Using Central Neuromodulators and Psychological Therapies to Manage Patients with Disorders of Gut-Brain Interaction

A Clinical Guide

W. Harley Sobin
Editor

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Foreword

Disorders of Gut-Brain Interaction: A Coming of Age for the Clinician

Perhaps, one of the great advances over the last decade within gastroenterology has been the biopsychosocial realignment in our understanding of what has typically been called functional GI disorders (FGIDs) to the more scientifically based disorders of gut-brain interaction (DGBI). As FGIDs, clinicians and scientists gave them no credit; they were understood as the absence of organic disease or possibly due to "psychiatric" difficulties. Then, as the field of neurogastroenterology emerged and has begun to thrive, early adapters began to study these disorders because they were now seen as not only legitimate but interesting and relevant. This has led to the rapid growth of the study of gut-brain interactions, neurophysiology of GI function, brain imaging, and central treatments. Because DGBIs relate to dysregulation of the gut-brain axis, the treatments that work are the central neuromodulators and behavioral methods that help to reestablish normality within this system and patients benefit. Furthermore, the aficionados who use these treatments also learn that by employing these treatments for a sufficient amount of time, the vicious cycle of pain and GI dysfunction may actually dissipate, via gut-brain neurogenesis.

I am one of a small number of academicians and clinicians who have made a career of promoting this new knowledge. Yet to date, I almost feel that this understanding is one of the best-kept secrets in our field. I say that because the areas of

biopsychosocial care, neurogastroenterology, psychopharmacology, and gut-brain interactions are applied by only a select few academicians who do the research but have limited practices. Presently, this new knowledge may seem to clinicians in practice as not relevant, "over their head," or belonging to the realm of behaviorists. So how can we disseminate this knowledge to clinicians in order to benefit our patients?

I met Dr. Harley Sobin less than 3 years ago and was struck by his passion for this area of work as a clinical gastroenterologist. He empirically learned that acquiring the latest understanding of these disorders, properly communicating this knowledge to his patients, and prescribing the correct treatments really work. Dr. Sobin is an early adapter who uses this knowledge successfully in his practice, and this has positively reinforced his desire to teach others.

The product of his desire to teach others is demonstrated in this, much needed, book. I believe its greatest value relates to Dr. Sobin's ability to reach clinicians through his personal experience as a gastroenterologist: one who applies the science he has learned into everyday practice. The book is practically organized to meet the needs of the clinician. It begins with a chapter on the meaning of gut-brain interactions, offers a practical guide to how to use central neuromodulators based on the dominant symptom features confronting the clinician, and includes the practical application of behavioral interactions including how to refer and why. There are also helpful guidelines about how to approach this topic to patients and much more. The book is written in a no-nonsense manner with case examples, practical knowledge from his own experience, and when needed relevant attributions of knowledge from others linked to the proper citations.

I highly recommend this book to clinicians seeking to go beyond gut-related treatments to care for patients with disorders

of gut-brain interaction, with chronic GI pain, or with psychiatric comorbidities. Applying this knowledge will help practitioners and their patients.

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Preface

This text is designed to discuss central therapies for managing patients with disorders of gut-brain interaction (DGBI) which replaces the older terminology – functional gastrointestinal disorders (FGIDs). It investigates the use of central neuromodulators and psychological therapies for treating these patients.

While there are many books that address the treatment of DGBI, particularly IBS, most of them concern themselves with treatments that focus specifically on gut-directed therapy.

However, the more challenging patients with recalcitrant DGBI will benefit from central therapies. That is the focus of this text. There are chapters, written by a gastroenterologist, on how central neuromodulators can help disordered gut function. There are specifics on choices of drugs for different disorders, along with dosages, and recommendations on their use. There are chapters, written by psychologists, that outline the use of cognitive behavioral therapy and exposure therapy in treating some of these patients. There is also a chapter, written by psychiatrists, that presents a tutorial on how internal medicine physicians should approach the use of psychiatric medications.

We feel that there is a niche that needs to be served. There are a limited number of texts that address the use of central therapies in treating the more challenging patients with DGBI.

Hopefully, this text will be seen as a significant adjunct in managing these patients.

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Chapter 1
The Gut-Brain Connection and Its Significance to Gastroenterologists

W. Harley Sobin

Why should gastroenterologists be interested in the use of psychiatric medications, the so-called central neuromodulators, and psychologic therapy to help with managing patients with gastrointestinal (GI) disorders? This text focuses on patients with disorders of gut-brain interaction (DGBI), which replaces the previous terminology of functional gastrointestinal disorders (FGIDs). Understanding the gut-brain connection is extremely relevant to managing these patients. Most gastroenterologists are trained with a very narrow focus on the GI tract itself. Gastroenterologists need to widen their focus to take the best care of these patients. Some examples of the significance of the gut-brain connection:

1. Some patients with more severe IBS and other DGBI will fail to improve on gut-directed therapy. Adding central neuromodulators will help a number of these patients.
2. There are cases where medications may fail to benefit symptoms of DGBI until psychological therapies are added.

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3. Some patients with DGBI become paralyzed with worry about their symptoms. The addition of central neuromodulators or psychologic therapies may benefit this hypervigilance.
4. Occasionally, recurrent GI symptoms may be caused by an undiagnosed anxiety disorder. If the patient presents to a gastroenterologist, it will be incumbent on the clinician to suspect the underlying disorder and refer appropriately. If the gastroenterologist has only a narrow GI focus, he may facilitate getting the patient trapped in a cycle of GI testing and treatments that may prove ineffective. This can end up impeding the patient's progress until an appropriate diagnosis is made.

Back in 1975, George Engel commented on the discrepancy that existed between physicians viewing a strict medical model to explain illness and psychologists viewing a strict psychological model to deal with disease states [1]. He argued that a continuum existed where there was a psychological undercurrent that affected many medical problems. Douglas Drossman has extensively discussed the presence of a biopsychosocial model for understanding DGBI [2, 3]. In his paradigm, there is an interplay between environmental issues, genetic issues, and psychosocial issues starting as early as childhood, along with traumatic events that might alter a patient's life at any time. These factors have a strong influence on the development of DGBI. Life stress is a common association in patients with IBS, and the likelihood of responding to medical therapy is strongly influenced by the number and severity of stressors in the patient's life [4, 5]. Stressful events in early life may increase a patient's susceptibility to developing IBS later in life [6]. The timing of the first onset of IBS symptoms may be directly related to stressors that occur in a patient's life [6, 7].

Several points are clear: Patients who have anxiety and depression are more likely to have DGBI. The more severe the anxiety and depression, the more severe the symptoms of DGBI tend to be and the more recalcitrant to medical therapy. Conversely, patients who have DGBI are more likely to

show signs of anxiety, depression, and somatization. They are more likely to have uncontrollable worry. Overall, there is an increased incidence of psychiatric illness in the DGBI population [8–11]. The most commonly observed psychiatric diagnoses in IBS patients are depression, panic disorder, social phobia, GAD, PTSD, and somatization disorder [12]. Anxiety is felt to be more prevalent early in IBS, and depression is more common in chronic IBS sufferers [12]. GAD is five times more common in patients with IBS, and IBS is 4.7 times more common in patients with GAD [13].

Patients who experience early life trauma and physical or sexual abuse are more likely to experience DGBI [14–16]. Sexual and physical abuse occur surprisingly frequently in the lives of women with DGBI who present to a tertiary center for consultation. Drossman's group reported a history of sexual or physical abuse (with all but one patient with physical abuse also experiencing sexual abuse) in 44% of 206 women seen consecutively in a university GI practice [14]. Of these abused women, only 17% had informed their doctors, and 1/3 had never discussed their experiences with anyone [14]. Women with a history of sexual abuse were more likely to have poor current health, more abdominal pain, more pelvic pain (four times more likely), more non-GI somatic symptoms, more operations, and worse disability than controls [15]. Walker's group found a rate of sexual abuse of 55% in women with IBS seen in a tertiary care practice but only 5% in women with IBD of similar severity [17].

There are other biopsychosocial factors that influence the development and outcome in patients with DGBI. Patients with more limited social support and depression are more likely to have a poor course [18–20]. Patients who have increased emotional distress are more likely to be candidates to develop postinfectious IBS [21]. A family that enables pain behavior and healthcare seeking can impact the future risk of developing DGBI [22, 23]. Patients with poorer cognitive coping as measured by higher catastrophizing and lower score on a self-perceived ability to decrease symptoms scale had poorer health outcomes [24].

Not every patient with IBS seeks medical attention. Only about 50% do. Patients who have psychiatric problems may be more likely to seek help for somatic symptoms. Patients who do not seek consultation for IBS appear to have psychological profiles similar to controls [25]. However, studies have shown that 50–90% of patients who do get consultation for IBS may have psychiatric disorders [12]. Patients seeking treatment for IBS have higher rates of neuroticism, exhibit more illness behavior, have poorer coping skills, have increased prevalence of psychiatric disorders, and have higher frequency of sexual and physical abuse than patients with IBS who don't seek medical attention [12]. One study showed 72% of patients seeking medical attention for DGBI had psychiatric problems, while only 18% of controls did [26]. The more severe the psychopathology, the more severe the gastrointestinal symptoms and the less likely the patient will respond to treatment. It appears that central mechanisms for processing pain are deleteriously altered in patients with poor coping mechanisms, poor social support, and underlying anxiety disorders [27].

There are structural and neurohumoral connections between the brain and the gut. These structures are hardwired. An afferent enteric nervous system transmits thousands of signals to the brain. Normally, these signals don't reach consciousness. However, in patients with psychological distress, there may be enhanced peripheral sensitization in some and a defect in central pain inhibition in others. This may lead to enhanced perception of these afferent signals and a chronic pain situation may occur [28]. Psychological and emotional events can alter the gut-brain interaction [29]. Altered brain activity has been demonstrated on fMRI studies in patients with severe IBS experiencing emotional stress [30]. Baseline changes in the brain have been noted in patients with IBS [31]. In some of these IBS patients, fMRI studies demonstrate an underactive anterior cingulate cortex, the part of the brain that generally inhibits the transmission of pain. The ACC has a high opioid content and inhibits pain via opioid, serotonergic, and noradrenergic pathways [32].

Conversely, the medial cingulate cortex, which conveys unpleasant and anxious sensations, is overactive in IBS. As a result, patients with IBS have an exaggerated response to pain and worry [33]. It has also been demonstrated that increased pain in IBS patients appears to be related to an increased tendency to report pain, which seems to correlate with increased psychiatric distress [34].

Patients with DGBI have a higher rate of somatization which contributes to a high rate of associated functional syndromes both GI and non-GI in patients with DGBI [35, 36]. Some of the functional disorders that are more common include functional dyspepsia, fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, sleep disturbances, and sexual dysfunction [37]. Patients with IBS tend to have an increased frequency of comorbid physical as well as functional disorders. The physical disorders include interstitial cystitis, chronic pelvic pain, migraine and/or tension headaches, and fibromyalgia. In Lackner's study, IBS patients had, on average, five comorbid conditions [36].

Treatments that help patients change their way of thinking about their illness can help relieve gastrointestinal symptoms. Psychologic treatments have been demonstrated in meta-analyses to benefit patients with DGBI [38, 39]. One advantage of psychological therapies is that the benefit continues even after the treatment is completed. Addressing underlying psychiatric difficulties can improve symptoms of DGBI. Patients who had panic disorder and IBS, who were treated and then followed for 2 years, and no longer met criteria for panic disorder or panic attacks, were much less likely to have IBS symptoms [40].

