Benzodiazepines' role in managing gastrointestinal disorders

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Benzodiazepines have been used broadly in gastroenterology, for instance in treating anxiety symptomatology associated with gastrointestinal (GI) illness, or in treating some underlying conditions (e.g., addressing alcohol dependence in liver disease), or in various diagnostic endoscopy procedures, and in preparation for surgery. It is known that anxiety and GI symptomatology/disorders frequently co-exist, with anxiety exacerbating GI disorders, and some GI symptoms provoking anxiety.

Association of anxiety and GI symptomatology

The complex relationship between anxiety and GI symptomatology has attracted limited attention over the years. In a study by Esler and Goulston (1) patients with the irritable-colon syndrome who had predominantly diarrhea were significantly more anxious and more neurotic than the control population of general medical patients. When analyzing results of the Epidemiological Catchment Area study, Walker and colleagues (2) compared subjects reporting unexplained GI symptoms to those not reporting any GI symptoms. Subjects reporting at least one unexplained GI symptoms were significantly more likely to have experienced lifetime episodes of panic disorder (2.5% vs. 0.7%), agoraphobia (10.0% vs. 3.6%) and major depression (7.5% vs. 2.9%) when compared to subjects with no unexplained GI symptoms. The lifetime prevalence rates differences were even higher for subjects with two unexplained GI symptoms: 5.2% for panic disorder, 17.8% for agoraphobia and 13.4% for major depression. In her review (3), Spinelli concluded that approximately 40-60% of patients with irritable bowel syndrome (IBS) have one or more concomitant psychiatric disorder, with anxiety, depression and somatoform disorders being the most common, and that psychosocial stress exacerbates GI symptoms, including symptoms of IBS. In a study on anxiety and depressive symptoms and medical illness among adults with anxiety disorders, Niles and colleagues (4) found that anxiety was independently associated with having ulcer and that severity of anxiety and depressive symptoms was strongly associated with having more medical conditions. They felt that bidirectional relation between anxiety and various diseases is likely. Goodwin and Stein (5) found a strong relationship between generalized anxiety disorder (GAD) and peptic ulcer disease (PUD) (five-fold increase over people without GAD). In his review on anxiety and medical

illness, Schuckit (6) suggested that three GI problems (colitis, ulcer, IBS) may be exacerbated by anxiety.

Potential mechanisms

The mechanism of the bidirectional relationship between anxiety and GI illness/symptomatology is not understood and has not been sufficiently investigated. In his review of this relationship, Clouse (7) postulated interaction of emotional or other stressful, non-intestinal stimuli on gastrointestinal tract function and possible direct relation of these stimuli to some gastrointestinal illnesses, with mechanisms being both neural and humoral. He wrote that "The substrate for modulation of the gastrointestinal tract by anxiety and other psychiatric disorders is provided by our knowledge of central nervous system control mechanisms of gastrointestinal functions:" (7, p.414). Other investigators (8) emphasized the role of stress in peptic ulcer disease. However, since the discovery of the role of Helicobacter pylori in the etiology of peptic ulcer disease, the interest in studying the role of stress in this entity decreased though many recognize its multicausal etiology, including stress and unhealthy lifestyle. Interestingly, some indirect evidence of the impact of anxiety on GI symptomatology comes from studies examining the impact of benzodiazepines (BZs) on various aspects of GI functioning.

Birnbaum and colleagues (9) found that oral administration of 10 mg of diazepam markedly reduced nocturnal human basal gastric secretion in duodenal ulcer patients when compared to placebo. They postulated that, since the decrease in secretion was achieved by a drug that has no anticholinergic effect in vitro, the mechanism should refer to regulatory autonomic functions in the central nervous system (9). One may wonder whether the decrease of anxiety and/or the improved sleep were the causative factors.

It is well known that anxiety, especially chronic one, increases smooth muscles tension throughout the human body, including the GI system. It is commonly believed that this is centrally mediated though we do not have full understanding of this process. Benzodiazepine tetrazepam (used as muscle relaxant) relieved spasm of isolated rat duodenum and guinea pig ileum (10), which suggests peripheral involvement. On the other hand, intravenous diazepam decreased the pressure of lower esophageal sphincter in humans (11) that may suggest both peripheral (myogenic influence) and central (anxiety) mechanism. These findings suggest the

possibility of using BZs for relieving spasm of musculature within the GI system. It would probably make sense to use longer acting BZs such as clonazepam rather than short-acting ones (e.g., alprazolam), considering constant and continuous changes in GI motility and tone.

Increasingly important areas to consider in the involvement of anxiety in GI symptomatology are the regulatory function of the brain-gut axis (12) and the impact of the microbiota (13), especially in view of the mentioned (4) bi-directional relationship between anxiety and GI symptomatology/illness. The brain receives constant stream of interoceptive input from the GI tract and after integrating them sends response back to different GI tract cells, including the mentioned GI smooth muscle cells (12). The brain can modulate the afferent signals from the GI system by endogenous pain facilitation or reduced endogenous pain inhibition (12), and may play a role in painful GI symptomatology, e.g. in the irritable bowel syndrome. Clearly, alteration of homeostatic reflexes could be associated with alteration in various GI functions, such as secretion and motility, thus leading to abdominal pain, discomfort, and alteration of bowel habits (12). The regulation of the gut includes sympathetic and parasympathetic nervous system, the HPA axis, and involves various neurotransmitters, including the gamma-aminobutyric acid (GABA) (13). Various gut signaling (in both directions) could be influenced by numerous neurotransmitters, and the release of some of them, such as GABA, could be influenced by BZs.

