Beyond Tricyclics:

New Ideas for Treating Patients with Painful and Refractory Functional GI Symptoms

Douglas A. Drossman, MD

UNC
SCHOOL OF MEDICINE

At our Center for Functional GI and Motility Disorders, we are always seeking new treatment methods for patients referred to us with painful and refractory functional GI Disorders (FGIDs). These patients have painful symptoms and associated motility disturbances as well as understandable emotional distress going back many years. They have been to many specialists and have been referred to our clinic because other gastrointestinal treatments have failed. Many have used narcotics which paradoxically can make them feel worse. They have "surfed" the internet seeking novel treatments that could help them, and joined IBS forums to share their difficulties and concerns. When the patients arrive to be evaluated, they feel hopeful that something previously missed will be found, and if that fails, they expect to receive a specific treatment to make their symptoms go away. Others may sit with arms folded, cautious and even skeptical. They have tried everything ("been there and done that"); their pessimism is obvious.

Some are guarded in their responses, concerned that they will not be believed or worse, considered crazy since "nothing has been found". Many will resist recommendations to take antidepressants or engage in psychological treatments because of the stigma: "I'm not depressed! What will I tell my family and friends?"

This scenario is challenging for any clinician. Yet in balance, it provides an opportunity to learn much about the patient's illness experience and to find novel approaches to their care: to go where others have not gone, by employing new treatment modalities. In this column, I will discuss some newer treatment methods for patients with refractory and painful functional GI symptoms. Many of these are not in common use, though the scientific data are beginning to accumulate. Their rationale is sound because they have been tried and tested in treatments of psychiatric disorders. Adapting these methods for patients with GI pain should not be surprising since the enteric nervous system of the intestines (ENS) and the gastrointestinal pain pathways are both responsive to central treatments. These two neural systems of brain and gut are connected, and began together. These treatments are part of the specialty practice of the Center for Functional GI & Motility Disorders, and they may not be found at other programs. General treatment approaches to the psychopharmacological and behavioral care of patients with FGIDs can be found elsewhere.[1-3]

General Approach

At the heart of it all, treatment begins with an effective physician-patient relationship[4]. It improves patient satisfaction, adherence to treatment and even the clinical outcome[5]. Also, it reduces litigation[6], and it may explain why complementary treatments like acupuncture work[7]. The physician-patient relationship remains the cornerstone, and the most important component of treatment.

Building upon the physician-patient relationship, treatment is biopsychosocial in concept and multi-component in method. We employ any combination of physiological, behavioral and pharmacological modalities.[3,8] We employ the most up to date treatments directed at GI motility and GI pain, and have several treatment trails going with new GI treatments. Psychological treatments such as cognitive behavioral therapy, hypnosis and stress management are safe, effective and long lasting[9], though do require clinicians who are skilled in these methods. The pharmacological treatments are directed toward the gut, the brain-gut axis and the CNS in various combinations.

Antidepressants and Psychotropic Agents

Antidepressants are being used more and more for both IBS and other painful FGIDs. In a recent international survey of IBS patients using the internet, 31% of 1,966 patients reported taking an antidepressant[10]. These treatments are most often used for patients with more severe symptoms, who form the majority of our tertiary care practice.

In general we employ either a tricyclic antidepressant (TCA) or a serotonin norepinephrine reuptake inhibitor (SNRI) because of their enhanced pain benefit, or a serotonin reuptake inhibitor (SSRI) when there are associated 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. We actively work with the patient to address any side effects because that is what reduces adherence to treatment[11]. However, we are cautious not to quickly adjust dosages up or down, or discontinue or switch to other medications,[12] Side effects are not always due to the medication itself.[13] We also select medications based on the associated symptoms: a TCA when there is diarrhea, an SSRI with constipation, mirtazepine with nausea, or buspirone with postprandial early satiety or fullness[14].