One therapy found effective for DGBI is cognitive behavioral therapy (CBT). It is felt that many patients with DGBI have what has been termed "maladaptive cognition" [41]. CBT acts to point out faulty cognitions and helps patients manage them, which helps improve symptoms [42, 43]. Hunt notes that with CBT [44], "Cognitive interventions are about helping (patients) learn to see the world as *accurately* and *objectively* as possible. The problem is that many, many, people

do have negative biases or filters that they use to interpret situations in their lives" [44]. It is these incorrect cognitions that create the impression of a severe threat. Hunt warns her patients, "Don't believe everything you think" [44].

It is important that CBT helps patients to modify the perceived level of a threat because ideas that are perceived as highly threatening make it almost impossible to respond to IBS treatment [4]. Toner [43] notes that patients go around thinking "There must be a medical explanation for this pain." As a result, they are more likely to pay increased attention to body sensations which subsequently become amplified. Patients develop an increased pain sensitivity and convince themselves that something must have been missed which leads to "further physiological arousal and self-scrutiny, which amplifies other bodily sensations. These new sensations may be taken as confirmatory evidence of a physical cause." [43] As Keefer [45] summarizes, "FGIDs are believed to be driven, at least in part, through the development of visceral anxiety, an emotional/affective response to seemingly benign GI sensations such as fullness, acid secretion, or the need to move one's bowels." Additionally she notes, "GI health psychologists typically conceptualize FGIDs as syndromes that may be initiated by a feedback loop of interoceptive sensations stemming from fear conditioning, anxiety, arousal, or stress but maintained by increased attentional focus or hypervigilance to interoceptive 'cues', mislabeling of sensations as dangerous, and avoidance of contexts in which symptoms are predicted; quality of life declines, and individuals become more isolated, further increasing their focus on the FGID" [45]. Cognitions that can be harmful include perfectionism, high need for approval, catastrophic thinking, high need for control [43]. Spiegel delineates four pathological cognitions related to locus of control, catastrophizing, anticipatory concerns, and embarrassment and stigma [41]. As a result of these faulty cognitions, patients tend to suffer helplessness, vulnerability, and low self-esteem [28].

Ongoing psychological stress is felt to result in a decrease in brain gray matter [46], and treatment with antidepressants

has been shown to increase gray matter in these areas of the brain [47, 48]. Patients with IBS have been found to have decreased gray matter in multiple areas of the brain [31]. These include brain networks concerned with attention and emotion modulation, others that act as pain-modulating areas, and to a smaller degree areas involved in processing interoceptive information [31, 49].

In closing, there have been two excellent analyses of the gut-brain interaction in IBS patients, the first of which is by Mayer and Brunnhuber [50]. They denote four major processes that occur in patients with debilitating IBS. First, there is an interaction between emotional factors and gastrointestinal symptoms. Second, the presence of "aversive early-life events" is a significant factor in determining the presence and severity of gastrointestinal symptoms in the adult. Third, GI physiology is influenced by the brain and can be altered by emotional and other learned experiences. And fourth, "Altered central processing and modulation of interoceptive information from the GI tract play a major role in symptoms of pain and discomfort, and prediction errors based on distorted interoceptive memories have been implicated in the pathophysiology of anxiety disorders as well as functional pain disorders" [50].

The second succinct analysis is by Dorn et al. [34]. They have determined that "The increased tendency to report pain and urge in patients with IBS may be the downstream result of multiple cognitive and psychological processes. Firstly, patients with IBS appear to be hypervigilant to gastrointestinal sensations. For example, on functional brain imaging they show similar, abnormal cortical responses to both actual and anticipated (sham) distensions. Secondly, hypervigilance may reduce the intensity at which they notice gut distension and sensations. Thirdly, once perceived, subjects with IBS interpret these sensations through a generally negative schema (framework for explaining reality), which leads them to attribute their sensations to disease. Finally, disease attribution in turn further increases attention to gastrointestinal symptoms through which a cycle of gastrointestinal sensory amplification is ultimately established" [34].

In any individual with a DGBI, there appears to be a continuum of responses. Some patients who have good coping skills, a good social network, and little anxiety may do very well following a minor GI insult. But take another patient with a similar insult who has a superimposed history of abuse and ongoing life stress in whom the disorder may become exaggerated with little likelihood of spontaneous remission [51]. Patients with maladaptive coping and a decreased self-perceived ability to decrease symptoms tend to have poorer results [24].

What is clear from this review is that many patients with hard-to-treat DGBI have a strong gut-brain interaction that requires attention. In initial encounters with patients, the gastroenterologist can get some idea if a patient's symptoms appear to relate to "more gut than brain or more brain than gut" [41] to help determine which patients are more likely to benefit from central therapies.

In subsequent chapters, we will address these central therapies. There will be an overview of the use of psychiatric medications. We will discuss the use of central neuromodulators by the gastroenterologist. We will go into more detail describing the mechanics of CBT and exposure therapy and how they can help patients with more recalcitrant DGBI disorders.

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Chapter 2
How to Use Central Neuromodulators (CNs) to Help Manage Patients with Disorders of Gut-Brain Interaction (DGBI)

W. Harley Sobin

The majority of patients with disorders of gut-brain interaction (DGBI), which was previously referred to as functional gastrointestinal disorders (FGIDs), will respond to peripherally acting drugs and dietary changes. The more complicated ones will not. For this group of patients, central neuromodulators (CNs) may be necessary to improve function [1–4].

Many patients with more intractable symptoms suffer from psychologic distress, anxiety, depression, catastrophizing, and hypervigilance, symptoms that can be alleviated with these drugs [5, 6]. In addition, many CNs have analgesic properties [7, 8]. Some can alter gut motility, slowing colon motility in patients with diarrhea, and speeding it in patients with constipation [3]. They can alter gut sensitivity, helping with nausea, dyspepsia, and bloating.

We will discuss the various CNs used in gastroenterology, how to select them, and how to use them. We will then follow

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up with an explanation of the mechanism of action of the various CNs, their potential side effects, and problems that might arise from their use.

Here are some examples of the types of cases where CNs may be utilized:

1. Patient with functional nausea responding to mirtazapine
   The patient is a 65-year-old male with persistent nausea. He avoids eating because of nausea. He has lost 12 lbs. in the last 3 months. His physical exam is unremarkable. He has had multiple investigations, including EGD, CT scan, gallbladder scintigraphy, which have all been negative. He worries about, and is more anxious because of, his unexplained symptoms. He has no past history of depression. He has been treated with prochlorperazine and ondansetron for nausea with no long-lasting relief. The decision is made to start the CN, mirtazapine, because of the presumed diagnosis of functional nausea. He responds quite quickly. Within a week his nausea has improved, and within a month he has gained back much of his weight loss.
2. Patient with functional dyspepsia responding to buspirone
   The patient is a 35-year-old female, who has chronic fullness and bloating. These symptoms worsen with eating. The symptoms have been ongoing for several months. An EGD, gastric emptying scan, helicobacter pylori testing, and gallbladder scintigraphy are all negative. There is no significant improvement with PPI therapy. She is diagnosed with functional dyspepsia-postprandial distress syndrome. Buspirone therapy is started. Over the next 2 months her symptoms improve 75%.
3. Patient with chronic abdominal pain responding to duloxetine
   A 48-year-old female complains of chronic abdominal pain continuing for several months. This was associated with mild constipation. The pain is fairly persistent, not altered much with meals or bowel movements. Physical exam and workup including labs, ultrasound, and colonoscopy were negative. The patient was treated with several medications including MiraLax, dicyclomine, linaclotide, and plecanatide without relief. A diagnosis of centrally mediated

abdominal pain syndrome (CAPS) was made. She was then started on duloxetine 30 mg a day for this diagnosis. Duloxetine was subsequently increased to 60 mg with significant reduction of pain.

4. Patient with chronic abdominal pain requiring augmentation therapy with quetiapine
   A 58-year-old female had a long history of abdominal pain. She was in an unhappy relationship where she was primary caretaker for a disabled husband who was mildly abusive. Her workup and exam failed to show any organic pathology that would explain pain. She had received dicyclomine, was started on tramadol, and lubiprostone, and had limited response. She was diagnosed with CAPS. The decision was made to try SNRI therapy. Her insurance would not cover duloxetine so venlafaxine was started instead. The patient had a moderate response initially, but then symptoms relapsed. Insomnia and symptoms of anxiety became exacerbated as well as pain. Subsequently, quetiapine was added in escalating doses from 25 mg up to 100 mg. Receiving the combination of venlafaxine and quetiapine she had remarkable improvement in pain, insomnia, and anxiety.
5. Patient with diarrhea and cramps responding to nortriptyline
   A 35-year-old woman with chronic diarrhea and rectal urgency suffered intermittent cramping which usually occurred before a bowel movement. She suffered significant anxiety related to her symptoms. Symptoms were present for at least 6 months. Physical exam and a limited workup were negative, and she was diagnosed with IBS-D. Dicyclomine and imodium had limited benefit. Because of concerns about side effects, she opted not to try alosetron. She was started on nortriptyline and had gradual improvement in pain and diarrhea.

When to Start Central Neuromodulators (CNs)

Before starting CNs, there are other first-line options to consider. Generally, a peripherally acting drug has been tried before starting a CN. Different agents that are used include

antispasmodics, antidiarrheal agents, and drugs for relief of constipation. Many of these agents may act to decrease pain as well. Drugs like dicyclomine, hyoscyamine, loperamide, lubiprostone, plecanide, linaclotide, loperamide, and even alosetron are generally tried before starting CNs.

If patients remain symptomatic in spite of the use of these agents, one can consider turning to a CN. The CNs can help in a multitude of ways. They can help temper anxiety. They can help if there is underlying depression. They can decrease obsessive thinking about symptoms. They can decrease pain. They can decrease visceral hypersensitivity. Various CNs have actions that can decrease symptoms of nausea, bloating, gassiness, diarrhea, constipation, rectal urgency, and stomach fullness.

There are different ways to explain the mechanism of action of the CNs including the monoamine hypothesis, the neuroreceptor hypothesis, glutamate-excitatory, and GABA-inhibitory pathways. The explanation used most often, however, is the monoamine hypothesis [9, 10].

The Monoamine Hypothesis

The monoamine hypothesis states that depression and anxiety are correlated with a deficit in the monoamines serotonin, norepinephrine, and dopamine. And most antidepressants act to increase levels of these monoamines.

Each monoamine is released from its specific neuron, then acts on specific receptors, then gets transported back into the neuron by a specific transporter. Many of our CNs act to specifically target and inhibit one or more of these transporters.

By inhibiting the transporters, these drugs will increase the level of one or more of the monoamines: serotonin, norepinephrine, and dopamine. Increasing levels of serotonin may improve symptoms of anxiety and depression. Increased norepinephrine will have analgesic properties, as well as benefitting anxiety and depression. Increased dopamine also helps anxiety and depression but is also more stimulating. When using these drugs, one needs to temper their use with associated side effects.

