LECTURE

Abuse, Trauma, and GI Illness: Is There a Link?

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Our understanding of the relationship of abuse and trauma history with gastrointestinal (GI) disorders has evolved over the last three decades. Although previously seen within a psychiatric context, ongoing studies continue to show that abuse can have multiple effects on GI symptoms, patient illness behaviors, and clinical outcomes. The prevalence of abuse history is greater among those who have more severe symptoms and who are seen in referral settings. Although abuse history may be present across all diagnostic categories, more severe abuse seems to occur in patients with functional GI disorders. The pathophysiological features that explain this association relate to stress-mediated brain–gut dysfunction and can range from altered stress-induced mucosal immune function to impaired ability of the central nervous system to downregulate incoming visceral or somatic afferent signals. For gastroenterologists and other health-care providers, it is important to understand when to inquire about an abuse history and what to do with that information. This is particularly relevant, as the data indicate that having a co-morbid abuse history leads to adverse health outcomes. Finally, there is growing evidence that centrally targeted interventions may have palliative effects on reducing symptoms, altering brain–gut dysregulation and structure, and improving the clinical outcome. This presentation tracks the history of our understanding of the effect of abuse and trauma on GI illness, provides the scientific rationale for this association, and offers guidelines as to when and how to inquire about this information and implement proper care for the patient.

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INTRODUCTION

Over the last several decades, the media, general public, and scientific community have noted an association of abuse history and other psychological life stressors with emotional and medical illness. In particular, and relevant to this paper, there has been growing awareness of the adverse health outcomes associated with abuse history among those with gastrointestinal (GI) symptoms. This knowledge is of more than passing interest given that this subset of GI patients are often high health-care utilizers, and they may challenge clinicians who feel limited in their ability to understand and care for them. My goal in this paper is to provide a summary of the knowledge about the association of abuse with GI symptoms and disorders (particularly functional GI disorders), their clinical impact, and the potential mechanisms to explain these effects. I will also provide an approach for the diagnosis and care of these patients.

I am honored to have been asked to present this overview; the topic has been a major area of my research and clinical practice for over 25 years. Back in the mid-1980s the association between abuse and GI illness was not recognized and was ignored, even denied. In fact, there was little scientific evidence available that abuse history could lead to anything but psychiatric consequences. For me, the challenge was to capture the emerging clinical observations being made, and link them to proper scientific inquiry.

At the time I had trained in Gastroenterology and had just joined the faculty at the University of North Carolina. I had previously completed a fellowship in Psychosomatic Medicine under the mentorship of George L. Engel, MD; Dr Engel, who first defined the term "Biopsychosocial Model" (1), was an icon in the psychosomatic field and a master of medical interviewing techniques. By acquiring both GI and biopsychosocial skills, I was comfortable with, and in fact quite interested in, seeing patients with complex and difficult-to-manage GI symptoms, patients whom my colleagues were eager to send to me. Understandably, my work soon gravitated toward seeing patients with painful and refractory functional GI disorders (FGIDs) or those with other structural diseases in which the pain reports and behaviors did not match the evident disease activity. What came up repeatedly was that these patients with severe and refractory symptoms were also disclosing histories of sexual and physical abuse. The reasons for such a link were not clear at first, but their association seemed highly prevalent, striking in its impact, and even predictable. The most notable example for me came when I saw an adolescent referred for abdominal pain and constipation. I followed this young woman for several years, never imagining at the time how much her story would shape my career (2).

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Case Report Part I: presenting as an adolescent with pain and constipation

A.L. a tall thin 12-year old was first scheduled to see me in May 1986 after having been hospitalized on the pediatric unit of the University of North Carolina Hospital for severe constipation and abdominal pain that began 5 years earlier. The constipation was associated with infrequent, but painful passage of hard stools every 10–12 days, and at times there were episodes of nausea and vomiting. She was treated on occasion with bronchodilators for recurrent asthma and was otherwise in good health. The medical evaluation was normal except for rectal and sigmoid dilatation seen on colonoscopy. A diagnosis of Hirschprung's disease was ruled out by a normal anorectal motility study and a rectal biopsy that showed ganglion cells. She left the hospital with a diagnosis of colonic inertia, and was prescribed mineral oil for laxation.

On the first visit, I made the commitment to continue to see her about 3–4 times a year along with her mother, who was a single parent. With symptomatic treatment, eventually the abdominal pain ameliorated, and her stool frequency increased to about 2–3 non-painful bowel movements every week. She did well in school, was socially active, and became a junior high-school cheerleader.

In mid-1989, at age 16, A.L. came for a routine visit and acknowledged that she was sexually active with a 19-year old, and was not using birth control. She agreed to return in a few weeks with her mother to discuss birth control options and to have a pelvic examination. On the next visit 1 month later, her condition had deteriorated. She was not eating well because of post-prandial pain and nausea, and had lost 4 lbs. She was feeling so poor that she gave up cheerleading, and her grades were falling. When asked why this was occurring, A.L. disclosed that right after the previous clinic visit she started having nightmares that gradually led to the recollection that from age 3 to 7, a friend of the family had sexually molested her. The mother indicated that when this was discovered the perpetrator left town, and her efforts to prosecute were unsuccessful. She told her daughter A.L. to "forget" about these traumatic events … and she did. Notably, her symptoms of abdominal pain and constipation began then, and they persisted as the dominant feature of her childhood, leading to frequent medical visits and hospitalizations; the earlier traumatic events remained out of memory until just preceding this clinic visit. Now she was intensely distressed, with full recollection of the events, and all her medical symptoms were in a flare.

I recognized this as the recovery of previously repressed memories, which was part of posttraumatic stress disorder (PTSD) (3). Over the next several visits, the patient discussed these traumatic experiences, and with the help of a counselor, we helped her to reduce feelings of shame, vulnerability, and responsibility. Concurrently, there was a gradual improvement in her GI symptoms and by age 18, in the winter of 1991, her symptoms were so much improved that the visits were discontinued.

SURVEY DATA

This account, along with similar ones from other patients, led me to believe there was a close link between abuse history and GI symptoms, but I also questioned whether my clinical observations were biased. Was I over-reading the data, or were these true clinical associations? A review of the literature reported mostly the consequences of abuse history on mental health, though a few studies noted that victims of abuse not infrequently reported GI and genitourinary symptoms (4,5). Similar to A.L.'s story, I was struck by a case series of 25 adolescent rape victims who were followed prospectively in a rehabilitation program (6). About half of the victims went through a period of denial of the rape event, and years later they returned for medical treatment with somatic symptoms, including abdominal pain, yet they did not recall the rape experience.

Therefore, our research group decided to survey our clinic patients to see how common abuse might be in a GI population (7). We administered a questionnaire over 2 months to a consecutive sample of all women coming to the UNC GI clinic. The survey contained questions on demography, health-care utilization, GI symptoms, and several sexual and physical abuse items borrowed from a national Canadian survey (8). Of 206 patients, strikingly, 89 (44%) reported sexual or physical abuse in childhood or later in life. Abuse history was found in all diagnoses, but those with FGIDs were more likely than those with structural diagnoses to report rape (odds ratio (OR) 2.1; 95% confidence interval (CI) 1.0–4.2) or frequent physical abuse (OR 11.4; 95% CI 2.2–58.4). In general, abuse history, regardless of diagnosis, was associated with more reports of pelvic pain (OR 4.1; 95% CI 1.4–11.7), multiple somatic symptoms (mean 7.1 vs. 5.8 symptoms; $P<0.001$), and lifetime surgeries (mean of 2.8 vs. 2.0; $P<0.01$). Notably, only about 17% of the patients with abuse history had discussed this with their physicians (this was reduced to 11% if my patients were excluded), and over 30% had not discussed the abuse with anyone. Thus, we were dealing with a hidden or non-disclosed event that potentially could be affecting the health status in these patients.