Rationale for Antidepressants, a Reappraisal

Non psychiatric physicians are not well trained in psychopharmacology and may prescribe antidepressants based more on misinformation than evidence. They may prescribe because they think IBS is a psychiatric problem, or as a means to reduce stress; neither is correct. The true reason is to reduce pain signals from the gut, or improve bowel motility. Higher dosages are used to treat psychiatric difficulties that can aggravate the pain. Brain imaging studies indicate that antidepressants may act on an area of the brain called the anterior cingulate cortex to reduce pain from the intestines[15].

In the last few years some newer ideas on the action of antidepressants for psychiatric disorders and chronic pain have emerged to add to or possibly replace older theories for depression. The monoamine hypothesis which has held ground for over 40 years, relates clinical depression to reduced activity of certain neurotransmitters in the brain. Thus, the SSRI's increase available neurotransmitter, and presumably this leads to clinical improvement.

This understanding doesn't explain why it takes up to 6 weeks to get a clinical response when the effect within the synapse is much sooner.

More recently, the concept of neuroplasticity i.e., loss of cortical neurons with stress and trauma and neurogenesis or regrowth of neurons with clinical treatment[16], is reshaping our understanding of psychiatric and possibly functional GI disorders. When I went to medical school in the 1960's we were taught that nerve cells are established at birth or soon after, and there was little evidence that these cells died. Furthermore, the brain was thought to be incapable of neurogenesis. Over the last decade studies began to show that brain cells can die in key areas of the brain, such as the hippocampus, after severe emotional trauma such as sexual abuse, or war trauma leading to PTSD[17]. In the last year or two, brain imaging studies are showing reduced cortical density in other areas of the brain including cortical regions involved with emotion and pain[18,19].

Adding to this is new evidence that antidepressant (and possibly psychological) treatments can restore lost neurons. Brain-derived neurotrophic factor (BDNF), a precursor of nerve cell growth (neurogenesis), appears to increase with antidepressant treatment and the increase correlates with longer periods of treatment and with the degree of recovery from depression[16,20]. Furthermore, from a clinical perspective, the longer patients are treated with antidepressants the lower the frequency of relapse or recurrence of the depression[21,22].

These findings give us new insight into how the brain functions in response to severe stress and closer to home, how we understand chronic visceral and somatic pain and their treatments. Now we are learning that patients with severe depression or chronic pain show reduced cortical density in the anterior cingulate and prefrontal cortex and thalamus, regions that interface between emotion and pain regulation[18,19].

These new data provide new and important opportunities for research and patient care using antidepressants for treatment of FGIDs, because the nerves of the bowel are similar to the nerves of the brain. From the clinical perspective, this effect on nerve cell growth regulation helps explain the observed benefit of using psychotropic agents in reducing GI pain.

It also raises questions as to whether neurogenesis might also occur in the nervous system of the GI system as well as the CNS; certainly neural degeneration is seen with severe motility disturbances[23], and perhaps with proper treatments this can be reversed or slowed. In fact one recent study[24] has shown that serotonin agonists can increase enteric neurons developing from precursors and increase neurite outgrowth and decrease apoptosis.

Detoxification from Narcotics

Unfortunately, and out of sheer desperation, clinicians sometimes prescribe narcotics for Functional GI pain even though there is no evidence that they provide long term benefit[25]. Prescriptions for narcotics have grown remarkably to treat chronic non-malignant pain and currently about 18% of patients with IBS are inappropriately taking narcotics[10]. This overuse may be encouraged because the health care system reimburses for it and it is a way to treat patients and get them quickly released from the hospital, ER or clinic, and seems to reduce the need to take the time to address more comprehensive management approaches. Furthermore, patients, not knowing of other treatment options, often demand it. The USA, which represents less than 5% of the world's population prescribes over 80% of narcotic prescriptions, and the use of oxycodone has increased 400% based on data from 1997-2002[26]. More importantly, there is growing evidence to suggest that these treatments are harmful, producing what has been called narcotic bowel syndrome (NBS)[25], a complication of narcotic treatment where there is increased pain which usually leads to severe disability over time. Patients with painful FGIDs who are taking narcotics must be detoxified, and in many cases the pain will then be reduced. A protocol for detoxification as well as further information on the mechanisms for NBS is available[25].