With serotonin, only 5% gets released into the central nervous system, but 95% acts upon the gut. In the gut, increased serotonin is associated with nausea and diarrhea. Increased norepinephrine can cause sweating, light-headedness, dry mouth, constipation, and rise in blood pressure. Increased dopamine may be associated with increased nausea.

SSRIs, SNRIs, and TCAs

The three major classes of CNs that work to inhibit monoamine transporters are the selective serotonin reuptake inhibitors (SSRIs), the serotonin norepinephrine reuptake inhibitors (SNRIs), and the tricyclic antidepressants (TCAs).

SSRIs

SSRIs inhibit SERT, thereby increasing levels of serotonin. They can benefit our patients by decreasing anxiety, depression, and hypervigilance [11–13]. Because they tend to cause diarrhea, we use them more to treat patients with functional constipation or IBS-C. Even though SSRIs generally don't have much analgesic properties, they have been found beneficial in treating functional chest pain in small case studies. Besides for causing diarrhea, SSRIs may also cause nausea and sexual side effects. The preferred SSRI is escitalopram, which has the purest SERT inhibition. It is better tolerated, has fewer side effects, and is probably the most efficacious SSRI. Citalopram and sertraline are other choices. Paroxetine and fluoxetine may also be used, but they tend to have more drug-drug interactions.

SNRIs

SNRIs inhibit SERT and NET, increasing levels of serotonin and norepinephrine. These drugs are strong central analgesics and outside of GI they are used to treat painful fibromyalgia

and neuropathy. In GI, we use them to treat painful syndromes including centrally mediated abdominal pain and IBS [13, 14]. Most of the controlled studies looking at the use of SNRIs to decrease pain have been in the realm of pain medicine and rheumatology. There have been limited controlled trials in gastroenterology, but efficacy is felt to be similar. Problematic side effects of SNRIs include nausea, and they do tend to be constipating, although less so than TCAs. They can also cause hypertension. The preferred SNRI tends to be duloxetine because at low doses it acts as both a SERT and NET inhibitor. Venlafaxine, on the other hand, at low doses is just a SERT inhibitor. To get NET inhibition, you have to go to levels of 150–225 mg. Milnacipran is an SNRI that is approved for fibromyalgia in this country, not depression, although it is approved for depression in Europe. Therefore, if you have a patient who needs to be on an SNRI but who objects to the use of a "psych drug," they may accept milnacipran.

TCAs

TCAs are like SNRIs, in that they inhibit SERT and NET. But they also act on many other receptors, causing various side effects. You can have anticholinergic, antihistaminic, and anti-alpha-adrenergic side effects. TCAs are also strong analgesics and anti-anxiety agents as well as antidepressants. In GI, they are also used for painful syndromes, including IBS and centrally mediated abdominal pain (CAPS) [3, 15]. But because they tend to be constipating, they are more useful for IBS-D than IBS-C. Other side effects include dry mouth and orthostatic hypotension (the latter symptom is due to alpha-adrenergic blockade). But in high doses, higher than we would generally use, they can also cause seizures and arrhythmias. The preferred TCAs are the secondary amines nortriptyline and desipramine. They cause fewer anticholinergic side effects. Amitriptyline is a tertiary amine. It tends to cause more anticholinergic side effects, including increased constipation. But this can be useful in some patients with severe diarrhea. Imipramine is another tertiary amine. Currently, it is used less than amitriptyline in the USA.

Action of CNs on Various Receptors

Besides for acting on monoamine transporters, the CNs act on a number of receptors. Although there are a multitude of receptors affected, there are a few most relevant to gastroenterologists. Neuromodulators that stimulate the 5HT1 receptor will increase gastric compliance and accommodation. Buspirone is an example. Drugs that inhibit the 5HT3 receptor decrease nausea and diarrhea. Ondansetron and alosetron are 5HT3 inhibitors. So are the central neuromodulators mirtazapine and olanzapine, which are potent drugs for treating chronic nausea. D2 inhibition, which is a property of all antipsychotics, also decreases nausea. Metoclopramide and domperidone are D2 inhibitors. We use many central neuromodulators that inhibit D2 including olanzapine and quetiapine. M1, or muscarinic receptor inhibition, represents anticholinergic action. This is generally felt to be an adverse side effect of all tricyclics and many atypical antipsychotics causing dry mouth and constipation. But this property can be a benefit to our patients with chronic diarrhea. That's why TCAs are more useful in treating IBS-D than IBS-C.

Paroxetine is an SSRI. But besides for inhibiting SERT, it also has significant M1 inhibition. Most SSRIs cause diarrhea, but paroxetine is the exception. Because of its M1 inhibition it can cause constipation.

H1, or histamine inhibition, is also generally felt to be an adverse side effect of all TCAs and many atypical antipsychotics. H1 inhibition tends to cause lethargy and weight gain. But, once again, these properties may benefit our patients with DGBI who also suffer from insomnia or anorexia.

Mirtazapine

Mirtazapine is another drug in our armamentarium, and it's extremely useful for the gastroenterologist [16, 17]. It's a strong 5HT3 inhibitor and has a long half-life. Therefore, one dose at bedtime helps control nausea for 24 hours. We use it to treat functional nausea and vomiting and functional dyspepsia. Psychiatrists favor mirtazapine because it's very safe

and fairly well tolerated in the elderly, it doesn't tend to cause sexual side effects, and it acts faster than other antidepressants. However, mirtazapine can cause excessive day time lethargy and weight gain. Nonetheless, weight gain is generally desirable in patients with functional nausea.

The ideal patient for mirtazapine is someone who has had chronic nausea for months, has lost weight, and has had investigations that fail to show any organic pathology (confirming the diagnosis of functional nausea). Patients generally become despondent as a result of these symptoms. If they are prescribed mirtazapine, some will have rapid relief of symptoms, start gaining weight, and experience an improvement in their mood. If patients are going to quit mirtazapine, it is generally because of excessive daytime lethargy. Mirtazapine intolerance may be more common in younger patients, under 35 years old. But this is certainly not a contraindication to trying the medication in the younger patient.

Buspirone

Buspirone is another tool in our tool kit. It's a 5HT1 agonist. It enhances gastric compliance and accommodation [18]. It can be useful for bloating, early satiety, and postprandial distress. In psychiatry, it is used as an antianxiety agent. Because it's not a benzodiazepine, it doesn't cause dependence or withdrawal. While dizziness and drowsiness are potential side effects, the drug does not tend to impair psychomotor skills [10].

Trazodone

Trazodone has been found to be beneficial in treating functional chest pain [19, 20]. It inhibits SERT and 5HT2. In psychiatry, it is primarily used to treat anxiety and insomnia.

Atypical Antipsychotics

Atypical antipsychotics (second-generation antipsychotics, also known as SGAs) have been used to treat functional

gastrointestinal disorders [21]. Of course, they were first developed to treat schizophrenia, other forms of psychosis, and bipolar illness. But now there are many other uses for SGAs, inside, and outside, of psychiatry. They are used as adjuncts in treating depression, pain, nausea and vomiting, and anxiety and insomnia. Doug Drossman's group studied the use of quetiapine [21] in patients with chronic pain, who were on TCAs or SNRIs but still suffered residual symptoms. They added low-dose quetiapine at night as an augmenting agent and found marked relief of symptoms. Quetiapine can be sedating and cause weight gain, and if these symptoms become problematic, aripiprazole and brexpiprazole are alternatives.

SGAs have also been used to manage chronic nausea and vomiting, particularly olanzapine, but also quetiapine. But while some SGAs benefit nausea, other SGAs, like aripiprazole, lurasidone, ziprasidone, and brexpiprazole can worsen nausea. The explanation for this is that some of the early atypical agents, including olanzapine and quetiapine, were found to be very effective in treating psychosis, but they tended to cause a lot of weight gain and metabolic syndrome. As a result, other agents were developed that were more weight neutral, including aripiprazole, lurasidone, and ziprasidone. These SGAs did not tend to increase appetite, but rather were more likely to cause nausea. An inverse correlation exists, where those SGAs that cause the most weight gain cause the least nausea. And those that cause the least weight gain cause the most nausea. If you are evaluating a patient for persistent nausea who is taking aripiprazole, lurasidone, or ziprasidone, it is worth checking with the patient's psychiatrist to see if they can be switched to olanzapine or quetiapine. Oftentimes making that change can alleviate symptoms.

The mechanism of action of the SGAs relates to their effect on a multitude of receptors and transporters. One example is olanzapine. This drug benefits our patients with chronic nausea because it inhibits 5HT3 and D2. But because it inhibits M1 it can cause constipation and other anticholinergic side effects. Its H1 inhibition may lead to weight gain and lethargy.

With quetiapine, there is NET inhibition, which helps explain analgesia, and D2 inhibition to help relieve nausea. Because it inhibits H1, it tends to cause lethargy and weight gain, and because of M1 inhibition, we see constipation and other anticholinergic side effects.

On Choosing a Neuromodulator for a Specific Symptom

Relief of Pain: If patients have chronic pain, particularly centrally mediated abdominal pain, or IBS, we tend to start with a TCA or SNRI. Both of these boost levels of norepinephrine and have strong analgesic properties. In GI, we have many more years of experience using TCAs. They are inexpensive and widely available. The TCA we generally prefer is one of the secondary amines, nortriptyline, or desipramine [3, 22]. With these agents, there are fewer anticholinergic side effects than with amitriptyline or imipramine. Dosing for these two drugs is equivalent. Therapeutic doses of these medications are generally in the range of 50 mg or more, but, to avoid intolerable side effects, you need to start with a lower dose and gradually escalate. The starting dose is usually 25 mg. This should be increased to 50 mg after a week or two. For patients with extreme medication sensitivity, you might start with 10 mg. However, it is important to increase dosing as quickly as possible to more therapeutic levels so that a clinical response may be achieved before the patient becomes frustrated [3, 22].

Patients need to be advised that side effects start immediately, but therapeutic benefit may take a month or more. If there is no response to 50 mg of nortriptyline or desipramine after a month, you can increase to 75 mg. After that, if there is insufficient response, you may turn to higher doses, or switch to an SNRI, or use augmentation therapy. Doses up to 150 mg have been studied but higher doses of TCAs are more likely to cause side effects.

SNRIs are often better tolerated than high-dose TCA. Therefore, if a patient does not respond to increasing doses of TCA, it is reasonable to switch to an SNRI. We generally suggest using duloxetine. The recommended starting dose of duloxetine is 30 mg. After 1–2 weeks, it is best to increase to 60 mg which is a more therapeutic dose. If after a month at 60 mg the patient isn't improving, one can increase the SNRI dose (up to 90 mg) or consider augmentation therapy. If venlafaxine is used, doses of 75–225 mg may be used.

Augmentation Therapy for Pain [3, 13, 22, 23]: If a patient's pain hasn't responded to a course of TCAs or SNRIs, it is reasonable to add another agent.

Atypical antipsychotics have been found beneficial as augmentation agents for patients who haven't responded to TCAs or SNRIs [21]. Quetiapine is the most frequently used SGA as augmentation for pain relief. Starting with a dose of 25 mg HS, and then slowly, if necessary, increasing the dose to 100 mg HS helps with sleep, anxiety, and pain. Quetiapine may cause excessive daytime lethargy and weight gain, and if these become problematic, other alternatives include aripiprazole or brexpiprazole. These two drugs are less sedating and less likely to cause weight gain (but more likely to cause nausea).