Although these data were surprising to the research team, more surprising was the response of others when we began to present the data at medical meetings. There was criticism of selection bias (although we consecutively recruited all clinic patients seeing all GI doctors), that we may have coerced patients to believe they were abused, i.e., "false memory syndrome" (though this was a confidential survey, not psychotherapy), or even that we misinterpreted the data. One noted gastroenterologist stated in a medical forum, "Abuse is not present in my patients; therefore, I do not ask them."

We believed that although the survey methods were methodologically sound, the high reporting frequency might relate to ascertainment bias; abuse history may lead to more severe symptoms, and these patients self-select or are preferentially referred to tertiary centers. This notion was supported several years later by Longstreth *et al.* (9). When using our same questionnaire in a large Health Maintenance Organization survey, they found that when compared with the prevalence of abuse in our patients with severe irritable bowel syndrome (IBS), the prevalence of abuse was 1/3 for mild IBS and 1/2 for moderate IBS in this setting. This supported

our hypothesis that the higher abuse rates relate to more severe symptoms and to patients referred to academic medical centers.

Later, a series of studies in the early 1990s also found a high prevalence of abuse among patients with GI conditions seen in other referral practices (30–56%) and in the general population (in Olmstead County, 41% of females and 11% of males) (10–14). Abuse history also seemed to be associated with patients reporting more IBS symptoms (15). In surveys, it was associated with an increased odds (OR 2.5; 95% CI 1.5–3.5) of having IBS, and of bringing these individuals to see physicians more often (OR 2.6; 95% CI 1.4–4.7)(14). But what was still needed was a well-characterized population of GI patients who could be properly identified by interview and then studied prospectively for the outcome effects.

CLINICAL DATA

Our group was fortunate to receive NIH support to evaluate our patients in a more rigorous manner (16–20). The design features included (16) (i) consecutive sampling of female patients; (ii) development and use of a standard questionnaire with operational definitions of abuse and validation by interview; (iii) administration of psychosocial assessment instruments to further characterize the study group; (iv) validation of medical diagnoses by the patients' physicians; (v) GI symptom assessment using diary cards and motility testing; and (vi) health status and utilization outcome assessment every 3 months using mailings over 1 year. However, because of the rigor of the design and the nature of assessment, only 33% of the subjects completed the study. For the most part, those screened for the study were similar to those completing the study, except that the latter group had a higher frequency of sexual abuse (49.4% vs. 38.2%; $P=0.011$). This suggests that, although the two groups were clinically similar, those with abuse history may have been more motivated to remain in the study.

The study led to several notable findings (16–20). (i) The prevalence of all abuse in this clinical setting (~50%; sexual or physical abuse, including touch rape and life threat) was not different based on functional vs. structural (organic) diagnosis, but those with functional diagnoses had more severe abuse (rape 33 vs. 20%, $P<0.03$; life threat 37 vs. 23%, $P<0.02$); (ii) those with abuse history had much poorer health status (measured as abdominal pain, days in bed, psychological distress, poorer daily function, and more physician visits and surgeries); (iii) there was a "dose effect," so those patients with rape had the poorest health status compared with those with less severe or no abuse, and those with physical abuse, including life threat, had poorer health status than those who had experienced physical abuse without life threat; (iv) patients with abuse history were more likely to report other symptoms (panic-like symptoms with palpitations and shortness of breath, depressive symptoms with fatigue and loss of appetite and sleep, and somatic symptoms with headaches, muscle aches, and pelvic pain); (v) abuse history and functional GI disorders had independent adverse effects on health status (As shown in **Figure 1**, when comparing diagnosis (functional and organic) and also abuse history on health status, those with functional diagnoses (after adjusting for abuse history) had poorer health status, and conversely, those with abuse history (after adjusting for diagnosis) also had poorer health status; furthermore, these effects were additive.); and (vi) of all variables studied, abuse severity was the strongest predictor of adverse health status (standard β 0.338; $P<0.0001$).

The data also indicated that abuse history was associated with other psychological factors such as maladaptive cognitions and coping, as well as anxiety, depression, and PTSD. Taking all these observations together, we created a model proposing that abuse history in combination with early-life factors led to susceptibility to GI symptoms and "body awareness," which could further be amplified by psychosocial co-morbidities. The combination of these factors leads to disability and high health-care utilization and referral status (**Figure 2**). To start to understand the potential mechanisms, we would wait another 10 years, until patient A.L. came back to see me.

Case Report Part II: as an adult with post-infectious IBS and recurrent abuse

Ms A.L. returned to see me in June 2000 at age 27. Her previous medical health had been good except for occasional hospitalizations for asthma and an episode in 1994 of possible autoimmune hepatitis that cleared after a brief course of prednisone. The reason for this visit was related to a 6-month history of diarrhea-predominant IBS that began promptly after developing *Clostridium difficile* colitis from amoxicillin/clavulanate prescribed for a severe asthma attack. Metronidazole and van-

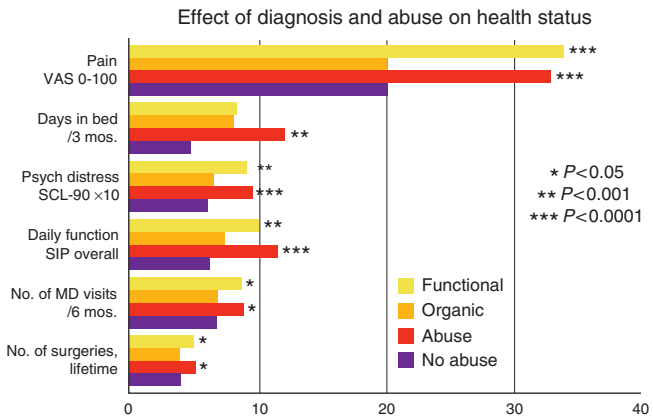

Figure 1. Effect of functional vs. organic diagnosis on abuse status. In this study of 239 women seen in the UNC tertiary care gastrointestinal (GI) clinic, 39% had a functional GI diagnosis (e.g., IBS, functional dyspepsia, etc.) and 61% an organic or structural diagnosis (e.g., inflammatory bowel disease, liver disease, etc.). A total of 60% reported a history of adult or childhood sexual or physical abuse. This figure compares these variables with regard to six health status measures: (i) abdominal pain on 0–100 visual analogue scale (VAS), (ii) no. of days in bed over 3 months, (iii) global score for psychological distress on SCL-90R, (iv) daily functional level on sickness impact profile, (v) no. of physician visits in the previous 6 months, and (vi) no. of lifetime surgeries. The bar graphs represent comparisons on these health status measures between functional (yellow) vs. organic (tan) diagnosis after adjusting for abuse history and abuse history (red) vs. no abuse history (purple) after adjusting for functional vs. organic diagnosis. Significant differences were seen with poorer health status for functional diagnosis and abuse history on virtually all health status measures. The data indicate that functional diagnosis and abuse history have independent adverse affects on the health status measures studied (16). SCL-90R, symptom checklist-90R; SIP, sickness impact profile.

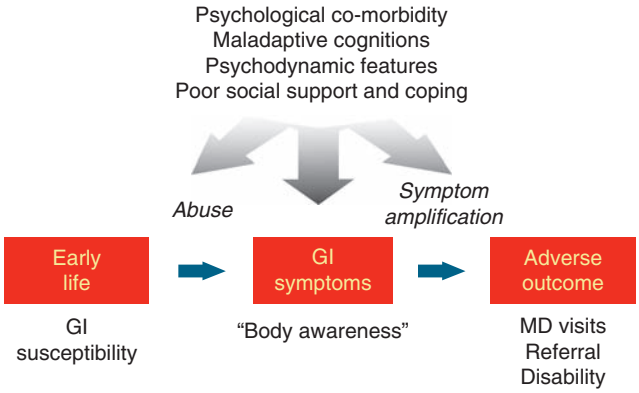

Figure 2. Conceptual relationship of abuse history and other psychosocial co-morbidities on gastrointestinal (GI) symptoms and adverse health outcomes. This model proposes that early-life factors (e.g., genetic factors, GI infection, and family environment) may be factors associated with susceptibility toward functional GI symptoms. Abuse history has an amplifying effect on the experience and clinical expression of these symptoms, which may be associated with greater "body awareness" due to the earlier trauma. Psychosocial factors as noted may further amplify the symptom experience and clinical state, leading to adverse health outcomes, including increased physician visits, referral gastroenterologists and referral centers and, when severe, disability. Figure modified from Drossman *et al.* (47).

comycin eradicated the bowel infection, but the post-prandial lower abdominal pain with diarrhea continued. The findings were consistent with post-infectious IBS.

