

Beyond Tricyclics: New Ideas for Treating Patients With Painful and Refractory Functional Gastrointestinal Symptoms

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At our Center for Functional GI and Motility Disorders (<http://www.med.unc.edu/medicine/fgidc>), we are always seeking new treatment methods for patients referred to us with painful and refractory functional gastrointestinal disorders (FGIDs). These patients have painful symptoms and associated motility disturbances as well as high levels of emotional distress going back many years. They have been to many specialists and have been referred to our clinic because all motility-type agents or other gastrointestinal treatments have failed. They have also used narcotics, which, paradoxically, can make them feel worse. They have searched the Internet seeking novel treatments that could help them and joined forums on irritable bowel syndrome (IBS) 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, done that”); their pessimism is obvious. Some are guarded in their responses, concerned that they will not be believed

or, worse, will be 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 using new treatment modalities. In this paper, the aim is to discuss some newer treatment methods for patients with refractory and painful functional gastrointestinal symptoms. Many of these have not been adequately tested, though the scientific data are beginning to accumulate. Their rationale is sound because they have been tried and tested in treatments of psychiatric disorders. Adaptation of these methods for patients with gastrointestinal pain should not be surprising, since the enteric nervous system and the gastrointestinal pain pathways are both responsive to central treatments. These two neural systems began from the same anlage and are hard-wired together. Although it is premature to recommend all of these approaches to the care of patients with FGIDs, they can be considered in referral practices where there is adequate support from psychopharmacologists and mental-health professionals. 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 such as acupuncture work (7). The physician–patient relationship remains the cornerstone and the most important component of treatment.

Building on the physician–patient relationship, treatment is biopsychosocial in concept and multicomponent in method. We use any combination of physiological, behavioral, and pharmacological modalities (3,8). These treatments are directed toward the gut, the brain–gut axis, and the central nervous system in varying combinations.

Psychological and behavioral treatments

Psychological and behavioral treatments such as cognitive-behavioral therapy, hypnosis, and stress management, for FGIDs are safe, effective, and long lasting (9). Recent systematic reviews of randomized trials showed statistical evidence that all were better than their control conditions (10,11). There are many advantages to psychological and behavioral treatments: they can show up to 70% benefit, and, importantly, their effects are additive to those of other medical treatments. Furthermore, benefit continues after the treatment period ends, there are no medical side effects, and treatment may

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reduce health-care costs (9,12). The factors associated with a poor response relate to low patient motivation and the need for a trained therapist in the community who is experienced in working with these disorders. Benefit occurs when the patient feels a sense of control over his or her condition, believes in the value of the treatment, and has a good relationship with the therapist. Finding a good therapist may be difficult. Ideally, as in our clinical program, a psychologist working at the same institution is the optimal clinical arrangement. In clinical practice, it might be helpful to seek out therapists in the community with an interest in treating patients with medical disorders such as IBS. A brief phone interview with the therapist may help to assess his or her motivation to treat patients with these disorders and may allow for ongoing collaboration in the patient's care. Organizations such as the International Foundation for Functional Gastrointestinal Disorders maintain a national list of medical providers and therapists interested in treating patients with FGIDs.

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, though it is unclear whether they were prescribed specifically for their IBS (13). These treatments are most often used for patients with very severe symptoms, who form the majority of our tertiary-care practice.

The three major antidepressant classes used are the tricyclic antidepressants, or TCAs (desipramine, amitriptyline, nortriptyline); the selective serotonin reuptake inhibitors, or SSRIs (fluoxetine, paroxetine, citalopram, escitalopram, sertraline); and the serotonin norepinephrine reuptake inhibitors, or SNRIs (duloxetine, venlafaxine, desvenlafaxine).

In general, we initially use either a TCA or an SNRI, because of their enhanced pain benefit, or an SSRI 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. If comorbid major depression is present, higher dosages than are typically used for FGIDs may be needed.