Gabapentin, pregabalin, and memantine (an NMDA antagonist) are other agents that may be used as augmentation therapy for pain. Gabapentin is used in gradually increasing doses from 100 to 1800 mg, pregabalin in doses of 75–300 mg, and memantine in doses increasing from 5 to 30 mg.

Underlying Bowel Function: In choosing a neuromodulator, you want to consider the patient's bowel function. SSRIs tend to cause diarrhea, with the exception of paroxetine, which can be constipating. TCAs tend to be constipating, with amitriptyline and imipramine being the most constipating. SNRIs are slightly constipating, generally less than TCAs. So,

for the patient with severe constipation an SSRI (not paroxetine) would fit well, if an appropriate choice otherwise. If an SSRI is not appropriate, an SNRI might be preferable to a TCA. In the constipated patient, you would prefer nortriptyline or desipramine to amitriptyline if a TCA is necessary. If a patient has diarrhea, an SSRI would be undesirable (except for paroxetine), but a TCA would work well. If there is severe diarrhea, amitriptyline might be the desired TCA of choice.

Underlying Energy Level: In choosing a neuromodulator, the patient's level of wakefulness needs to be taken into consideration. For patients with insomnia, quetiapine, mirtazapine, and trazodone can all help with sleep. For lethargic patients, bupropion, sertraline, and fluoxetine are more stimulating.

Functional Dyspepsia-EPS Type

For the patient with functional dyspepsia-epigastric pain syndrome (EPS) type, the TCAs have been used most frequently. Much of this experience has been with amitriptyline. The dosage for amitriptyline is the same as for nortriptyline or desipramine, generally starting with 25 mg and then increasing to 50 mg after 1–2 weeks. For patients who are intolerant of amitriptyline because of anticholinergic side effects, nortriptyline or desipramine may be considered. SNRIs may also be used.

Functional Dyspepsia-PDS Type

For the patient with functional dyspepsia-postprandial distress syndrome (PDS) type, buspirone and mirtazapine have been found beneficial. Early satiety, bloating, and epigastric fullness will often improve with buspirone, which acts to improve gastric accommodation. Starting doses of 7.5 mg bid

(or 5 mg tid before meals) can then be increased to 15 mg bid in 1–2 weeks. If after a month of treatment the response is incomplete, the dose can be raised to 30 mg bid (or as high as 45 mg bid). Alternatively, mirtazapine can be tried. Mirtazapine is given once nightly. Starting dose should be either 7.5 or 15 mg. We usually aim for a dose of 15 mg by week 2. This dose is generally effective, but if not, it may be gradually increased after a month to 30 or 45 mg.

Nausea and Vomiting

For patients with chronic nausea who don't respond to ondansetron or prochlorperazine, mirtazapine maybe effective. For patients with functional nausea that is prolonged, particularly if there is associated weight loss, mirtazapine should be considered. It is effective in keeping nausea in remission and also acts to control anxiety and insomnia. As outlined earlier, the dosage for mirtazapine is 7.5 or 15 mg given HS as a starting dose. By week 2, most patients should be on 15 mg. If this is insufficient, doses can be increased to 30–45 mg.

For patients intolerant of mirtazapine, or who don't respond, an alternative is olanzapine. Olanzapine is also a very potent medication for controlling nausea due to its 5HT3 and D2 inhibition. Some patients who have excessive lethargy with mirtazapine may have less lethargy with olanzapine. The starting dose for olanzapine is 2.5 mg. This can be increased in week 2 to 5 mg. If necessary, the dose may subsequently be increased to 10 mg.

Cyclic Vomiting Syndrome

For patients with cyclic vomiting syndrome (CVS), amitriptyline is the most frequently used drug for prophylaxis. But, if patients have persistent nausea and vomiting, both mirtazapine and olanzapine have been used effectively. Of course, it is essential with CVS to insure patients are not taking cannabinoids.

Side Effects of Central Neuromodulators

Sexual Side Effects: Sexual side effects are most common with drugs that inhibit SERT. Although this may be seen with all SSRIs, it is most common with paroxetine. Sexual side effects are less common in patients taking SNRIs or TCAs in the low doses used in gastroenterology. The CNs least likely to cause sexual dysfunction are bupropion and mirtazapine. Trazodone is also unlikely to cause problems except for rare cases of priapism. Psychiatrists frequently deal with issues of sexual dysfunction in their patients. They generally manage this problem by changing their patient over to bupropion, or mirtazapine, or adding sildenafil.

Nausea and Vomiting: As described earlier, nausea can be seen in patients started on SSRIs and SNRIs, particularly in the first few days and weeks. The nausea that occurs with SNRIs may be more problematic. This adverse effect may be lessened if the drugs are taken with food.

For patients taking atypical antipsychotics (SGAs), certain SGAs are more likely to cause nausea. These include aripiprazole, lurasidone, and ziprasidone. Others, like olanzapine or quetiapine, are more likely to benefit nausea.

The drugs bupropion and topiramate are associated with an increased incidence of nausea. Both of these drugs have been used to promote weight loss. Many drugs that prevent weight gain tend to be associated with an increased frequency of nausea.

Change in Bowel Habits: Most SSRIs can cause diarrhea, with the exception of paroxetine, which can cause constipation. TCAs are all constipating, with amitriptyline the most constipating. Some SGAs can be constipating like olanzapine and quetiapine (due to anticholinergic properties).

GI Bleeding: SSRIs are capable of exacerbating GI bleeding due to their action inhibiting serotonin reuptake by platelets, which can interfere with clotting. This property is exacerbated if patients are also on NSAIDs. The increased risk of bleeding has been variably cited at 1.66–2.36 times increase if on SSRIs

alone or 4.25–6.33 times increase if on combined SSRI and NSAIDs [24, 25]. In addition, a fourfold increased risk of bleeding after PEG placement has been cited [26].

In spite of this increased risk, we do not recommend discontinuing SSRIs prior to an endoscopic or surgical procedure. In general, NSAIDs should be avoided in patients on SSRIs, and if patients are at increased risk of bleeding, prophylactic PPIs may be considered. It is not wise to stop SSRIs prior to procedures because it can cause discontinuation syndrome in patients on drugs with a short half-life, and would have to be stopped for a long period of time for drugs with a long half-life.

Unmasking a Bipolar Disorder: If an antidepressant (AD) is given to a patient with an occult bipolar illness, it can precipitate an episode of hypomania or mania. Usually this would commence fairly soon after starting the AD. While this is an unlikely event, if a patient receiving a CN for a DGBI starts showing signs of mania, the CN should be discontinued and the patient referred to a psychiatrist.

Disclaimer: The use of antidepressants and other CNs has been associated with serious side effects and occasional increased risk of suicide (particularly in those aged 25 and younger). It is important to enlist the assistance of psychiatrists in dealing with patients with significant depression or in cases where the practitioner is unfamiliar with the use of these drugs or treatment combinations.

Questions That Are Frequently Asked

1. How do you deal with a patient's reluctance to take what they consider "psych meds"? Often times their reaction is to ask "Do you think I'm just crazy? Do you think it's all in my head?"

   First, we use the term central neuromodulators, rather than psychiatric medications, to help convey the idea that we don't "think they are crazy," and there are other purposes for using these drugs. What we tell them is that these drugs are used extensively outside of psychiatry to

treat conditions other than anxiety and depression. They are used to treat migraines, fibromyalgia, insomnia, vasomotor symptoms of menopause, and neuropathy. As mentioned previously, we are using these drugs to benefit DGBI by decreasing pain, altering gut motility, and relieving various other symptoms.

2. How do you get a patient to accept the idea of taking an "atypical antipsychotic"?

   Once again, we let them know that these drugs have varied uses. Olanzapine has been used in anesthesia and in oncology to manage nausea. Quetiapine has been used in fibromyalgia to treat pain and has been used as an adjunct for managing insomnia and anxiety. The term "antipsychotic" may elicit alarm, but most patients taking SGAs today are taking them for indications other than psychosis.

3. Why does it take weeks for many of these drugs to take effect?

   Shortly after starting an SSRI, SNRI, or TCA, the inhibition of monoamine transporters leads to elevated levels of monoamines. However, the receptors for these monoamines are upregulated and therefore shut off to neurotransmission. It takes weeks before the receptors can downregulate. Once the receptors downregulate, neurotransmission occurs. The downregulation of the receptors requires some genetic changes. It is these changes that take several weeks to occur and explains the delay in efficacy.

4. What happens if patients miss doses of their CNs?

   For drugs with a long half-life, this is not much of a problem. Fluoxetine and mirtazapine have long half-lives. However, for drugs with a short half-life, missing a dose or several doses can lead to the discontinuation syndrome, which includes diarrhea, insomnia, nausea, and excitability. Paroxetine has the shortest half-life of the CNs used in GI, followed by sertraline.

5. When using CNs, why not just start everyone on the lowest possible doses? For example, with TCAs why not start everyone on 10 mg desipramine or nortriptyline?

   The problem with starting at these low subtherapeutic doses is that it will take longer to get to a full therapeutic

dose. Remember that the therapeutic benefit is delayed even with full therapeutic doses. Starting at lower doses causes further delay. While patients are waiting for clinical benefit to take place, they may get increasingly frustrated and stop the drug prematurely.

6. Are side effects always related to drug dosage?

   In practice, we generally recommend starting CNs at a lower dose and then relatively quickly, in 1–2 weeks, going to a more therapeutic dose. The argument for starting at a lower dose is to decrease the side effects some patients may experience when starting these medications. However, Drossman's group [27] did a study demonstrating that other factors were also significant. They evaluated the level of side effects in patients on desipramine, many of whom were anxious at the initiation of the study. They found that, indeed, there were increased reports of side effects in these patients. However, the degree of side effects didn't correlate with the dose of drug or the blood level. Indeed, many of the symptoms (later called side effects) were present before the patient started the drug, then blamed on the drug later. Indeed, the factor that correlated the most with side effects was the patient's baseline anxiety level.

7. Do the CNs help patients with DGBI by acting as antidepressants, or do they act by other mechanisms? And do CNs act centrally or peripherally?

   While anxiety and depression can exacerbate symptoms in patients with DGBI, the CNs tend to work whether a patient is depressed or not. Much of the action is central, working on nausea centers, pain pathways, worry, fear pathways. Some of the action is peripheral, at gut level, i.e., constipation from amitriptyline and diarrhea from sertraline. Benefit in managing nausea and pain occurs by both central and peripheral mechanisms.

8. How do you address concerns about toxicities with atypical antipsychotics?

   One concern people have is fear of permanent extrapyramidal side effects and tardive dyskinesia. First, the incidence of EPS is much lower with SGAs than with

first-generation antipsychotics. Second, and a theme we will keep repeating, is that we are using very low doses of the SGAs, so the likelihood of EPS is much lower.

Metabolic syndrome is another possible side effect of SGAs, and it is a concern, particularly with olanzapine and quetiapine. Again, it is less likely because we are often using smaller dosages. Second, once we start getting a response to the drug (i.e., relief of nausea with olanzapine or pain with quetiapine), we will try to gradually decrease the dosage. Third, if a patient has too much lethargy or weight gain from quetiapine, they can switch to aripiprazole or brexpiprazole.