The psychosocial history included the PTSD from the previous childhood abuse, and the development of obsessive–compulsive disorder late in adolescence, which was briefly treated with paroxetine. Now she was experiencing emotional and sexual abuse that developed during her 3-year marriage. A.L. believed that the previous abuse made interactions with her husband particularly difficult to cope with. She felt less able to assert her views or defend herself from his advances. Over the last several months, the abuse became worse, and this exacerbated the bowel symptoms. She was placed on Fluoxetine 20 mg and Alosetron 1 mg BID and was referred to a psychologist for cognitive behavioral treatment in addition to my ongoing care.

Over the next year, there was little improvement. A.L. surreptitiously obtained narcotics for pain control from other physicians, and the pain, nausea, and occasional vomiting and diarrhea continued to be of moderate severity. Although she talked about leaving her husband, she was unable to do so. She reported feelings of depression, helplessness, vulnerability, and poor self-esteem, and experienced catastrophic thoughts, stating that she could not continue with the symptoms and emotional distress she was experiencing. In addition, she stopped seeing her psychologist.

TOWARD UNDERSTANDING THE MECHANISMS OF EFFECT

Brain-imaging research

By the late 1990s, our group was seeking to understand the mechanisms for pain reporting in patients with IBS and abuse. Although visceral hypersensitivity was considered a factor in understanding IBS, it was not found to be as predictive of abdominal pain scores or adverse clinical outcome (16). Also, our group was finding that abuse history was not associated with lower visceral sensation threshold (21), and we later determined (22) that pain reporting in IBS seemed to be more related to central psychological factors such as response bias, rather than peripheral visceral neurosensory discriminating capability.

Accordingly, our research was directed toward the central mechanisms of effect: i.e., studying how the central nervous system (CNS) might explain the greater pain reporting among patients with FGIDs and abuse history (23). Concurrently, brain-imaging studies from other groups using positron emission tomography and functional magnetic resonance imaging (fMRI) were beginning to show (24,25) that IBS patients, when undergoing painful rectal distension, had greater activation of the rostral anterior cingulate (anterior midcingulate) than healthy subjects, a region of the brain that may be associated with the noxiousness of the pain experience. Therefore, we hypothesized that there may even be greater activation of this region in patients having IBS and abuse history, and perhaps the activation would decrease with clinical improvement.

Case Report Part III: clinical improvement

In August 2001, while still having severe symptoms, A.L. volunteered to participate in our study of brain imaging by functional magnetic resonance imaging in response to rectal distention and psychosocial assessment (2). Her questionnaires indicated clinically significant psychological distress, depression, high life stress, and poor coping and health-related quality of life. With rectal distension she scored 5 on the 5-point pain intensity scale, and the brain imaging (**Figure 3**) showed prominent activity in the rostral anterior cingulate cortex or anterior midcingulate (MCC) cortex, prefrontal areas 6/44, and the somatosensory cortex (top row, second and third images) consistent with earlier published data for IBS. Subsequently, the patient recovered from an inpatient detoxification, returned to weekly counseling, separated from her husband, and was placed on Luvoxamine, an antidepressant medication that is also helpful for OCD. Over the next several months she regained her self-confidence, experienced increased self-esteem, and felt less depressed with improved daily function and quality of life. Concurrently, the pain and diarrhea almost completely resolved.

In April 2002, 8 months after the first study, and during the period of clinical improvement, a second brain-imaging study was performed (**Figure 3**, bottom row). At this time there was minimal activation of the rostral anterior cingulate (anterior MCC), and there were smaller reductions in activity in the primary somatosensory cortex and frontal areas 6/44. These findings correlated with marked reduction in pain (score of 3/5 to rectal distention) when compared with the previous study. In addition, there was improvement in all measures of psychological distress, depression, and stressful life events, as well as improved coping and reduced health-care utilization.

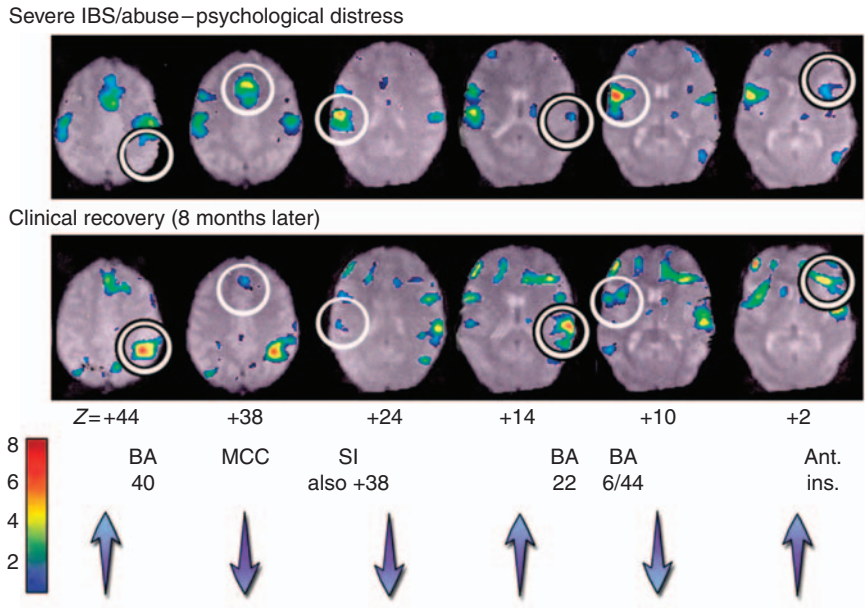

Figure 3. Functional magnetic resonance imaging (fMRI) imaging of A.L. with severe irritable bowel syndrome (IBS) symptoms and after recovery. This figure shows pairs of horizontal sections of fMRI studies in A.L. when she experienced severe IBS (top row) and after clinical recovery with both antidepressant and psychological treatment (bottom row) 8 months later. Images are a subtraction of bold signal generated during baseline rectal distension (15 mm Hg) from that at 50 mm Hg distension. The cortical areas with high initial activation during the severe IBS state on top are circled in white and include midcingulate cortex (MCC—second figure), primary somatosensory cortex (SI—third figure). Also noted on the bottom row are the reductions in cortical activity of the same two areas that may account for resolution of stimulus-evoked pain and psychosocial factors. See reference for more complete information. Reprinted with permission from Drossman *et al.* (2). BA, Broca's area.

The results from this one case report suggested a way using brain imaging to link abuse history and psychosocial distress with increased pain symptoms. The anterior midcingulate activation correlated with high rectal distension pain scores and psychosocial distress, and concordantly improved with clinical and psychosocial recovery. We now needed to understand whether the combination of abuse and IBS had synergistic negative effects on pain over and above those with IBS alone as previously reported clinically (16).

This information came several years later as we continued to study more patients. Eventually, we had evaluated four cohorts of patients, including the target group of five patients with IBS and abuse history, and a comparison group of patients with IBS alone ($n=4$), abuse history alone ($n=5$), or neither IBS nor abuse ($n=5$) (26). We questioned whether the combination of abuse and IBS history led to synergy, i.e., greater cingulate activation and pain scores when compared with the other three groups combined. As shown in **Figure 4a**, the subtraction images show greater activation for IBS and abuse in the anterior midcingulate (MCC) and posterior cingulate (PCC) cortex, with deactivation in the anterior cingulate cortex supragenual region (sACC), an area associated with down-regulation of pain signals. Furthermore, as shown in **Figure 4b**, the activation in the anterior and posterior cingulate was significantly associated with greater pain reporting at 50 mm rectal distention, and this was reflected in greater pain scores to the rectal distention compared with the three control groups combined (**Figure 4c**).