We actively work with the patient to address any side effects, because they are what reduce adherence to treatment (14). The side effects are dose related and, for TCAs, include sedation, constipation, dry mouth and eyes, weight gain, and sexual dysfunction; thus the medication is usually given as a single nighttime dose. The SSRIs, because of their higher serotonergic effect, produce more active side effects of insomnia, agitation, sexual dysfunction, diarrhea, and diaphoresis; they are usually given as a single dose in the morning. The SNRIs, such as duloxetine, are more likely to produce nausea and, in rare cases, liver dysfunction and may be taken with a meal in divided doses. We are cautious not to quickly adjust dosages up or down, or discontinue or switch to other medications. Our studies have shown no relationship of dosage level of TCAs with clinical benefit (15), and, interestingly, the “side effects” commonly reported after the beginning of treatment relate more to concurrent anxiety than to true side effects of the medication itself (16). We also select medications on the basis of the associated symptoms: a TCA when there is diarrhea, an SSRI with constipation, mirtazapine with nausea, or buspirone (an azapirone antianxiety agent) with postprandial early satiety or fullness (17). **Table 1** offers a general approach to the use of psychopharmacological agents.

Rationale for antidepressants: a reappraisal

Nonpsychiatric physicians are not well trained in psychopharmacology and may prescribe antidepressants based more on misinformation than on evidence. They may prescribe because IBS is perceived as a psychiatric problem, or as a means to reduce stress; neither is

correct. The true rationale for their use relates to reducing afferent signals from the gut, or modulating bowel symptoms. Higher dosages are used to treat psychiatric comorbidities that can aggravate the pain. Brain imaging studies indicate that antidepressants may act on anterior cingulate cortical functioning to down-regulate incoming visceral signals (18).

In only the past 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 such as the monoamine hypothesis for depression. The monoamine hypothesis, which has held ground for more than 40 years, relates clinical depression to reduced activity of certain neurotransmitters in the synaptic clefts of the brain. Thus, the SSRIs, for example, prevent reuptake of serotonin in these clefts, thereby increasing available neurotransmitter, and presumably this leads to clinical improvement. This hypothetical model has not been ideal, since it does not explain why it takes up to 6 weeks to get a clinical response when the pharmacological effect within the synaptic space occurs much sooner.

More recently, the concept of neuroplasticity, i.e., loss of cortical neurons with psychiatric trauma and neurogenesis or regrowth of neurons with clinical treatment (19), is reshaping our understanding of psychiatric and possibly of functional gastrointestinal disorders. When I went to medical school in the 1960s, we were taught that neural cells are established at birth or soon after, and there was little evidence that these cells died, unless there were major events such as an ischemic stroke or brain hypoxemia. Furthermore, the central nervous system was thought to be incapable of neurogenesis. Over the past decade, studies have shown 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 post-traumatic stress disorder (20). In the past year or two, functional magnetic resonance imaging studies are showing reduced cortical density in other areas of the brain,

including cortical regions involved with emotional and pain regulation (21,22).

Adding to this is the evidence that antidepressant (and possibly psychological) treatments can restore lost neurons. Brain-derived neurotrophic factor (BDNF), a precursor of neurogenesis, increases with antidepressant treatment and correlates with longer periods of treatment and with the degree of recovery from depression (19,23). Furthermore, from a clinical perspective, the longer patients are treated with antidepressants, the lower the frequency of relapse or recurrence of the depression (24,25).

These findings give us new insight into how the central nervous system functions in response to emotional trauma and, closer to home, how we understand chronic visceral and somatic pain and its treatment. So, with post-traumatic stress disorder, there is a loss of neurons from the dentate nucleus of the hippocampus, where memory and the linkage between emotion and cognitions are encoded (20). 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 (21,22).

These new data provide new and important opportunities for research and patient care using antidepressants for treatment of FGIDs. From the clinical perspective, this effect on neuronal growth regulation in key areas of the central pain matrix helps explain the observed benefit of using psychotropic agents in reducing gastrointestinal pain. It also raises questions as to whether neurogenesis might also occur in the enteric nervous system as well as the central; certainly neural degeneration is seen with severe motility disturbances (26), and perhaps with proper treatments this can be reversed or slowed. In fact, one recent study (27) has shown that 5HT4 agonists can increase the development of enteric neurons from precursors and increase neurite outgrowth and decrease apoptosis.