Cardiac toxicity is another concern. This was more of a problem with first-generation antipsychotics. The drug thioridazine (Mellaril) was taken off the market because of concerns of cardiac toxicity, after many years of wide usage. In spite of the relative infrequency of cardiac problems, it is prudent to restrict these drugs in patients with active arrhythmias or recent MI.

9. Can CNs be used in patients with liver disease?

In general, the use of CNs is relatively safe in patients with liver disease unless they have advanced cirrhosis. There are rare instances of hypersensitivity reactions to CNs that can cause liver failure. One example of this is duloxetine. However, these appear to be idiosyncratic, unpredictable, and fortunately rare. In patients with advanced cirrhosis dosages of CNs may need to be decreased, and sedating drugs need to be avoided. The most common concern about liver disease related to CNs is weight gain and metabolic syndrome. These may be harbingers of fatty liver and NASH.

10. Can CNs be used in patients with heart disease?

There are certain guidelines, and concerns, regarding use of CNs in patients with cardiac disease. First, EKGs should be obtained in all patients on TCAs who have a history of heart disease, as well as all patients over 50 whether or not they have a history of heart disease. How do TCAs cause cardiac problems? First, they act like type 1 anti-arrhythmia agents, because they inhibit the voltage-

sensitive sodium channel, also known as the cardiac fast channel. In higher doses, they can lead to arrhythmias like torsade de pointes and heart block.

In general, SSRIs are safer than TCAs in patients with heart disease. The one exception is citalopram, where there is more of a risk of QT prolongation and heart block, and if used in patients with cardiac disease (as well as the elderly), lower doses should be used (generally no more than 20 mg in this group). Although escitalopram does not carry the same FDA arrhythmia risk assigned to citalopram there may be some QT prolongation. Therefore, it should also be avoided in patients at risk of QT prolongation or who had a recent MI.

Patients receiving SGAs who have a history of cardiac disease should also have a baseline EKG (and serial EKG monitoring on the drugs). Patients with a prolonged QT interval (greater than 450 ms) should not be given TCAs, SGAs, citalopram, or escitalopram.

11. Is there concern about serotonin syndrome in patients receiving CNs?

    Serotonin syndrome is a set of symptoms, including fever, muscle rigidity, hyperreflexia, and delirium caused by elevated levels of serotonin. Serotonin syndrome is most common in patients on high doses of SSRIs, generally in association with high levels of TCAs (which also increase serotonin levels). Other drugs that may increase serotonin levels are triptans, tramadol, and ondansetron. That being said, serotonin syndrome is very uncommon in our patients with the low doses of drugs generally being used.

12. Which CNs are most problematic in the elderly?

    Drugs with muscarinic inhibition, like high-dose TCAs, because of their anticholinergic effects. In the elderly, these drugs may cause confusion, urinary retention, and constipation. TCAs have a more narrow therapeutic window in the elderly, and higher doses may lead to heart block and arrhythmias. SSRIs are believed to be safer in the elderly than TCAs, having a wider therapeutic window. Also, the use of SGAs in elderly patients with dementia is specifically contraindicated (black box warning) because of increased mortality. Drugs with

alpha 1 adrenergic blockade are more likely to cause postural hypotension in the elderly.

13. How may CNs that inhibit dopamine lead to side effects?

    The CNs that we use that are dopamine inhibitors are the SGAs.

    There are several different dopamine pathways and inhibition of each one has different actions and side effects. Inhibition of the nigrostriatal pathway may be associated with movement disorders. EPS and tardive dyskinesia are movement disorders that were more common with first generation antipsychotics than the currents SGAs. Inhibition of the tuberoinfundibular pathway may lead to excessive prolactin release. Galactorrhea and sexual side effects were more common with first-generation antipsychotics than SGAs. Psychosis itself is generally felt to be associated with an excess of dopamine in the mesolimbic pathways, and inhibition of dopamine in these pathways is the hallmark by which all antipsychotic drugs work. In psychosis, the mesocortical pathways are felt to be associated with negative affective symptoms and theorized to be related to a deficit of dopamine. Theoretically blocking dopamine in these pathways could worsen these negative symptoms.

14. Why are there fewer side effects with SGAs compared with first-generation antipsychotics?

    The SGAs are called serotonin-dopamine antagonists because they all block 5HT2A receptors as well as D2 receptors. Normally, 5HT2A receptors block the release of dopamine. If 5HT2A receptors are blocked, there is increased dopamine release. We see this increased dopamine release in the nigrostriatal, tuberoinfundibular, and mesocortical pathways, but it does not occur to the same extent in the mesolimbic pathway. It is this increased dopamine release in these critical brain regions that makes undesirable side effects less likely. Therefore, with SGAs there is less EPS, less hyperprolactinemia, and fewer negative affective symptoms, but the antipsychotic effects remain active.

15. How are pain pathways altered in patients with DGBI?

    First, patients with DGBI tend to have altered peripheral pain perception, visceral hypersensitivity. Second,

they may have segmental central sensitization, which is an excessive response to peripheral stimuli (hyperalgesia). Third, there may be a defect in the usual inhibitory descending pathways, the anterior cingulate cortex (ACC), or excessive stimulation of the MCC. Fourth, they may have an increased pain response in the absence of increased stimulation of peripheral pain fibers (allodynia). This is the case in patients with CAPS and also in patients with fibromyalgia.

16. Which CNs may benefit anxiety?

    With chronic use, SSRIs and SNRIs are felt to be first-line agents in controlling anxiety. The alpha 2 delta ligands, pregabalin and gabapentin, may help treat anxiety. Trazodone, buspirone, and mirtazapine are excellent anxiolytic agents. Of course, benzodiazepines are useful for anxiety, but we recommend limiting their use because of concerns with addiction and withdrawal symptoms. If a benzodiazepine is used, we recommend clonazepam because of its longer half-life.

17. How do antianxiety meds work?

    Benzodiazepines work by stimulating GABA. GABA is an inhibitor working on the fear and worry loop in the amygdala and the CSTC loop in the brain. Alpha 2 delta ligands are also used as antianxiety meds. These act on voltage-sensitive calcium channels to decrease glutamate release. SSRIs and SNRIs are also antianxiety meds. These act to increase levels of serotonin and norepinephrine in the fear and worry circuits of the brain where levels are disturbed.

18. Which CNs are the most sedating?

    Mirtazapine, quetiapine, trazodone, paroxetine, and olanzapine.

19. What properties of CNs tend to lead to weight gain and which weight loss?

    H1 blockade, 5HT2c blockade, and 5HT3 blockade all tend to promote increased appetite and weight gain. Dopaminergic agents tend to cause weight loss (bupropion, aripiprazole, brexpiprazole).

Pitfalls in Management

1. Patients expect rapid results with minimal side effects. They need to be well informed that it may take over a month to see benefit, yet side effects will occur right away. As part of the education, they can be informed that the severity of side effects often improves as time goes on.
2. When SSRIs and SNRIs are first started, they may increase levels of anxiety. This seems paradoxical, since SSRIs and SNRIs are felt to be excellent first-line treatments in the management of chronic anxiety. And yet it is true. Early, there may be increased anxiety. One way to manage this is to educate the patient and start with lower drug dosages. But another possible strategy for managing a very anxious patient being started on these drugs is to use a long-acting benzodiazepine. You can start clonazepam 0.25 mg bid going to 0.5 mg bid, if need be, but with the understanding that you are going to taper off the benzodiazepine after a month, once the CN is expected to kick in.
3. Patients may abandon the CNs early on without informing their doctor. Because people are used to getting very rapid results, they may misinterpret the slower onset of action of these drugs as drug failure. Therefore, it is important to have a short-term follow-up with the patient over the phone or in the office to insure there are no misunderstandings and that they don't abandon the drug prematurely.
4. Patients need to be educated that they shouldn't abruptly quit a CN they have been on for a few weeks or more. If they do, they may suffer a discontinuation syndrome. This is more common with drugs with a shorter half-life, like paroxetine and sertraline.
5. One possible mistake by the physician, is not increasing the patient's drug dosage to sufficient levels. As a result, the patient may never receive a truly therapeutic dose. While it is prudent to start with a lower dose of CN, a true therapeutic dose may be significantly higher. Abandoning a CN prematurely, because of lack of efficacy, before giving the

drug in a high enough dosage, is a pitfall some practitioners may fall into.

6. A few patients will respond to the lower dose range of the CN but be intolerant of higher doses. It is certainly acceptable to maintain patients on the lower dose. If over time, they start to relapse one should reattempt the higher dose.

Dosing of central neuromodulators to treat functional bowel disorders

Drug	Class	Dosage
Amitriptyline	TCA	25–150 mg
Aripiprazole	SGA	2.5–5 mg
Buspirone	MISC	15–45 mg bid
Brexpiprazole	SGA	1–1.5 mg
Desipramine	TCA	25–150 mg
Duloxetine	SNRI	30–90 mg
Escitalopram	SSRI	5–20 mg
Fluoxetine	SSRI	10–40 mg
Imipramine	TCA	25–150 mg
Minacipran	SNRI	50–100 mg bid
Mirtazapine	MISC	7.5–45 mg
Nortriptyline	TCA	25–150 mg
Olanzapine	SGA	2.5–10 mg
Paroxetine	TCA	10–40 mg
Quetiapine	SGA	25–200 mg
Sertraline	SSRI	50–150 mg
Trazodone	MISC	75–150 mg
Venlafaxine	SNRI	75–225 mg

SGA second-generation antipsychotic, *SNRI* serotonin and norepinephrine inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant

Unless noted otherwise, dosages are once daily

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Chapter 3
A Psychopharmacology Guide by Psychiatrists for Non-psychiatrists

Thomas W. Heinrich, Julie Ruth Owen, and Deepa S. Pawar

Introduction

The optimal care of patients experiencing a psychiatric illness, whether depression, anxiety, or schizophrenia, requires the clinician to consider both pharmacologic and nonpharmacologic approaches to treatment. There are an ever-increasing number of effective pharmacotherapy options available, and many have multiple psychiatric or medical indications. However, psychopharmacology should only be considered one component of a larger overall therapeutic approach or treatment plan. Research has also revealed that a wide variety of therapeutic nonpharmacologic interven-

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tions exist. These range from various evidence-based psychotherapies (cognitive behavioral therapy), lifestyle modifications (exercise), and somatic therapies (rTMS) [1–3]. The clinician and patient must carefully analyze the risks and benefits of the variety of possible therapeutic interventions as they relate to that specific patient before embarking on the most appropriate, and hopefully effective, treatment plan.

Principles of Psychopharmacology

Diagnosis and Symptom Assessment

A solid working diagnosis is required for optimal pharmacologic treatment of all disease states [4]. Effective treatment is also further augmented by an appreciation of the specific symptoms that are most burdensome to the patient. The longitudinal assessment for improvement in these specific "target symptoms" may allow for improved patient engagement in ongoing care and subjective evaluation of the effectiveness of treatment. The utilization of validated screening and severity scales, such as the Patient Health Questionnaire (PHQ-9) [5] may also serve the dual purpose of aiding in diagnosis and providing a more objective measure of the patient's symptom burden when utilized longitudinally during clinical follow-up.