Thus, the co-occurrence of abuse history and IBS had synergistic effects: greater pain reports and poorer health status that was mediated via cingulate activation. Possibly, this area of activation might be a marker for the patient's clinical state of pain and distress and may even be responsive to treatments with psychotropic medication and psychological treatment as occurred with Ms A.L. In fact, two small studies so far have shown an effect of centrally targeted treatments, amitriptyline (27), and cognitive behavioral treatment (28) on cingulate activation. Further investigation will be needed to confirm this hypothesis.

Effects of war trauma on IBS development

Another line of information was accumulating that would further help us understand the possible mechanisms relating major psychological trauma on symptom experience and reporting with the diagnosis of IBS and other functional somatic disorders. The Federal Government commissioned the Institute of Medicine to report on the impact that deployment in a war zone could have on the mental and physical health of war veterans. I was asked to join the Institute of Medicine committee: Gulf War and Health, to study the effects on the digestive system disorders (29,30). The systematic review, as presented in the final report in April 2010 (31), found sufficient evidence for an association of war deployment with only a few clinical conditions: psychiatric disorders, including PTSD and generalized anxiety disorder, substance abuse, and also functional GI disorders. With regard to the FGIDs, the report stated:

> The committee concludes that there is sufficient evidence for an association between deployment to the Gulf War and gastrointestinal symptoms consistent with functional GI disorders, such as irritable bowel syndrome and functional dyspepsia.

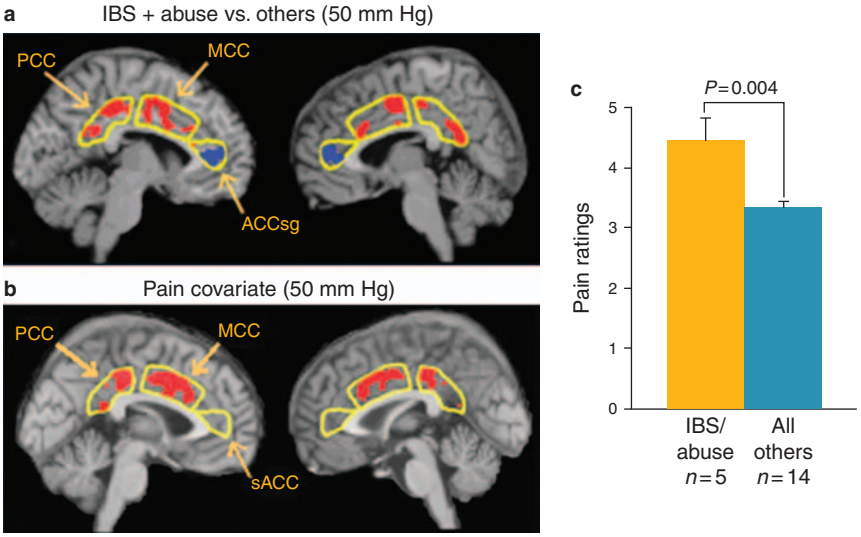

Figure 4. Composite figure comparing functional magnetic resonance imaging (fMRI) and pain scores of patients with irritable bowel syndrome (IBS) and abuse with those of controls of the fMRI study comparing patients with abuse history and IBS ($n=5$) with patients with abuse and no IBS ($n=5$), IBS and no abuse ($n=5$), and patients with neither IBS nor abuse ($n=4$) in response to painful 50-mm Hg rectal distension. As shown in (**a**), the subtraction images show greater activation for IBS and abuse in the anterior midcingulate (MCC) and posterior cingulate (PCC) cortex (red), with deactivation in the anterior cingulate cortex supragenual region (sACC—blue), an area associated with downregulation of pain signals. Furthermore, as shown in (**b**), the activation in the anterior and posterior cingulate was significantly associated with greater pain reporting at 50-mm rectal distention (magnitude of pain covariate shown as red). Finally, the bar graphs (**c**) indicate greater pain scores to the mean rectal distention for IBS and abuse group (4.5±0.3 score out of 5) compared with the three control groups combined (3.35±0.74 score out of 5; $P=0.004$). (**a, b**) Reprinted with permission from Drossman *et al.* (26).

This association was supported by the following lines of evidence that parallel those for post-infectious IBS in a setting of exposure to war trauma (30):

- The incidence of acquiring an acute gastroenteritis during deployment is >50%.
- Deployed vets experiencing war trauma who are also exposed to gastroenteritis are at greater risk to later develop IBS.
- Deployed vets with IBS symptoms have increased microscopic inflammatory changes in the bowel mucosa.
- Microscopic inflammation in IBS is associated with increased cytokine activity that may lead to enhanced visceral sensitivity and abdominal pain.
- Post infectious IBS symptoms are facilitated by psychological distress via CNS (hypothalamic–pituitary–adrenal axis), effects on mucosal inflammation, and enhanced pain via anterior cingulate cortex activation.

The data from the Institute of Medicine further support a brain–gut model of stress occurring at the time of exposure to a GI infection (32). Notably, Ms A.L. developed post-infectious IBS after *C. difficile* infection at the time of stress from marital abuse. This model is shown in **Figure 5**. IBS, for example, can develop after an enteric infection, which can produce dysmotility and mucosal inflammation along with increased mucosal permeability (33). The stressful experience can facilitate mast cell degranulation and release of peripheral corticotrophin-releasing hormone, a pro-inflammatory factor, along with inflammatory cytokines that sensitize myenteric neurons and lead to visceral hypersensitivity (34,35). In addition, at the central level, the stress of abuse or war trauma can increase anterior midcingulate activation, which is associated with disinhibition and lowering of pain thresholds. This combination of visceral and central sensitization enhances the experience of pain and other symptoms (26) (**Figure 5**).

Effects of central dysfunction on symptom reporting and somatization

Another important observation coming from this report is related to the evidence that returning vets exposed to war trauma tended to report many somatic and visceral functional complaints, but the prevalence of structural diseases was not increased. In effect, war trauma appears to lower the "sensation threshold" for symptom reporting in general. In one study, four diagnoses were seen to occur commonly: IBS, chronic fatigue syndrome, PTSD, and multiple chemical sensitivity. They clustered together so frequently that it was called "Gulf war syndrome" (36). Further analysis indicated that there were many symptoms reported, similar to patients with somatization disorder. The concept evolving was that we were dealing not so much with increased bodily disorders, but with some type of CNS dysfunction in the filtering mechanism for incoming visceral and somatic symptoms. It was as though a volume switch was turned up on a speaker. In fact, some studies show that there is a strong association between the number of symptoms reported and the level of anxiety and depression experienced (16,37), suggesting that another effect of traumatic exposure might be in the way in which the brain processes bodily signals.