Detoxification from narcotics

Unfortunately, and out of sheer desperation, clinicians sometimes prescribe narcotics for functional gastrointestinal pain, even though there is no evidence that they provide long-term benefit (28). Prescriptions for narcotics have grown

remarkably to treat chronic non-malignant pain, and currently about 18% of patients with IBS are inappropriately taking narcotics (13). This overuse may be encouraged because the health-care system reimburses for it, and it is seemingly an efficient way to treat patients

Table 1. Approach to management of FGIDs with psychopharmacological agents

| | |
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| 1. Choosing the agent | Specific symptom treated (e.g., TCAs with diarrhea, SSRIs with constipation, mirtazapine with nausea) |
| | Side-effect profile |
| | Cost of the drug |
| | Patient experiences and preferences with previous agents |
| | Coexisting psychiatric conditions targeted (e.g., SSRIs with anxiety) |
| 2. Initiating treatment | Negotiate treatment plan. |
| | Consider previous drugs that worked. |
| | Start with a low dosage (e.g., 25 mg/d of TCA). |
| 3. Continuing treatment | Escalate dosage by 25–50% every 1–2 weeks to receive therapeutic effect with the lowest possible dosage. |
| | Watch for side effects. Counsel that most side effects disappear in 1–2 weeks. If they do not, try to continue the same or a lower dosage from the same class before switching to a different class. |
| | Follow up (by phone or e-mail) within the first week and then within 2–3 weeks to ensure adherence. |
| | Gauge treatment on the basis of improved well-being, daily function, quality of life, and emotion as well as symptoms. |
| | If there is a poor initial response: |
| | Readdress patient concerns. |
| | Consider switching to a different class. |
| | Consider combination therapies (e.g., SSRI + TCA, pharmacological and psychological treatment). |
| | If needed, obtain pharmacotherapy consultation. |
| | Increase dosages up to full psychiatric dosages if the patient can tolerate it before discontinuing. |
| | If there is no benefit in 6–8 weeks on higher doses, consider alternate strategies (e.g., adding psychological treatment or referral). |
| | Depending on the response and side effects, another agent with a different mechanism of action can be added to augment treatment efficacy and minimize side effects. |
| 4. Stopping treatment | Continue treatment at minimum effective doses for 6–12 months. Long-term therapy may be warranted to prevent symptom relapse. Taper gradually to prevent withdrawal symptoms. |
| SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. | |