Selecting a Psychopharmacology Treatment

Once the clinical decision is made to initiate medications as part of a broader treatment plan, one must choose an appropriate medication. There are often multiple different medications available to treat a specific condition, and these medications often share similar efficacy. As a result, medication selection should be individualized and based on historic response, safety profile, anticipated side effects (desired and undesired), drug interactions, patient preference, convenience, and cost [6]. When considering safety and tolerability, the clinician must appreciate co-occurring psychiatric or general

medical conditions along with potential drug interactions. A careful accounting of the patient's current medications as well as their utilization of over-the-counter medications and supplements is imperative to help prevent potentially dangerous drug interactions.

Regardless of the diagnosis or target symptoms being treated, patients benefit from education. This is true whether the selected treatment is pharmacologic or psychosocial. Education should focus on the clinical diagnosis, rationale for treatment, expected efficacy, potential adverse effects, and treatment course/duration. These important discussions will also serve to enhance the clinician-patient relationship, a key component to successful therapeutic outcomes. Another treatment consideration is the identification of factors that may adversely impact treatment adherence. If possible, these barriers must be addressed to mitigate a possible contributing factor to treatment failure. When evaluating a patient with a history of medication treatment failures, a detailed treatment history should be conducted which should include a detailed review of the dose, duration, tolerability, adherence, and reason for discontinuation for each prior treatment. Many prior treatment failures are the unfortunate result of inadequate dosing, inadequate treatment duration, or nonadherence due to adverse effects or lack of understanding of the intended treatment course.

Drug-Drug Interactions

The prevention of potential drug interactions is based on an understanding of a couple of foundational principles of pharmacology: pharmacodynamics and pharmacokinetics. Pharmacodynamics is the study of how medications exert their effect. This mechanism of both therapeutic and potential adverse effects is accomplished through the medication's interaction(s) with a receptor or receptors. It is the extent of a medication's ability to impact the receptor(s) that determines its therapeutic action and potential for non-therapeutic adverse effects. Receptors may be impacted in multiple ways,

depending on the medication. For example, receptors may experience activation/agonism, inhibition/antagonism, or alteration when exposed to a medication. Drug interactions and possible toxicity may occur when multiple drugs impact the same receptors.

Pharmacokinetics is the study of a drug's absorption and distribution throughout the body as well as its subsequent metabolism and excretion. Absorption rates differ among the various routes of administration, with parenteral administration often facilitating more rapid effects than oral administration. Oral absorption is generally similar among psychiatric medications but may be impacted by various factors; for example, absorption is often decreased in a less acidic gastric environment, often related to the chronic use of antacids. Psychiatric medications experience a wide volume of distribution due to their lipophilic properties. Highly protein-bound compounds, such as most psychiatric medications, may displace other medications from circulating proteins. This displacement has the result of increasing the "free" and biologically active form of the displaced medication which may lead to toxicity. The high level of protein binding of psychiatric medications is also relevant as protein levels often decrease with age, malnutrition, and chronic illness thereby leading to increased levels of active drug and a resulting risk of adverse events. This risk necessitates initiating medications at a lower dose to avoid high free drug levels in at-risk patients.

The metabolism of medications most often takes place in the liver, where enzymes produce either active or inactive metabolites. These metabolites may be subsequently excreted by the kidney or in feces. The liver utilizes two main processes to metabolize medications: oxidative metabolism utilizing the cytochrome P450 enzyme system or conjugation. The oxidative process and its P450 enzymes are impacted by many factors including disease states, genetic variation, and drug interactions. There are four P450 enzymes that are especially significant in the metabolism of psychiatric medications (1A2, 2C, 2D6, and 3A4). These enzymes may be subject, through either genetics or pharmacology, to induction or inhibition of

the dependent metabolism. If a P450 enzyme is inhibited, metabolism of medications through this specific enzymatic pathway is slowed, and drug levels increase, potentially leading to toxicity. Alternatively, if a P450 enzyme's metabolism is induced, the metabolism of medications via that pathway will be accelerated potentially leading to a reduced drug level and a loss of efficacy. As some parent compounds (lithium and gabapentin) and metabolites of psychiatric medications are excreted via the kidney, it is important to recognize impaired renal function or other factors that may adversely impact renal excretion and contribute to the development of toxicity.

Treatment Course

When initiating a medication, it is important that the patient has a clear appreciation of the rationale for the medication (benefit), potential adverse effects (risk), other treatment options (alternatives to proposed treatment), as well as the expected treatment course. The clinician should also actively elicit the patient's understanding about their illness and the anticipated role that the prescribed medication will play in the disease course.

Following the initiation of the selected pharmacotherapy, a deliberate schedule of longitudinal follow-up needs to be maintained to ensure clinical efficacy. This is best accomplished through an ongoing inquiry of target symptoms, tolerability of treatment, and medication adherence along with any changes in the patient's general health status or medication regimen. The treatment goal should be complete symptomatic relief and functional recovery. Clinicians should be diligent in monitoring the clinical response to each medication and, if a medication has failed to provide benefit after an adequate trial, consider discontinuing the treatment before initiating another treatment to avoid unnecessary polypharmacy. When assessing the tolerability of a medication in a specific patient, it is often helpful to specifically query the

Potential reasons for treatment failures
Incorrect diagnosis
Inadequate dose of the medication related to • Inadequate dosing • Pharmacokinetic issues
Poor adherence
Insufficient treatment duration
Psychosocial factors
The use of other drugs that may exacerbate the underlying condition under treatment
Previously unidentified comorbidities (e.g., substance use disorders)

Figure 3.1 Factors to consider in treatment-refractory conditions. (From Huffman and Alpert [4])

patient about potential side effects. Patients may be hesitant to reveal side effects or may not even recognize that the bothersome symptoms are related to the medication.

Treatment failures are often secondary to multiple factors (Fig. 3.1). Therefore, when evaluating a patient with a history of medication treatment failure(s), a patient-specific treatment history should be obtained exploring relevant issues such as the highest dose tolerated, duration of treatment, tolerability, adherence, and specific reason(s) for medication discontinuation for each specific agent.

General Comments on Discontinuation

When a current treatment course is concluding, either due to success or failure to treat the disease state, a thorough discussion of the pending discontinuation of treatment with a patient is imperative. As with the initiation of pharmacotherapy, the discontinuation relies on a weighing of the associated risks against the benefits of stopping the medication. The potential risks of stopping medication, including that of relapse, along with the potential for withdrawal or rebound symptoms, must be carefully considered. A plan for follow-up and monitoring must be in place after discontinuation to ensure a safe cessation of the medication. Due to the risk of withdrawal, the gradual tapered discontinuation of some medications should be considered by the clinician.

Antidepressants

Antidepressants are utilized to treat several conditions, including depressive and anxiety disorders, but also post-traumatic stress disorder, obsessive-compulsive disorder, and pain disorders. The first generation of antidepressants includes monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), which have been largely supplanted by the second-generation antidepressants. The second-generation antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, and serotonin modulators. While these antidepressants are comparable in terms of effectiveness in treating major depressive disorder, they vary in terms of side effect profile, making the second-generation antidepressants more favorable [4, 7]. Regardless of class, some general principles apply in terms of initiating, monitoring, and discontinuing antidepressants.

Initiating

Initiating an antidepressant, like all medications, occurs after the diligent process of gathering a careful patient history, examining the patient, reviewing or ordering labs or studies, and formulating a diagnosis [4]. Given the comparable effectiveness of the antidepressants, selection of a specific agent might depend on past response to a medication, family history of response to a medication, target symptoms, comorbid conditions, or adverse effect profile (Table 3.1). For example, if a patient has a past response to sertraline without significant adverse effects, it would be a logical choice to resume. For a patient with comorbid pain, trying a SNRI makes sense. A patient struggling with appetite and sleep might be open to mirtazapine.

For moderate to severe major depressive disorder, one should generally initiate a medication at the recommended starting dose (Table 3.2). For anxiety disorders or geriatric patients, one should initiate the medication at 50% of the recommended starting dose. Starting at a very low dose can

Table 3.1 Selection of second-generation antidepressants based on symptom or concern

Symptom or concern	Antidepressants to consider	Antidepressants to avoid
Apathy, anergy, amotivation	Fluoxetine, sertraline, bupropion, venlafaxine	Paroxetine, citalopram, mirtazapine
Elevated risk of seizures		Bupropion
Comorbid attention deficit disorder	Bupropion	
Comorbid cognitive concerns	Duloxetine, milnacipran, vortioxetine	
Comorbid GI symptoms	Mirtazapine	Sertraline and SNRIs (but GI symptoms can be mitigated by taking with food)
Comorbid pain	SNRIs	
Comorbid vasomotor symptoms	Duloxetine, desvenlafaxine, venlafaxine	
Discontinuation symptoms	Fluoxetine	Paroxetine, venlafaxine, desvenlafaxine
Drug-drug interactions	Sertraline, escitalopram, and desvenlafaxine	Fluoxetine, paroxetine, fluvoxamine, duloxetine
Poor appetite	Mirtazapine	Bupropion
Poor sleep	Mirtazapine, paroxetine, citalopram	Avoid nighttime dosing of activating antidepressants: fluoxetine, sertraline, bupropion, venlafaxine

Table 3.1 (continued)

Symptom or concern	Antidepressants to consider	Antidepressants to avoid
QTc prolongation		Citalopram and escitalopram
Sexual dysfunction	Mirtazapine, bupropion (monotherapy or augmentation), vilazodone, vortioxetine	SSRIs and SNRIs (similar incidence of sexual dysfunction)
Weight gain	Bupropion, venlafaxine	Paroxetine, citalopram, mirtazapine

From Stahl [15]
SNRI serotonin and norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

also be helpful for patients who are very hesitant to try psychotropics or those with a tendency to be sensitive to medications. This can help build rapport with patients and promote ongoing engagement.

One should counsel the patient on taking antidepressants daily at approximately the same time each day, what time is best to take the medication (e.g., nighttime for sedating medications), common adverse effects and expected duration, when to start expecting an improvement in depressive symptoms, possible discontinuation symptoms, and potential medication interactions such as serotonin syndrome [6].