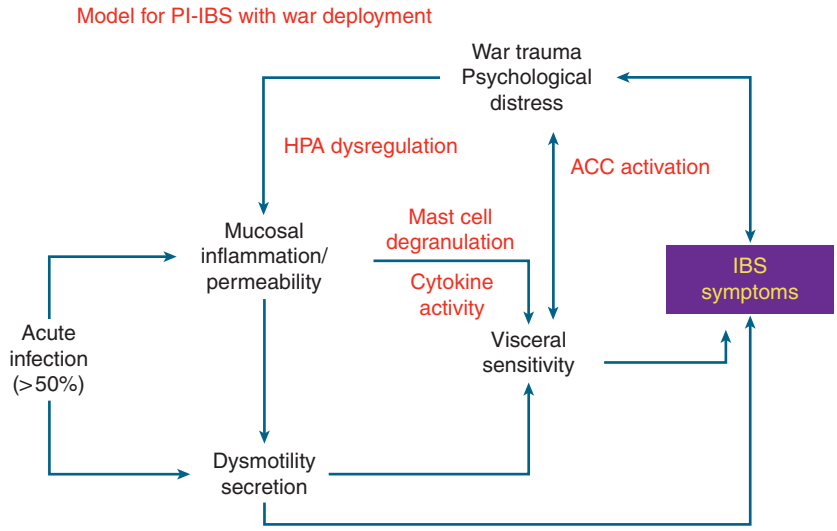

Figure 5. Conceptual model for post-infectious irritable bowel syndrome (PI-IBS) related to exposure to war trauma. IBS can develop after an acute enteric infection, and among soldiers in battle this can occur in over 50% of those deployed. The infection can produce intestinal dysmotility and secretion, as well as mucosal inflammation, leading to increased mucosal permeability. The stressful experience of war can facilitate possibly through hypothalamic–pituitary–adrenal dysregulation, direct neuroenteric action mast-cell degranulation, and release of peripheral corticotrophin-releasing hormone, a pro-inflammatory factor, along with other inflammatory cytokines. These factors can sensitize myenteric neurons and lead to visceral hypersensitivity. In addition, at the central level, the stress of abuse or war trauma can increase anterior midcingulate activation, which is associated with disinhibition and lowering of pain thresholds. This combination of visceral and central sensitization enhances the experience of pain and other symptoms.

This putative concept, the effect of war trauma on impairing CNS processing of incoming neural signals, leading to the reporting of clusters of symptoms and their co-occurrence with psychosocial distress and poor health status, is illustrated in **Figure 6**. IBS and the FGIDs are represented on the left, and also seen are other medical disorders as examples (yellow triangles). The relative prevalence of peripheral (outer part of the circle) to central influences (center) on pain and symptom severity is also displayed. As the severity of these conditions becomes greater, there is an increasing contribution of CNS factors and the disorder moves toward the center. Thus, with greater CNS input there is greater symptom severity associated with increased psychosocial distress, poorer health status, and poorer health-related quality of life. Thus, patients with the most severe symptoms share common psychosocial difficulties and other co-morbidities.

Clinically, it is not uncommon to see patients in the GI clinic with severe IBS and abuse history having psychosocial difficulties along with other functional somatic diagnoses, such as fibromyalgia, chronic fatigue syndrome, or chronic back pain. However, as gastroenterologists we may only be looking at one piece of the puzzle: these patients are going to other doctors for other conditions. These cohorts of patients are characterized by having previous trauma, psychosocial distress, and multiple somatic symptoms associated with central dysregulation of somatic and visceral input. They have a lower threshold for symptoms and report them more to others.

A BIOPSYCHOSOCIAL TREATMENT APPROACH

Approach to the patient

Given the scientific evidence of the association between abuse history and GI illness and the potentially adverse effects of this association on clinical outcome (16), it is important to elicit this history among patients at high risk and to then initiate appropriate referral with the expectation that the clinical condition will improve. The process of understanding and caring for the patients requires skill and sensitivity. Several factors need to be considered.

When to consider an abuse history. It is not an obligation for clinicians to ask patients about abuse when they are coming for GI problems. However, the discerning clinician needs to decide when the effects of an abuse history might interfere with proper clinical care. There are several clinical features that may alert the clinician to the possibility that a patient has experienced sexual, physical, or emotional trauma (**Table 1**). The items listed in **Table 1** are meant to be neither diagnostic nor inclusive; rather, they are guidelines from a literature review and my personal experience. Although none of these factors may be present, the greater the number of items present, the more likely that an abuse history may be contributing adversely to the clinical presentation. If the clinical care is compromised by these factors, identification of this history may be needed, as it may require further involvement of a mental health professional, which can provide concurrent care and help to optimize the clinical response.

The psychological factors relate to the ways in which previous or existing traumatic events are seen as a violation that erodes a sense of trust in others, leads to feelings of lack of control in life circumstances (often manifest with regard to lack of control over their illness), and results in helplessness, dependency, and shame. This may be exhibited in the interactions with health-care providers. Therefore, sensitivity is needed to understand these feelings and to avoid reacting in counter-therapeutic ways. The clinician needs

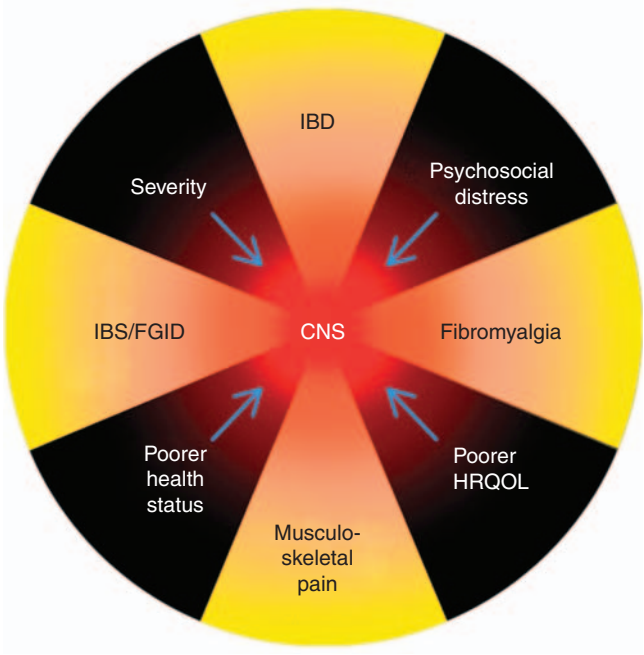

Figure 6. Relation of peripheral to central (central nervous system (CNS)) activity contributing to pain symptoms and health status in visceral and somatic medical disorders. This figure displays irritable bowel syndrome (IBS) and other functional gastrointestinal disorders (FGIDs) as a triangle on the left, and also seen as yellow triangles are other medical disorders. The periphery of the circle represents the larger proportion of patients with primary peripheral (visceral or somatic) contributions to the clinical condition. When moving toward the center, a less prevalent group of patients are seen to have greater central nervous system (CNS) influences on pain and symptom severity. Greater severity and CNS influence is also associated with increased psychosocial distress, poorer health status, and poorer health-related quality of life. Thus, patients having a variety of medical diagnoses when they display more severe symptoms tend to share psychosocial features and often share co-morbidities. HRQOL, health-related quality of life; IBD, inflammatory bowel disease.

Table 1. Factors suggesting an abuse history that may require intervention

Psychological factors
Difficulties establishing trust
Difficulties perceiving a sense of control over the illness and life events
Feelings of helplessness and dependency
Feelings of vulnerability, shame, and guilt
Gastrointestinal and other medical conditions
Chronic pain (including functional abdominal pain syndrome)
Severe constipation (slow transit constipation and pelvic floor dyssynergia)
Chronic pelvic pain
Narcotic bowel syndrome
Morbid obesity
Unexplained vomiting
Sexual dysfunction
Multiple functional GI and functional somatic conditions
Co-morbid psychiatric disorders
Anxiety disorders, including:
Posttraumatic stress disorder 309.81[a]
Obsessive–compulsive disorder 300.3
Panic disorders (300.01, 300.21)
Somatoform disorders, including:
Somatization disorder 300.81
Conversion disorder 300.11
Pain disorder (307.80, 307.89)
Dissociative disorders, including:
Dissociative amnesia 300.12
Dissociative identity disorder 300.14
Factitious disorders, including:
Factitious disorder with physical signs and symptoms 300.19
Malingering V65.2
Eating disorders, including:
Anorexia nervosa 307.1
Bulimia nervosa 307.51
Personality disorders, including:
Borderline personality disorder 301.83
Histrionic personality disorder 301.50
Illness-related behaviors
Strong denial that psychological factors may influence symptoms
Disability disproportionate to the clinical data
Frequent and excessive use of health-care services
Multiple diagnostic procedures, treatments, and surgeries
Marked anxiety and difficulties with procedures (endoscopy, vaginal, or rectal examinations)

to give patients choices in the care rather than enforce decisions. Certain GI and other medical conditions listed have more often been reported with histories of abuse (38–45). In particular, the presence of multiple medical diagnoses should prompt this consideration. Particular disorders, such as pelvic floor dyssynergia, morbid obesity, or sexual dysfunction, may have more direct links to the abusive experience. One recent meta-analysis of 23 studies from 1980 to 2008 showed a significant association between sexual abuse and lifetime diagnosis of FGIDs (OR 2.43; 95% CI 1.36–4.31), nonspecific chronic pain (OR 2.20; 95% CI 1.54–3.15), chronic pelvic pain (OR 2.73; 95% CI 1.73–4.30), and fibromyalgia specifically for rape (OR 3.35; 95% CI 1.51–7.46) (46). As listed, there are many co-morbid psychiatric disorders that are frequently associated with abuse history, and when present, further evaluation by a mental health professional may be helpful. Finally, there are several illness-related behaviors that define the degree to which symptoms are reported, and how thoughts and feelings are communicated or acted upon (47). In particular, these behaviors can directly impact the quality of the patient–physician interaction. For example, the clinician may have to acknowledge

Table 1. Continued.