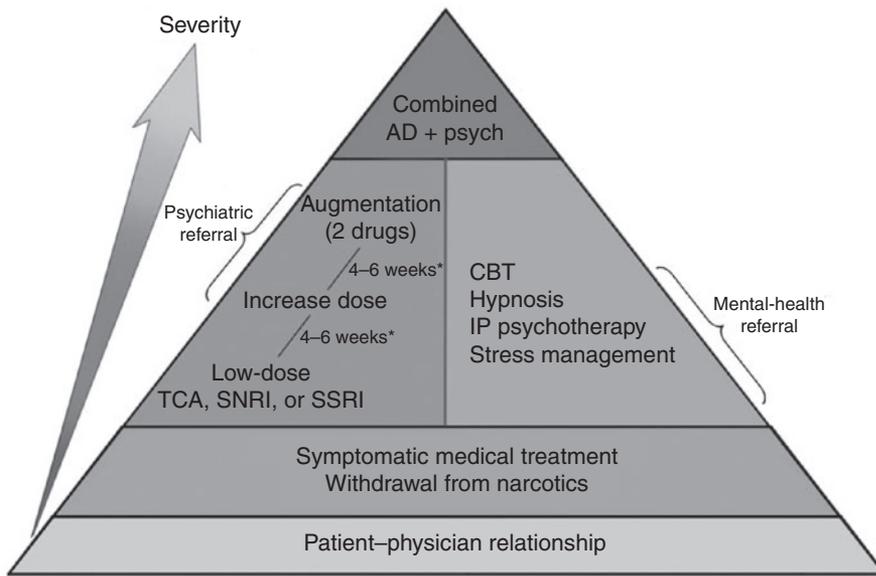


Figure 1. Augmentation treatment. Beginning with an effective patient–physician relationship, treatments are added on the basis of symptom severity. A low-dose tricyclic antidepressant or serotonin norepinephrine reuptake inhibitor is started and, after 4–6 weeks, can be increased along with monitoring for clinical benefit and side effects. If this is unsuccessful, augmentation treatment using another antidepressant, buspirone, or an atypical antipsychotic is considered, and this decision may require psychiatric consultation. On occasion, the patient may first be referred to a mental-health counselor for psychological treatment. With more severe symptoms, combined pharmacological and behavioral intervention is used. See text for further details. *Monitor side effects. AD, antidepressant; CBT, cognitive-behavioral therapy; IP, interpersonal; psych, psychotherapy; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. (Reprinted from ref. 1.)

and get them quickly released from the hospital, emergency room, or clinic, without needing to take the time to address more comprehensive management approaches. Furthermore, the patients, not knowing of other treatment options, often demand it. The United States, which represents less than 5% of the world's population, prescribes more than 80% of narcotic prescriptions, and the use of oxycodone has increased 400%, according to 1997–2002 data (29). More important, there is growing evidence to suggest that these treatments are harmful, producing what has been called narcotic bowel syndrome (28), a complication of narcotic treatment in which there is increased pain that usually worsens over time. Patients with painful FGIDs who are taking narcotics must be detoxified from them, and in many cases the pain will be reduced. A protocol for detoxification as well as further information on the mechanisms of narcotic bowel syndrome is available (28).

Augmentation treatment

If single-medication treatments are not successful, we consider intensifying the treatment by using combinations of treatments (Figure 1). In our referral population, sequencing one medication after another sometimes fails, because of lack of response or side effects.

When this occurs, what is needed is an approach that uses multiple treatment modalities to achieve synergistic effects. Augmentation is the use of two or more treatments that act on 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 (30). This approach is particularly helpful when multiple single treatments are unsuccessful even at higher dosages or have side effects. In most cases our patients are already taking peripherally acting agents for their FGIDs (e.g., probiotics, antispasmodics, chloride channel activators, or peripheral neural agents such as gabapentin). In some cases these agents are discontinued because of co-side effects (e.g., removal of an antispasmodic with anticholinergic properties when a TCA is added) or added for augmentation (e.g., addition of an antidepressant to gabapentin or a bowel symptom regulator such as alosetron or lubiprostone). The different combinations of central 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 cognitions, and cognitive 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 subcortical 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) (31). Finally, over the past 10–15 years, clinical trials have shown added benefit of combining these two treatments for depression and other psychiatric disorders (32–35) and for migraine headache (36), among other disorders. In fact, the effect-size difference for combined treatment can be 50% or greater, more than for either monotherapy treatment (33,36). The Rome III committees have recommended this type of augmentation treatment for patients with more severe functional abdominal pain (2).

Treatment with two or more psychotropic agents. We often use combinations of psy-

chotropic 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 who have associated anxiety and/or postprandial early satiety, we might add buspirone to an antidepressant. This agent has known ability to augment antidepressants (30) and also has peripheral effects that improve sensorimotor gut function (17,37). 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 (38,39). 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 (40).

With all combinations, we prefer to use low dosages to minimize side effects, the most concerning being the serotonin syndrome (41). This most often occurs with higher dosages or combinations of higher dosages of serotonin-enhancing agents. The clinical features include tremor and hyperreflexia, 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 on this are the use of antidepressants targeted toward various symptom features and the removal of narcotic agents when prescribed. The benefit of antidepressants may now extend to include reduction of neuroplastic effects associated with visceral hypersensitivity and, possibly, an increase in neurogen-

esis. Finally, augmentation treatments, combining behavioral interventions with antidepressants or combinations of psychotropic agents, should be considered. The latter will require input from a psychopharmacologist or psychiatrist.

CONFLICT OF INTEREST

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