Monitoring

In terms of monitoring medications, one should monitor for adverse effects, adherence, and response. Follow-up is recommended within 4 weeks of starting an antidepressant. One should ask patients about transient side effects, such as sleep changes, headache, and gastrointestinal symptoms, which are very common, but generally improve after a few weeks. It is

Table 3.2 Second-generation antidepressants

Class	Generic medication	Brand name medication	FDA-approved indications	Starting dose	Maximum dose	Renal adjustment	Hepatic adjustment
SSRI	Citalopram	Celexa	MDD	20 mg/day	40 mg/day; 20 mg/day in >60 year olds	Severe impairment—use cautiously	Max 20 mg/day
	Escitalopram	Lexapro	MDD, GAD	10 mg/day	20 mg/day; 10 mg/day in elderly	Severe impairment—use cautiously	Max 10 mg/day
	Fluoxetine	Prozac	MDD, OCD, bulimia nervosa, panic disorder, bipolar disorder depression,[a] treatment-resistant depression[a]	20 mg/day	80 mg/day	No adjustment	Decrease dose or frequency
	Fluvoxamine	Luvox	OCD, social anxiety disorder	50 mg/day	300 mg/day	No adjustment	Decrease dose or frequency; titrate slowly
	Paroxetine	Paxil	MDD, OCD, panic disorder, social anxiety disorder, GAD, PTSD, PMDD, vasomotor symptoms	20 mg/day	60 mg/day; 40 mg/day in elderly	Decrease dose	Decrease dose
	Sertraline	Zoloft	MDD, OCD, panic disorder, social anxiety disorder, PTSD, PMDD	50 mg/day	200 mg/day	No adjustment	Decrease dose or frequency

SNRI	Duloxetine	Cymbalta	MDD, GAD, diabetic peripheral neuropathic pain, fibromyalgia, musculoskeletal pain (chronic)	20 mg	120 mg/day, but unclear benefit above 60 mg/day	Do not use in severe impairment or ESRD	Avoid use
	Venlafaxine	Effexor	MDD, GAD, social anxiety disorder, panic disorder	37.5 mg/day XR formulation	225 mg/day	Decrease dose by 25–50%; decrease dose/frequency in HD	Decrease dose by at least 50%
	Desvenlafaxine	Pristiq	MDD	50 mg/day	100 mg/day	Moderate impairment–50 mg/day; severe impairment–50 mg every other day	Decrease dose
	Milnacipran	Savella	Fibromyalgia	12.5 mg/day	200 mg/day, in two divided doses	Decrease dose for moderate to severe impairment; do not use in ESRD	No dose adjustment, but do not use in chronic liver disease
	Levomilnacipran	Fetzima	MDD	20 mg/day	120 mg/day	Decrease dose	No dose adjustment

(continued)

Table 3.2 (continued)

Class	Generic medication	Brand name medication	FDA-approved indications	Starting dose	Maximum dose	Renal adjustment	Hepatic adjustment
Atypical antidepressant	Bupropion	Wellbutrin	MDD, seasonal affective disorder, nicotine addiction	150 mg/day XL formulation	450 mg/day, but rarely used above 300 mg/day	Decrease dose or frequency	Decrease dose or frequency
	Mirtazapine	Remeron	MDD	15 mg/day	45 mg/day	Use with caution	Decrease dose and use with caution
Serotonin modulator	Vilazodone	Viibryd	MDD	10 mg/day[b]	40 mg/day[b]	No dose adjustment	No dose adjustment for moderate impairment; not studied in severe impairment
	Vortioxetine	Trintellix	MDD	5–10 mg/day	20 mg/day	No dose adjustment	No dose adjustment for moderate impairment; not studied in severe impairment

From Stahl [15]

GAD generalized anxiety disorder, *HD - hemodialysis*, *MDD* major depressive disorder, *OCD* obsessive-compulsive disorder, *PMDD* premenstrual dysphoric disorder, *PTSD* post-traumatic stress disorder, *SNRI* serotonin and norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a]In combination with olanzapine

[b]bMust be administered with food

important to ask patients about sexual dysfunction, which occurs in up to 70% of patients taking antidepressants and tends to be more chronic [7]. One should also monitor for suicidality [4], as well as remain vigilant for possible hypomanic or manic symptoms. Asking about adherence to the antidepressant can reveal if the patient had an adequate trial in terms of dose and duration or may help uncover side effects that led to suboptimal adherence. For certain antidepressants, monitoring vitals or labs is indicated. For instance, for venlafaxine, one should periodically monitor blood pressure. For TCAs, obtaining a therapeutic drug level can help guide dosage adjustments.

The clinician should monitor for response during follow-up visits every 4–6 weeks. This involves both clinical interviews and structured tools such as the Patient Health Questionnaire-9 (PHQ-9) [5] or the Generalized Anxiety Disorder 7-Item Scale (GAD-7) [8] to help monitor for response or remission of depressive or anxiety symptoms, respectively. One may notice some improvement in depressive symptoms between 2 and 4 weeks, but the full effect of the medication might take a few months. It is important to assess response based on changes in symptom severity, changes in function, and achievement of specific patient goals. For patients who are tolerating a medication and have a partial response by 4 weeks, consider increasing the dose of the medication. If a patient has a partial response, but further dose increase is limited by maximum dose or side effects at higher doses, consider augmenting with another agent. For patients with no response after 4 weeks or intolerable side effects, consider switching medications.

Discontinuing

Another important consideration is how to stop an antidepressant and the potential for discontinuation syndrome. This syndrome general occurs with abrupt cessation of antidepressants. The symptoms include flu-like symptoms, such as dizziness, nausea, headache, paresthesias including a sensation often described as "brain zaps," and sleep disturbances. While the syndrome is very uncomfortable, it is not life-threatening [9]. It is more

common with medications with a short half-life, such as paroxetine and venlafaxine. Discontinuation syndrome can be minimized or avoided by slowly tapering off the antidepressant or cross-titrating with another medication. The duration of the taper may range from days to weeks or months, depending on the dose of the medication, duration of treatment, and severity of discontinuation symptoms. Fluoxetine is not generally associated with a discontinuation syndrome because of its long half-life.

First-Generation Antidepressants

Monoamine Oxidase Inhibitors

MAOIs were the first medications to be used clinically to treat depression, but now are considered third-line agents. While effective, MAOIs are associated with numerous side effects compared to the second-generation antidepressants, as well as greater potential for drug-drug interactions such as serotonin syndrome. MAOIs irreversibly block monoamine oxidase, an enzyme responsible for breaking down dopamine, serotonin, norepinephrine, and tyramine. Monoamine oxidase is found throughout the body and has an important function in the gastrointestinal tract where it breaks down a sympathomimetic called tyramine. Thus, patients taking MAOIs must follow dietary restrictions to avoid consuming tyramine-rich foods, such as aged cheeses and meats, to prevent a hypertensive crisis. One exception to this is the selegiline patch, which bypasses the gastrointestinal tract and does not require dietary restrictions at low doses. If a patient is on an antidepressant, it should be stopped for at least 2 weeks (5 weeks in the case of fluoxetine) before starting on MAOI. Similarly, an MAOI should be stopped for at least 2 weeks before starting another antidepressant (or serotonergic agent).

Tricyclic Antidepressants

The other first-generation antidepressants are TCAs. TCAs work by inhibiting the reuptake of both serotonin and norepinephrine. Nortriptyline and desipramine tend to have

more noradrenergic activity compared to the other TCAs which have greater serotonergic activity. While effective, TCAs are not usually first-line agents due to their risk of lethality in overdose and side effect profile relative to second-generation antidepressants. TCAs can be lethal and should not be prescribed for patients in which suicidality is a concern. Common adverse effects of TCAs include antihistaminergic effects like weight gain and sedation, anticholinergic effects like constipation and dry mouth, and anti-alpha-adrenergic effects such as orthostatic hypotension. Sexual dysfunction is also common. TCAs have cardiac effects and should not be used in patients with cardiac conduction issues or in the acute recovery phase after a myocardial infarction [10]. In patients with ischemic heart disease, TCAs may increase risk of sudden death; so, a careful risk-benefit analysis is warranted. TCAs can also lower seizure threshold in a dose-dependent relationship. Nevertheless, for select patients a TCA might be a good choice, especially to target depressive symptoms, sleep disturbances, or comorbid pain. Compared to the other TCAs, nortriptyline is often preferred due to less anticholinergic effects, sedation, and orthostatic hypotension. Before utilizing a TCA, one should gather personal and family history of cardiac disease and obtain a baseline EKG in patients with a cardiac history or those over age 50. In patients at risk for electrolyte disturbances, consideration should also be given to checking baseline potassium and magnesium, followed by periodic monitoring. One may consider checking plasma levels for certain TCAs if there is a failure to respond to treatment, concern of drug-drug interaction, or if uncertainty surrounds the patient's ability to absorb the medication.

Second-Generation Antidepressants

Selective Serotonin Reuptake Inhibitors

SSRIs, along with other second-generation antidepressants, are considered first-line agents in treating depressive and anxiety disorders, along with several other behavioral health

conditions [11]. In general, for patients with mild depressive or anxiety disorders, psychotherapy alone may be sufficient. For patients with moderate to severe depressive or anxiety disorders, one should consider psychotropic medication alone or in conjunction with psychotherapy [12]. The SSRIs are comparable in terms of effectiveness in treating depression and anxiety disorders; so, selection is based on several factors. If a patient had a prior response to an SSRI and tolerated it without adverse effects, resuming the medication makes sense. Sometimes a patient knows that a family member had a good response to a particular SSRI, which might suggest the patient will have a similar response. For other patients, the side effect profile can help guide SSRI selection.

In terms of adverse effects, the most common adverse effects occur with initiation of an SSRI or dose increase and include headache, sleep disturbance, gastrointestinal symptoms, and activation or agitation. These side effects tend to improve within the first 1–2 weeks. Other adverse effects include weight gain and sexual dysfunction. If the SSRI is effective, but the patient is having sexual dysfunction, one could consider augmentation with bupropion [13]. SSRIs can induce a switch from depression to hypomania or mania. If this occurs, the SSRI should be discontinued. Resolution of the hypomanic/manic symptoms suggests a medication-induced adverse effect, but continuation of the symptoms suggests an underlying bipolar spectrum disorder. One should also monitor for suicidality, which could be related to the underlying behavioral health disorder or an adverse effect of the medication. If this occurs and medication side effect is suspected, one should discontinue the SSRI. Lastly, the clinician should monitor for potential drug-drug interactions, including serotonin syndrome. Serotonin syndrome can be life-threatening. Symptoms include altered mental status, autonomic instability such as hyperthermia and hypertension, diaphoresis, flushing, diarrhea, and neuromuscular excitability such as myoclonus. While antidepressants are known to be serotonergic, one must also consider other serotonergic medications and substances.

Serotonin and Norepinephrine Reuptake Inhibitors

SNRIs represent the next wave of antidepressants. They include venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran. SNRIs work by inhibiting reuptake of both serotonin and norepinephrine. These medications vary in terms of relative serotonin:norepinephrine action, with duloxetine having greater serotonergic activity and levomilnacipran having greater noradrenergic activity. SNRIs have comparable effectiveness to other antidepressants. An SNRI may be utilized as a first-line agent, especially for patients with depression or anxiety and comorbid pain. Duloxetine also has "stand alone" indications for chronic musculoskeletal pain, diabetic peripheral neuropathic pain, and fibromyalgia.

Adverse effects of SNRIs are similar to those of SSRIs, but with a higher likelihood of gastrointestinal symptoms. This adverse effect can be mitigated by taking the medication with food and generally improves within a few weeks. Venlafaxine has been associated with a modest, dose-dependent, elevation in blood pressure. Similarly, levomilnacipran has been associated with elevations in heart rate and blood pressure. Both medications tend to be weight neutral [14]. Venlafaxine tends to be more activating than duloxetine. Duloxetine tends to have a greater likelihood of drug-drug interactions via CYP2D6 inhibition. Desvenlafaxine is metabolized independently of CYP2D6, making drug-drug interactions less likely compared to some of the other SSRIs and SNRIs. Similar to SSRIs, the SNRIs are associated with sexual dysfunction.

Atypical Antidepressants

Bupropion is considered an atypical antidepressant and can be used as monotherapy or adjunctive therapy for depression. It may be a good choice for patients with low energy because it tends to be activating. It is helpful in depressed patients with concentration symptoms or comorbid ADHD, a desire for smoking cessation, or concerns about sexual dysfunction or

weight gain. For patients with a partial response to an SSRI or SNRI, bupropion can be used for augmentation to treat residual depressive symptoms or minimize sexual side effects [13].