"Borderline" behaviors (intense and chaotic emotional attachments, "splitting," difficulty with uncertainties)
Substance abuse (alcohol, medications, illegal drugs)
Disability seeking

GI, gastrointestinal.
Modified from Drossman *et al.* (47).
[a]Based on Diagnostic and Statistical Manual of Mental Disorders-IVR classification (66).

the patient's unwillingness or inability to address psychosocial issues rather than try to "correct" him or her, or may feel compelled to order more tests out of a sense of uncertainty when the patient has severe pain and disability out of proportion to the evident clinical data. Some patients may have intense emotional responses to endoscopic procedures or rectal or vaginal examinations or may refuse to have them done. This can be manifested by a startle response to touching, unanticipated tearfulness before or during the procedure, or cognitive or emotional dissociation during the procedure. If any of these signs occur, it can be an opportunity to gently and supportively inquire about the basis for these concerns and discontinue the procedure if needed. Finally, patients may also exhibit maladaptive health behaviors, including narcotic seeking and alcoholism, and may seek disability.

How to inquire about an abuse history. If it is judged that the data obtained indicate a need to inquire further about the possibility of abuse, one concern that may arise is whether asking about abuse might "open up Pandora's Box", that is, lead the patient to respond with a great deal of emotional distress that the clinician may feel ill equipped to manage. From personal experience with hundreds of patients and discussion with colleagues in the field of abuse and trauma, an uncontrollable situation is rarely, if ever, the case. Most patients who are aware of this history are often motivated to discuss their history, provided they sense that the person at the other end is willing to listen.

The inquiry can often be done over 5–10 min, provided it is discussed in a comfortable (distraction free) clinic environment and there is the option for additional time if further discussion or support is needed. Some clinicians may not feel they have the time or ability to do so, or may feel uncomfortable addressing the issues. In those cases it is understandable and appropriate to defer the inquiry and refer the patient to a mental health colleague if a reason for this referral can be developed, i.e., to help the patient in his/her adjustment to the illness, to develop coping strategies, or to address other factors that are affecting adequate management of the disorder(s).

Questioning should be done after a sense of rapport and mutual trust has been developed (47). This usually is done during the first visit. Rather than directly ask about abuse history, the clinician can follow the patient's lead and look for an opportunity. If during the medical history the patient refers to a difficult experience (e.g., "Things were pretty horrible back then…."), the patient can be encouraged to elaborate ("…it sounds like it was difficult; can you tell me more?"). If such information is not volunteered, the clinician can provide the opportunity to do so ("Is there anything else you would like to discuss that you think is important?"). If the information is still not forthcoming, the physician can ask more directly ("As you may know it's not uncommon these days for persons to have had unwanted emotional, physical or sexual experiences at some time in their life. This can affect how people manage with their medical condition. Has this ever happened to you?"). This approach communicates that the patient is not alone with this type of experience and also allows the patient to define victimization in personal terms. Importantly, the patient stays in control of the discussion and can choose to discuss what he or she feels is relevant and safe.

During this time, periods of silence must be permitted so the patient can collect thoughts and feeling in order to coherently present them. Some emotional distress is expected and should be permitted. A common behavior observed is for the clinician to quickly give the patient a tissue box to be helpful, but the patient may perceive this as an attempt to "close off" the emotion. Conversely, if the patient begins to change the discussion or physically turn away with arms folded, the physician should end that line of discussion and move to another topic. At times the patient may have concerns about the inquiry ("But what does this have to do with my pain?"). Here, it is important to communicate that this information may be medically important ("We often see that patients who have such difficult experiences can have more difficulty managing their condition. They may feel helpless or not in control of their symptoms, or even blame themselves. Those thoughts and feelings are not uncommon, and understanding them may help us find better ways to get you back in control"). I often find it helpful to discuss some of the newer data (as discussed above) about how high levels of distress can alter the brain's ability to control pain, and proper treatment can improve that.

The way in which the patient responds helps determine how to proceed. If the patient strongly denies this history but the nonverbal response is incongruent, the physician should register the information for future inquiry and say no more. If the patient acknowledges a history of abuse, the clinician should remain nonjudgmental and encourage the patient to continue. If the patient feels it is not relevant and does not want to pursue further discussion, the clinician will end the discussion and note that he/she is available for further discussion in the future if the patient desires. Obtaining the details of the experience is not as important as being supportive and empathic; this allows the patient to discuss memories, thoughts, and feeling in his or her own way, and can be therapeutic.

Making a referral. In the course of the discussion, if the patient freely and congruently discloses the abuse experience, the physician should acknowledge that he or she has shared important and meaningful experience and that they have clearly affected the patient's feelings and ability to cope with the illness. Therefore, referral for further psychological treatment to permit further discussion should be indicated. However, if the patient sees this as irrelevant, the clinician should clarify that referral to a mental

health professional helps in many ways: to help deal with feelings of helplessness and inability to cope with the illness, or to treat symptoms of anxiety and depression that can lower the symptom threshold. Finally, if the patient feels ashamed or embarrassed to discuss these experiences, the clinician can acknowledge that sharing such information must be difficult and it is ok to think about the possibility of referral in the future and that the clinician will continue to work with the patient on the medical issues. This is an important statement because some patients may think of referral as an abandonment of medical care.

The mental health consultant should serve as a member of the patient's health-care team and can take several roles as needed: (i) further elicit and help manage the dialog around the abuse history in a therapeutic manner, (ii) identify and treat co-morbid psychological conditions, (iii) initiate stress management or cognitive behavioral treatment or initiate treatments targeted toward patients with more severe abuse history (e.g., dialectic behavioral therapy or eye movement desensitization and reprocessing), or (iv) (when referring to a psychiatrist) to make recommendations on psychopharmacological treatment (see below).

Use of centrally targeted treatments

One therapeutic option available to the clinician in the care of patients with painful GI disorders, with or without abuse history or other psychological co-morbidities, is to initiate antidepressants and other centrally targeted medications. Ideally this is done concurrent with behavioral interventions because they have additive effects for patients with psychiatric and medical conditions (48,49). However, if the patient chooses not to see a mental health professional or if it is not clinically necessary, these medications can still be used to reduce symptom intensity, treat psychological co-morbidities such as anxiety and depression, and improve the overall well-being.

The three major antidepressant classes include the tricyclics or TCAs (desipramine, amitriptyline, and nortriptyline), the selective serotonin reuptake inhibitors (fluoxetine, paroxetine, citalopram, escitalopram, and sertraline) and the serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine, desvenlafaxine, and milnacipran). In general, we initially employ either a TCA or a serotonin norepinephrine reuptake inhibitor because of their enhanced pain benefit, or a selective serotonin reuptake inhibitor when there are dominant symptoms of anxiety, obsessive features, or phobic behaviors. Treatment is begun in modest dosages, increased to an optimal level of benefit, and continued for 6–12 months or longer. For further information on this management approach, the reader is referred elsewhere (50–52).

