar Therapeutics, Jazz Pharmaceuticals, CVS, Boehringer Ingelheim, Neura Therapeutik, Orexo, Quintiles, Theravance Darren Brenner: Consultant and speaker for Salix, Consultant for Perrigo, Speaker Bureau for Ironwood/Forrest Robert L. Rolleri: employee of and holds stock in Salix Pharmaceuticals, Inc. Andrew C. Barrett: employee of and holds stock in Salix Pharmaceuticals, Inc. Enoch Bortey: employee of and holds stock in Salix Pharmaceuticals, Inc. Craig Paterson: employee of and holds stock in Salix Pharmaceuticals, Inc. William P. Forbes: officer and employee of and holds stock in Salix Pharmaceuticals, Inc.



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Anti-vinculin Antibodies: Multicenter Validation of a Diagnostic Blood Test for Irritable Bowel Syndrome

ACG Governors Award for Excellence in Clinical Research

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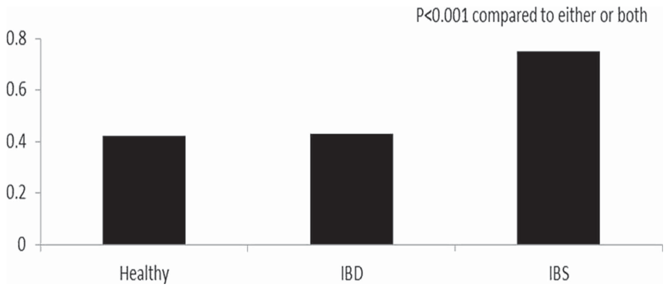
Purpose: Data have accumulated that a significant portion of irritable bowel syndrome (IBS) cases begin after acute gastroenteritis. Human and animal work suggests that exposure to acute gastroenteritis leads to small intestinal bacterial overgrowth (SIBO) through neuropathic events. Cytolethal distending toxin B (CdtB) from bacteria known to cause gastroenteritis is important in this process through molecular mimicry and auto-antibodies to vinculin (cell migration and adherence protein found predominantly on nerves and epithelium). In this multicenter study, we assess anti-vinculin antibodies as a predictor of IBS compared to healthy subjects and inflammatory bowel disease (IBD).
Methods: Subjects (18-65 years) with Rome-positive IBS were recruited from Cedars-Sinai Medical Center and Beth Israel Deaconess Medical Center. Subjects were assessed for symptoms and demographics followed by collection of sera. Subjects were excluded if they had concomitant GI disease, previous GI surgery, adhesions, unstable thyroid disease, diabetes, or HIV. Healthy controls were recruited based on the completion of a GI symptom questionnaire. On this questionnaire, subjects had to have marked <10 for bloating, diarrhea, abdominal pain, and constipation, inclusive on a 0-100 VAS. Subjects with IBD were recruited from an expert tertiary care medical center. Subjects with Crohn's disease or ulcerative colitis were excluded if there was a history of biologic therapy and current prednisone use. Serum from all three groups was used to perform and ELISA to determine antibodies to human recombinant vinculin.
Results: In total 165 IBS, 30 IBD, and 26 healthy control subjects were evaluated. Demographics were similar between groups. Overall, IBS had a significantly greater optical density in the ELISA for anti-vinculin antibodies compared to IBD and healthy subjects. Comparing the two major centers for IBS recruitment, results from both centers were similarly abnormal (P=NS). Interestingly, subjects with a history of acute gastroenteritis, even higher levels of antibodies were seen (p<0.05).
Conclusion: Anti-vinculin antibodies are elevated in IBS compared to non-IBS. This is the first diagnostic test for IBS based on serum and a pathophysiologic mechanism of IBS through acute gastroenteritis precipitated molecular mimicry and autoimmunity.



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PTSD, Depression, and Gastrointestinal Symptoms in Veterans of the Afghanistan and Iraq Conflicts: What's the Relation?