The mechanism of anxiety involvement in GI symptoms/disorders though widely known is not well understood. It seems, however, that medications such as benzodiazepines, may alleviate GI symptoms, possibly both centrally and peripherally.

BZ use and efficacy

Most of the studies examining the use of BZs in the treatment of GI symptomatology were done during the 1970s and 1980s.

In 1973, Baume and Cuthbert (14) noted that medazepam was significantly better than placebo in relieving major symptom complexes of functional bowel disease, e.g. aerophagy, nervous dyspepsia and gastrointestinal pain of 30 patients in a double-blind cross-over clinical trial. Expanding their research on BZs in GI symptoms, Baume and colleagues (15) compared diazepam (5 mg BID) and lorazepam (1 mg BID) to placebo in a double-blind, cross-over study

of 28 patients with functional GI symptoms. Both BZs were significantly better than placebo. The authors noted that lorazepam (at that time it was fairly new medication) was well tolerated.

Lorazepam was found to be useful in the treatment of GI illness with anxiety component in several other studies. Kasich and colleagues (16) reported that lorazepam (0.5 mg to 4.0 mg/day) was better than placebo and comparable to diazepam (2.5 to 30 mg/day) in a double-blind parallel treatment study of 120 patients with chronic gastrointestinal disease associated with anxiety. They concluded that lorazepam is an effective, safe and useful adjunct in the management of functional and organic GI disorders where anxiety has negative influence. Caplan and Vanov (17) found lorazepam significantly more helpful than placebo in 61 anxious patients with demonstrable "organic" or "functional" GI diseases in a double-blind placebo-controlled study of lorazepam (mean daily dose 3 mg). Lorazepam was helpful not just in relieving anxiety, but also in some GI symptoms, such as heartburn, constipation, aerophagia, bad taste and others. Finally, Stokes (18) reported that lorazepam was effective in a double-blind placebo comparison of lorazepam. The initial dose of lorazepam was 3 mg/day; 21% of patients were on a higher dose at the end of the study. The improvement was significantly greater with lorazepam than with placebo on all measures (anxiety, global, GI symptomatology).

The place of BZs in the management of GI symptoms/illness was also examined in studies combining BZs with other medications used in treatment of GI problems. Huscher and colleagues (19) studied ranitidine and prazepam or ranitidine and placebo in a double-blind study of 50 patients with an active, endoscopically proven duodenal ulcer. At the end of their 4 -week study, duodenal ulcer healed in 95.6% of patients on ranitidine + prazepam and 75% of patients on ranitidine + placebo ($p = 0.03$) (there were 2 dropouts in prazepam group and one in placebo group). Combination of octatropine methyl-bromide (anticholinergic agent) and diazepam (40 mg/2.5 mg twice daily) in patients with IBS was not significantly different from placebo in a study by Pace and colleagues (20).

It is important to note that the side effects in all mentioned studies were usually mild, mostly sedation and sleepiness.

The evidence from these studies suggests an important role of BZs in managing various GI symptoms and disorders.

BZs versus antidepressants

Considering their favorable side effects profile, BZs should be preferred to antidepressants in the management of GI symptoms with anxiety. BZs are usually not associated with GI side effects, while antidepressants are frequently associated with a number of adverse events. Tricyclic antidepressants, effective in the treatment of functional GI disorders (21, 22), also in conjunction with cognitive behavioral therapy (23) may cause constipation. Second generation antidepressants, such as SSRI and SNRI, may have a more profound unfavorable impact (24, 25), causing nausea, vomiting, dyspepsia, diarrhea and abdominal pain (24).Even short-term use of SSRI may be significantly associated with GI bleeding, suggesting that the same precautions that are used with non-steroidal anti-inflammatory drugs and aspirin are appropriate (25). As a result, newer generation antidepressants do not seem to be suitable for the treatment of anxiety associated with GI symptomatology, and BZs should be preferred.

Conclusion

The role of BZs in the management of various troublesome gastrointestinal symptoms, (e.g., aerophagia and gastrointestinal pain), or some acute and chronic GI disorder (e.g., peptic ulcer disease, colitis, and IBS) has not been fully appreciated. Their use should be expanded. In addition to anxiety frequently accompanying these conditions, BZs may, through either decreased gastric secretion and/or relaxation of smooth muscles tone, alleviate GI symptomatology, and contribute to patient well-being. The use of BZs in GI disorders may facilitate a transition of patients from pharmacotherapy to psychotherapy, which is an effective treatment particularly for functional symptoms (26, 27), and may provide more enduring results.

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