If single-medication treatments are not successful, we consider intensifying the treatment by using combinations of treatments to achieve synergistic effects. This concept of augmentation is the use of two or more treatments that function upon different receptor sites or areas of the brain to enhance the therapeutic effect. The medications can be used at lower dosages to minimize side effects (53). For example, we might use a low-dose selective serotonin reuptake inhibitor with a low-dose TCA, to address multiple symptoms of anxiety, depression, pain, and diarrhea. Here, the selective serotonin reuptake inhibitor provides relief of anxiety and the TCA helps to control the pain and diarrhea. For patients not responding to a single antidepressant, and who have associated anxiety and/or post-prandial early satiety, we might add buspirone to an antidepressant. This agent has a known ability to augment antidepressants (53) and also has peripheral effects that improve sensorimotor gut function (54,55). More recently, we have added a low-dose atypical antipsychotic (e.g., quetiapine) to a TCA or serotonin norepinephrine reuptake inhibitor to augment pain control, reduce anxiety, and enhance sleep (51,56).

Notably, recent investigations in psychiatry have begun to focus interest in the ability of antidepressants to have a more permanent effect on restoring normal neuronal function and structure. The concept of neuroplasticity, i.e., loss of cortical neurons with psychiatric trauma such as abuse and neurogenesis or regrowth of neurons with clinical treatment (57), is reshaping our understanding of psychiatric and possibly functional GI disorders. For over 10 years it has been recognized that patients with severe abuse history, either from sexual or from war trauma, lose neurons in critical areas of the brain, such as the hippocampus (58,59). A recent study using positron emission tomography imaging in response to gastric distention in patients with dyspepsia shows decreased hippocampal activation in those with an abuse history, suggesting that for this group of patients there may also be loss of neuronal structure in this region (60). Other data for patients with chronic painful conditions, including IBS, show reduced cortical neuron density in the cingulate and orbitofrontal cortex, areas associated with emotional and symptom regulation (61,62), though one other study did not support this finding in IBS (63) and confirmatory studies are needed.

If this is true, then an important question is whether treatment with centrally targeted medications may reverse this process of neuronal cell loss. Recent theories of neurogenesis propose that behavioral and antidepressant treatment may potentially help regrow these neurons, and possibly re-establish normal cortical or even myenteric neuronal growth (50,57,64), possibly restoring more normal neural function. Within psychiatry, longer treatment with antidepressants is associated with a lower rate of relapse, possibly because it takes more time to restore lost neurons to produce clinical recovery from psychiatric disorders (65). We apply this method of relapse prevention in our clinic by keeping patients on antidepressants for their painful FGIDs for at least a year in order to see a more optimal clinical response. Thus, with the benefit of future studies, we may see that behavioral and centrally targeted medications may do more than just treat the symptoms; they may restore normal structure and function to the areas damaged by the trauma of abuse.

CONCLUDING COMMENT

The role of abuse and trauma history in medical and in particular GI illness and the scientific basis for this association have evolved over the last three decades. Rather than being seen solely within a psychiatric context, we now understand that there are multiple effects on medical symptoms, illness behaviors, and clinical outcomes. The

scientific basis for understanding these associations embraces many aspects of the brain–gut axis. For gastroenterologists, abuse history can be highly prevalent in the patients they see and can have a major impact on the clinical care that needs to be provided. Therefore, understanding this association and knowing when to inquire about abuse history and how to provide directed care is an obligation, particularly for patients with more severe GI symptoms. Hopefully, the information provided herein will be of help to the patients and their providers.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ There is growing knowledge on the role of abuse history in gastrointestinal (GI) illness, but the reason for this association is not known.
- ✓ Physicians, although aware of the possibility of abuse history affecting GI illness, may not feel skilled to know when and how to get this information or what to do with the information once obtained.

WHAT IS NEW HERE

- ✓ Abuse history is common in GI practice and is more prevalent in patients with more severe symptoms or who are seen in referral academic practice.
- ✓ Patients with functional GI diagnoses tend to have more severe abuse history.
- ✓ There is new knowledge on the pathophysiological determinants related to stress-mediated brain–gut dysfunction.
- ✓ This presentation offers further information on the impact and mechanisms for the role of abuse history in GI illness and provides guidelines to help the clinician identify when to obtain this history and how to use this information to obtain referral or optimal patient care.

REFERENCES

1. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129–36.
2. Drossman DA, Ringel Y, Vogt B *et al.* Alterations of brain activity associated with resolution of emotional distress and pain in a case of severe IBS. Gastroenterology 2003;124:754–61.
3. Calhoun KS, Resick PA. Post-traumatic stress disorder. In: Barlow DH (ed). Clinical Handbook of Psychological Disorders, 2nd edn. Guilford Press: New York, NY, 2009, pp. 48–62.
4. Bachmann G, Moeller T, Bennett J. Childhood sexual abuse and the consequence in adult women. Obstet Gynecol 1988;71:631–42.
5. Rimsza ME, Berg RA, Locke C. Sexual abuse: somatic and emotional reactions. Child Abuse Negl 1988;12:201–8.
6. Felice M, Grant J, Reynolds B *et al.* Follow-up observations of adolescent rape victims. Clin Pediatr 1978;17:311–5.
7. Drossman DA, Leserman J, Nachman G *et al.* Sexual and physical abuse in women with functional or organic gastrointestinal disorders. Ann Intern Med 1990;113:828–33.
8. Badgley R, Allard H, McCormick N *et al.* Occurrence in the Population. Sexual Offences Against Children, 1st edn, Vol 1. Canadian Government Publishing Centre: Ottawa, 1984, pp. 175–93.
9. Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees. Prevalence, demographics, and clinical correlates. Dig Dis Sci 1993;38:1581–9.
10. Talley NJ, Helgeson S, Zinsmeister AR. Are sexual and physical abuse linked to functional gastrointestinal disorders? Gastroenterology 1992;102:A523.
11. Scarinci IC, Haile JM, Bradley LA *et al.* Pain perception and psychosocial correlates of sexual/physical abuse among patients with gastrointestinal disorders. Gastroenterology 1992;102:A509.
12. Delvaux M, Denis P, Allemand H. French Club of Digestive Motility. Sexual and physical abuses are more frequently reported by IBS patients than by patients with organic digestive diseases or controls. Results of a multicenter inquiry. Eur J Gastroenterol Hepat 1997;9:345–52.
13. Leroi AM, Bernier C, Watier A *et al.* Prevalence of sexual abuse among patients with functional disorders of the lower gastrointestinal tract. Int J Colorect Dis 1995;10:200–6.
14. Talley NJ, Fett SL, Zinsmeister AR *et al.* Gastrointestinal tract symptoms and self-reported abuse: a population-based study. Gastroenterology 1994;107:1040–9.
15. Talley NJ, Fett SL, Zinsmeister AR. Self-reported abuse and gastrointestinal disease in outpatients: association with irritable bowel-type symptoms. Am J Gastroenterol 1995;90:366–71.
16. Drossman DA, Li Z, Leserman J *et al.* Health status by gastrointestinal diagnosis and abuse history. Gastroenterology 1996;110:999–1007.
17. Leserman J, Drossman DA, Li Z *et al.* Sexual and physical abuse in gastroenterology practice: how types of abuse impact health status. Psychosom Med 1996;58:4–15.
18. Leserman J, Li Z, Drossman DA *et al.* Impact of sexual and physical abuse dimensions on health status: development of an abuse severity measure. Psychosom Med 1997;59:152–60.
19. Leserman J, Li Z, Drossman DA *et al.* Selected symptoms associated with sexual and physical abuse history among female patients with gastrointestinal disorders: the impact on subsequent health care visits. Psychol Med 1998;28:417–25.
20. Drossman DA, Li Z, Leserman J *et al.* Effects of coping on health outcome among female patients with gastrointestinal disorders. Psychosom Med 2000;62:309–17.
21. Whitehead WE, Crowell MD, Davidoff AL *et al.* Pain from rectal distension in women with irritable bowel syndrome: relationship to sexual abuse. Dig Dis Sci 1997;42:796–804.
22. Dorn S, Palsson OS, Thiwan SM *et al.* Increased colonic sensitivity in irritable bowel syndrome is the result of increased perceptual response bias rather than increased perceptual sensitivity. Gastroenterology 2006;130 (4 Suppl 2): A-443.
23. Drossman DA. Brain imaging and its implications for studying centrally targeted treatments in IBS: a primer for gastroenterologists. Gut 2005; 54:569–73.
24. Naliboff BD, Derbyshire SWG, Munakata J *et al.* Cerebral activation in irritable bowel syndrome patients and control subjects during rectosigmoid stimulation. Psychosom Med 2001;63:365–75.
25. Verne GN, Himes NC, Robinson ME *et al.* Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. Pain 2003;103:99–110.
26. Ringel Y, Drossman DA, Leserman JL *et al.* Effect of abuse history on pain reports and brain responses to aversive visceral stimulation: an fMRI study. Gastroenterology 2008;134:396–404.
27. Morgan V, Pickens D, Gautam S *et al.* Amitriptyline reduces rectal pain-related activation of the anterior cingulate cortex in patients with irritable bowel syndrome. Gut 2005;54:601–7.
28. Lackner JM, Coad ML, Mertz HR *et al.* Cognitive therapy for irritable bowel syndrome is associated with reduced limbic activity, GI symptoms, and anxiety. Behav Res Ther 2006;44:621–38.
29. Mayeux R, Drossman DA, Basham KK *et al.* Gulf War and Health: Physiologic, Psychologic, and Psychosocial Effects of Deployment-Related Stress. The National Academies Press: Washington, DC, 2008.