Augmentation Treatment

If single medication treatments are not successful, we consider intensifying the treatment by using combinations of treatments. In our referral population, sequencing one medication after another sometimes fails, due to lack of response or side effects, so when this occurs what is needed is an approach that employs multiple treatment modalities to achieve synergistic or additive effects. The concept of augmentation relates to the use of two or more treatments that act upon different receptor sites or areas of the brain to enhance the therapeutic effect. Frequently, medications can be used at lower dosages to minimize side effects[27]. This approach is particularly helpful when multiple single treatments are unsuccessful even at higher dosages or have side effects.

Some of the different combinations of treatments are described below.

Psychological Treatment and Antidepressants

One logical approach is to combine antidepressants with psychological treatment. Clinically we know that antidepressants can improve pain and vegetative signs of depression. In addition, psychological treatments improve higher levels of brain functioning such as coping, reappraising of maladaptive thinking and adaptation to previous losses and trauma. Also, being in psychological treatment can improve adherence to taking a medication, and conversely taking an antidepressant can increase psychic energy to improve the efficiency of the work of therapy. Brain imaging studies have shown that antidepressants work in areas such as the anterior cingulate cortex and insula to improve connectivity to prefrontal and other cortical areas ("bottom up" effects) while psychological treatments work on prefrontal or cognitive ("executive") areas, "top-down" effects.[28] Finally, over the last 10-15 years, clinical trials show added benefit of combining these two treatments for depression and other psychiatric disorders [29-32] and migraine headache[33] among other disorders. In fact the difference for combined treatment can be 50% or better than either single treatment.[30, 33] The Rome III committees have recommended this type of augmentation treatment for patients having more severe functional abdominal pain.[2]

Treatment with two or more Psychotropic agents

We often employ combinations of psychotropic (i.e., anti-depressant or anti-anxiety) agents when a single treatment has failed. For example we might use a low dose SSRI with a low dose TCA, to address multiple symptoms such as anxiety, depression, pain and diarrhea. Here the SSRI provides anxiolysis 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 postprandial early satiety, we might add buspirone to an antidepressant. This agent has known ability to augment antidepressants[27] and also has peripheral effects that improve sensorimotor gut function [14,34]. More recently, we have added a low dose atypical antipsychotic (e.g., quetiapine) to a TCA or SNRI to augment pain control, reduce anxiety and enhance sleep[35,36]. Finally, if the patient has a musculoskeletal component to the pain, e.g., abdominal wall pain or fibromyalgia, we might add gabapentin or pregabalin to the antidepressant[37].

With all combinations, we prefer to use low dosages to minimize side effects, especially the serotonin syndrome[38]. This most often occurs with higher dosages or combinations of higher dosages of serotonin enhancing agents. The clinical features include tremor and hyper-reflexia, spontaneous clonus and muscle rigidity with fever. In general augmentation treatment using multiple psychotropic agents should be prescribed by a psychiatrist, psychopharmacologist or gastroenterologist with advanced training in the use of these medications.

Concluding Comment

Patients presenting with severe and refractory FGIDs have been prescribed many treatments without benefit. Effective treatment requires a broader range of treatment options. At the base is an effective physician-patient relationship. Building upon this are the use of antidepressants targeted toward various symptom features, and the removal of narcotic agents when prescribed. Their benefit may now extend to include reducing neuroplastic effects associated with visceral hypersensitivity and possibly increasing neurogenesis. Finally, augmentation treatments, combining behavioral interventions with antidepressants or combinations of psychotropic agents should be considered. The latter will require input from a psychopharmcologist or psychiatrist.

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To make an appointment at our clinic, please contact Linda Miller at:

919-966-0141

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