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Purpose: Veterans returning home from the Iraq and Afghanistan conflicts are entering the Veterans Affairs (VA) healthcare system with high rates of physical and psychological symptoms. Both veteran and non-veteran studies have reported high rates of comorbidity between post-traumatic stress disorder (PTSD), depression, and gastrointestinal (GI) symptoms. The aim of the current medical chart review is to evaluate associations between screening positive for PTSD and/or depression and reporting gastrointestinal (GI) symptoms at the initial visit to the VA clinic specifically for veterans from Iraq and Afghanistan (the Operation Enduring Freedom/Iraqi Freedom/New Dawn [OEF/OIF/OND] screening clinic).
Methods: A retrospective, cross-sectional chart review was conducted on 1,171 consecutive patients seen at the Northport VA Medical Center OEF/OIF/OND clinic for first visit appointments between January 2001 and December 2012. Data was extracted from the electronic medical record between October 2012 and February 2013. As has been federally mandated, all patients were given two screening questionnaires to assess PTSD and depression symptoms; this information was coded in our data as positive or negative screens for each. In addition, information about GI symptoms such as diarrhea, constipation, abdominal pain, and gastroesophageal reflux disease (GERD) were extracted from the clinic notes to determine if there is a relationship between PTSD and depression screenings and GI symptoms.
Results: Nearly 45% of patients screened positive for PTSD and 23% screened positive for depression symptoms. While only 11% of patients reported GI symptoms, 73.4% of these patients had a positive screen for PTSD, indicative of a significant relationship (OR 3.9; 95% CI 2.6-5.9). The five most common GI symptoms were diarrhea (55%), GERD (28%), abdominal pain (11%), constipation (11%), and IBS (9%). A positive screening of PTSD was significantly associated with these GI symptoms (ORs 3.5, 4.5, 6.6, 4.6, and 3.7, respectively). Similar results were found for a positive screening of depression, with one exception: depression was not significantly related to IBS. Significant ORs between depression and the other GI symptoms are as follows: diarrhea (2.8), GERD (2.0), abdominal pain (3.3), and constipation (4.6).
Conclusion: Veterans with a positive PTSD or depression screen may be more likely to have GI symptoms that should be screened for by their primary care physicians. These patients may benefit from both psychiatry and gastroenterology follow-up visits.

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Psychological Comorbidities in Dyspeptics and Their Relationship to Gastric Emptying

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Purpose: Dyspeptic patients, including the subpopulation with gastroparesis, may have psychological distress. Furthermore, this psychological distress may impact their clinical presentation and/or be a contributing factor in the pathogenesis of dyspepsia. Our aim was to measure psychological factors in dyspeptic patients in the context of symptom severity and gastric retention.
Methods: Data from medical histories, symptom (GCSI), and psychological (HADS: anxiety/depression; PHQ15: somatization; PANAS: positive/negative affect; PSS4: stress; TAS20: alexithymia) questionnaires, and 4-hour gastric emptying scintigraphy (GES) were obtained from consecutive patients referred for GES to evaluate dyspeptic symptoms. Logistic regression was used to further evaluate associations with abnormal gastric emptying after controlling for age, gender, and BMI.
Results: A total of 266 patients were enrolled (195 females; mean age 49.1 ± 17.6 years). Approximately 75% met Rome III criteria for functional dyspepsia. Gastric emptying was delayed in 33.1% at 2 hours and 28.2% at 4 hours; the delay was mild in 13.5%, moderate in 5.6%, and severe in 9%. Dyspeptic symptoms were measured before the GES. Symptom severity decreased during the GES (GCSI total score at baseline, 2 hour, and 4 hour: 2.44±1.01, 1.56±1.05, and 1.59±1.08, respectively). No difference in symptoms was seen in relation to normal or abnormal gastric emptying, irrespective of the severity of the delay. Although there were numerical trends for higher prevalence of anxiety, depression, and somatization in those with abnormal GES, these did not reach statistical significance. The depression score was higher (p=0.04) and positive affect score was lower (p=0.04) in those dyspeptics with an abnormal GES; a trend (p=0.059) toward higher alexithymia score was also noted, primarily due to a higher externally oriented thinking subscore (p=0.024). When stratified by the severity of gastric emptying delay (mild, moderate, severe), the only psychological factor that was statistically significant was depression (p=0.05), a finding driven by those with a mild delay in emptying (p=0.028). Results of the logistic regression analysis will be available for the meeting.