30. Institute of Medicine. Gulf War and Health: Update of Health Effects of Serving in the Gulf War, 8, 1–298. 2010. The National Academic Press: Washington, DC.
31. Institute of Medicine. Gulf War and Health: Update of Health Effects of Serving in the Gulf War: Diseases of the Digestive System, 8, 155–163 2010. The National Academic Press: Washington, DC.
32. Drossman DA. Mind over matter in the postinfective irritable bowel. Gut 1999;44:306–7.
33. Ohman L, Simren M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. Nat Rev Gastroenterol Hepatol 2010;7:163–73.
34. Soderholm JD, Perdue MH. Effect of stress on intestinal mucosal functions. 2006.
34. Barbara G, Wang B, Stanghellini V *et al.* Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. Gastroenterology 2007;132:26–37.
36. Gray GC, Reed RJ, Kaiser KS *et al.* Self-reported symptoms and medical conditions among 11,868 Gulf War-era veterans: the Seabee Health Study. Am J Epidemiol 2002;155:1033–44.
37. Vaccarino AL, Sills TL, Evans KR *et al.* Multiple pain complaints in patients with major depressive disorder. Psychosom Med 2009;71:159–62.
38. Leroi AM, Berkelmans I, Denis P *et al.* Anismus as a marker of sexual abuse. Dig Dis Sci 1995;40:1411–6.
39. Felitti VJ. Long-term medical consequences of incest, rape, and molestation. South Med J 1991;84:328–31.
40. Clouse RE, Mayer EA, Aziz Q *et al.* Functional abdominal pain syndrome. In: Drossman DA, Corazziari E, Delvaux M, *et al.* (eds). Rome III: The Functional Gastrointestinal Disorders, 3rd edn. Degnon Associates, Inc.: McLean, VA, 2006, pp. 557–93.
41. Salmon P, Skaife K, Rhodes J. Abuse, dissociation, and somatization in irritable bowel syndrome: towards an explanatory model. J Behav Med 2003;26:1–18.
42. Reiter RC, Shakerin LR, Gambone JC *et al.* Correlation between sexual abuse and somatization in women with somatic and nonsomatic chronic pelvic pain. Am J Obstet Gynecol 1991;165:104–9.
43. Harrop-Griffiths J, Katon W, Walker E *et al.* The association between chronic pelvic pain, psychiatric diagnoses, and childhood sexual abuse. Obstet Gynecol 1988;71:589–94.
44. Grunkemeier DMS, Cassara JE, Dalton CB *et al.* The narcotic bowel syndrome: clinical features, pathophysiology, and management. Clin Gastroenterol Hepatol 2007;5:1126–39.
45. O'Brien S, Hyman N, Osler T *et al.* Sexual abuse: a strong predictor of outcomes after colectomy for slow-transit constipation. Dis Colon Rectum 2009;52:1844–7.
46. Paras ML, Muramoto MH, Chen LP *et al.* Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis. JAMA 2009;302:550–61.
47. Drossman DA, Talley NJ, Olden KW *et al.* Sexual and physical abuse and gastrointestinal illness: review and recommendations. Ann Intern Med 1995;123:782–94.
48. Keller MB, McCullough JP, Klein DN *et al.* A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342:1462–70.
49. Holroyd KA, O'Donnell FJ, Stensland J *et al.* Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination. JAMA 2001;285:2208–15.
50. Drossman DA. Beyond tricyclics: new ideas for treating patients with painful and refractory functional GI symptoms. Am J Gastroenterol 2009;104:2897–902.
51. Grover M, Dorn SD, Weinland SR *et al.* Atypical antipsychotic Quetiapine in the management of severe, refractory functional gastrointestinal disorders. Dig Dis Sci 2009;54:1284–91.
52. Grover M, Drossman DA. Psychotropic agents in functional gastrointestinal disorders. Curr Opin Pharmacol 2008;8:715–23.
53. Trivedi MH, Fava M, Wisniewski SR *et al.* Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006;354:1243–52.
54. Chial HJ, Camilleri M, Ferber I *et al.* Effects of venlafaxine, buspirone, and placebo on colonic sensorimotor functions in healthy humans. Clin Gastroenterol Hepatol 2003;1:211–8.
55. Tack J. Prokinetics and fundic relaxants in upper functional GI disorders. Curr Opin Pharmacol 2008;8:690–6.
56. Baune BT, Caliskan S, Todder D. Effects of adjunctive antidepressant therapy with quetiapine on clinical outcome, quality of sleep and daytime motor activity in patients with treatment-resistant depression. Hum Psychopharmacol 2007;22:1–9.
57. Perera TD, Park S, Nemirovskaya Y. Cognitive role of neurogenesis in depression and antidepressant treatment. Neuroscientist 2008;14:326–38.
58. Bremner JD, Randall P, Vermetten E *et al.* Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. Biol Psychiatry 1997;41:23–32.
59. Bremner JD, Innis RB, Ng CK. Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. Arch Gen Psychiatry 1997;54:246–54.
60. Van OL, Vandenberghe J, Dupont P *et al.* Regional brain activity in functional dyspepsia: a H(2)(15)O-PET study on the role of gastric sensitivity and abuse history. Gastroenterology 2010;139:36–47.
61. Blankstein U, Chen J, Diamant NE *et al.* Altered brain structure in irritable bowel syndrome: potential contributions of pre-existing and disease-driven factors. Gastroenterology 2010;138:1783–9.
62. Valet M, Gundel H, Sprenger T *et al.* Patients with pain disorder show gray-matter loss in pain-processing structures: a voxel-based morphometric study. Psychosom Med 2009;71:49–56.
63. Seminowicz DA, Labus JS, Bueller JA *et al.* Regional gray matter density changes in brains of patients with irritable bowel syndrome. Gastroenterology 2010;139:48–57.
64. Gershon MD, Liu MT. Serotonin and neuroprotection in functional bowel disorders. Neurogastroenterol Motil 2007;19:19–24.
65. Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol 2008;11:1169–80.
66. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders—DSM-IV, 4th edn. American Psychiatric Association: Washington, DC, 1994.