Bupropion is generally well tolerated, but it is associated with a dose-dependent increase in risk of seizures. Thus, bupropion should be avoided in patients with a history of seizures or patients at high risk for seizures such as those with eating disorders or intracranial pathology. Common adverse effects include insomnia, agitation, and restlessness, making it suboptimal for first-line monotherapy for patients with prominent anxiety. Sweating, headaches, dizziness, gastrointestinal symptoms, and tremors are also common. Tachycardia and hypertension may also occur.

Mirtazapine is another atypical antidepressant that can be used as monotherapy or adjunctive therapy for both depressive and anxiety disorders. Mirtazapine is especially helpful in patients with poor sleep and appetite or when trying to avoid sexual dysfunction. For patients who cannot tolerate the SSRIs or SNRIs due to gastrointestinal side effects, mirtazapine may be a good choice. Common adverse effects of mirtazapine include weight gain and sedation, as well as orthostatic hypotension. For patients prescribed mirtazapine, weight should be monitored periodically. Mirtazapine may also cause clinically significant elevation in transaminases; however, routine laboratory monitoring is not currently recommended [15]. Bone marrow suppression is a rare but serious adverse effect and one should monitor for clinical symptoms that might be suggestive. With that said, the medication is used commonly in patients with malignancy and immunosuppression to target mood, anxiety, appetite, and sleep.

Serotonin Modulators

A newer class of antidepressants is serotonin modulators, including vilazodone and vortioxetine. Vilazodone has a mechanism of action that is similar to combining an SSRI with buspirone (5-HT_{1A} partial agonism). So, it may be a good choice in patients with depression with prominent anxiety.

Due to increased bioavailability with a meal, vilazodone should be taken with food. It is metabolized primarily by CYP3A4 and requires dose reduction or increase if taken with a strong CYP3A4 inhibitor or inducer, respectively. It has a low incidence of sexual dysfunction compared to SSRIs and SNRIs. Interestingly, due to action at 5-HT_4 in the GI tract, the medication is also thought to have potential benefit in irritable bowel syndrome [14]. Nevertheless, common adverse effects include GI symptoms and headache.

Vortioxetine is another serotonin modulator which acts on several serotonin receptors leading to an increase in activity of dopamine, norepinephrine, and acetylcholine in the prefrontral cortex. This medication has been shown to be effective for treating depression and improving cognition. Thus, it may be a good choice in geriatric patients who are depressed and have cognitive impairment [14]. Another advantage is that vortioxetine appears to be fairly weight neutral and without significant sexual side effects. Common adverse effects include GI symptoms.

Benzodiazepines and Related Sedatives

Benzodiazepines

Benzodiazepines are one of the most commonly prescribed medications in the United States. In 2008, approximately 5% of US adults used a benzodiazepine. Interestingly, the percentage of adults who used a benzodiazepine increased steadily with age from 2.6% (18–35 years) to 8.7% (65–80 years) [16]. All benzodiazepines bind to the γ-aminobutyric acid (GABA) type A receptor. GABA is the primary inhibitory neurotransmitter in the CNS, and the binding of benzodiazepines to the GABA receptor further potentiates the inhibitory effect of GABA on the CNS. This provides the pharmacodynamic mechanism by which benzodiazepines exert their potent inhibitory effect on the CNS.

The inhibitor activity of benzodiazepines in the CNS makes them useful agents for the treatment of anxiety disor-

Table 3.3 Benzodiazepines

Benzodiazepine	Dose equivalents	Usual dose range
Alprazolam	0.5 mg	0.25–1 mg tid
Chlordiazepoxide	25 mg	5–25 mg tid
Clonazepam	0.25 mg	0.25–1 mg bid
Lorazepam	1 mg	0.5–2 mg bid
Diazepam	5 mg	2–10 mg bid
Temazepam	15 mg	7.5–30 mg qhs

Adapted from: Sadock et al. [42]

ders, insomnia, agitation, and seizure disorders. They are also commonly used as sedative agents in hospital settings and as a treatment for alcohol withdrawal. There are many different benzodiazepines available for use, and they vary by potency, onset of action, metabolism, and half-life (Table 3.3). The selection of which benzodiazepine to prescribe to a patient depends on how these individual differences interact with several important disease- and patient-specific factors. For example, a benzodiazepine with rapid onset of action and short half-life may be optimal for someone with infrequent, intense panic attacks, but suboptimal for someone with chronic, frequent panic attacks due to the required dosing frequency and potential for rebound anxiety. Lorazepam and oxazepam may be more beneficial when used for patients with impaired hepatic metabolism due to their lack of oxidative metabolism.

Although very effective anti-anxiety agents, there are multiple potential disadvantages associated with benzodiazepines that should temper their use by clinicians to treat these often-chronic conditions. Because of these disadvantages, as well as the proven effectiveness of the antidepressants in treating various anxiety disorders, the SSRI and SNRI antidepressants have become the pharmacological mainstay of treatment for most anxiety disorders [17]. However, patients with anxiety disorders tend to experience increased anxiety or activation with initiation of the antidepressant. To counter this, it is rec-

ommended that the starting dose of the antidepressant should be half the initial dose used in the treatment of depression. This lower dose should be continued for about 1 week and, if tolerated, increased to the normal antidepressant starting dose at that time. Although the starting dose is lower, the therapeutic dose of the antidepressant for anxiety disorders is the same for depression. Few patients should require prolonged as-needed treatment, and fewer still will need long-term scheduled use of benzodiazepines given the effectiveness of antidepressants in managing chronic anxiety disorders. Initiating a benzodiazepine with the start of the antidepressant for the management of an anxiety disorder may be indicated to help blunt the temporary activation or exacerbation of anxiety symptoms commonly experienced by patients in the first weeks of treatment with an SSRI or SNRI. This temporary use of a benzodiazepine may also help "bridge" the often-delayed onset of therapeutic efficacy observed with antidepressants (4–6 weeks). Once a positive therapeutic response to the antidepressant has been established, the benzodiazepine should be tapered and discontinued to avoid unnecessary polypharmacy (Fig. 3.2). Informing the patient of this planned taper, upon initiation of the treatment, is imperative to maximize the success of the treatment plan. The chronic use of as-needed benzodiazepines is not a preferred treatment for anxiety disorders when the symptoms are frequent and chronic in nature. With "as needed" use, the medication is only addressing the anxiety once the patient is suffering, not actually preventing the symptoms and associated dysfunction. The treatment goal should be to prevent the occurrence of anxiety. If using benzodiazepines as the primary treatment

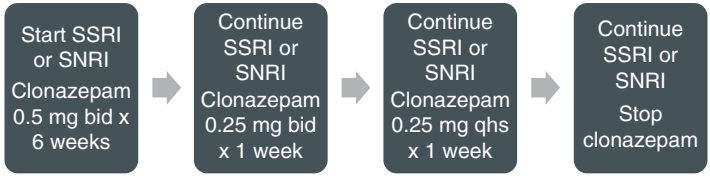

Figure 3.2 Benzodiazepine "bridge"

modality, this would require regularly scheduled doses. This predisposes the patient to breakthrough symptoms, physiological tolerance, the subsequent need for escalating doses, misuse, and a risk of withdrawal if there is abrupt discontinuation of the benzodiazepine. Antidepressants, such as the SSRIs and SNRIs, treat the underlying anxiety disorder thereby preventing the patient from experiencing attacks without the associated risk of misuse, rebound, or withdrawal from benzodiazepines.

Benzodiazepines are also suboptimal as a primary treatment for insomnia due to potential daytime sedation, potential rebound insomnia when discontinued, and their negative effects on sleep architecture [18]. The best treatment for insomnia is not pharmacologic, but rather the practice of good sleep hygiene and cognitive behavioral therapy [19]. Benzodiazepines are not recommended for the treatment of insomnia, agitation, or delirium in the elderly and, if prescribed in this population, should be restricted to low doses and short-term use.

Adverse Effects

As mentioned earlier, the use of benzodiazepines is not without risk. The most common side effects are drowsiness, fatigue, impaired coordination, and disturbances of attention. As a result, benzodiazepines have been associated with increased risks of falls and fractures in the elderly [20]. In addition, paradoxical reactions of activation and agitation have been reported with the use of benzodiazepines in the elderly. There has also been a controversial association made between benzodiazepine use and dementia [21]. Benzodiazepines are also known to lead to physiologic dependence and the potential for misuse and psychological dependence (Table 3.3). As a result, a thorough and ongoing evaluation of the need for continued treatment with benzodiazepines is imperative. Education, adherence to prescription parameters, avoidance of multiple prescribers, and appropriate planned discontinuation are all important considerations to reduce the risk of misuse.

Benzodiazepines also contribute to the occurrence of delirium and respiratory depression in at-risk individuals. Benzodiazepines potentiate the sedative effects of opioids, and co-administration presents an increased risk for adverse outcomes [22]. There is also the concern of benzodiazepines contributing to respiratory suppression in patients with pre-existing respiratory disease. This may also be exacerbated when a benzodiazepine is combined with an opiate resulting in an increased mortality in this at-risk patient population [23]. As a result, co-administration of an opiate and benzodiazepine should be considered rarely and carefully, if at all.

Benzodiazepines have a low overall mortality rate in overdose. However, dangerousness escalates rapidly when ingestion is combined with other sedative agents, such as alcohol. Drug interactions are often related to the co-administration of multiple sedative medications that potentiate sedation and related adverse effects. Other than lorazepam, oxazepam, and temazepam, all benzodiazepines are metabolized by oxidation and are, therefore, sensitive to inhibition and induction of their metabolism.

Whenever possible, benzodiazepines should be used for as brief a period as possible and at the lowest effective dose to reduce the risk of tolerance and development of dependence. Symptoms and signs of withdrawal usually develop more quickly following abrupt discontinuation of shorter-acting benzodiazepines than with longer-acting agents. As the use of benzodiazepines induces a state of relative CNS inhibition, their withdrawal, therefore, will create a state of relative CNS hyperexcitability. This hyperexcitability presents with varying degrees of severity observed through escalating physical and psychological signs and symptoms. The mildest form of withdrawal is usually experienced as an exacerbation of the patient's original symptoms. These symptoms are often called "rebound" symptoms and are frequently seen with discontinuation of benzodiazepines when they are used to treat insomnia or panic attacks.

The most common presentation of benzodiazepine withdrawal includes muscle tension and/or spasms, anxiety, and

sleep disturbances. As withdrawal progresses, symptoms may progress to diffuse pain, appetite loss, restlessness, and irritability. The physiological hyperarousal may also eventually manifest with tachycardia, hypertension, diaphoresis, and seizures. The most severe form of withdrawal is benzodiazepine withdrawal delirium associated with the previously mentioned signs of severe physiological arousal along with impaired attention and cognitive dysfunction. Withdrawal delirium is also often associated with delusions and perceptional disturbances (illusions and hallucinations).

Discontinuation

Because of the potential for withdrawal and associated morbidity, a gradual taper of benzodiazepines is recommended. A slow and measured withdrawal of benzodiazepines should be considered for anyone using a benzodiazepine on a regular basis for over 2 months. The severity of the withdrawal is often determined by the duration of treatment and dose (the longer duration and higher the dose, the more severe). The shorter the half-life of the benzodiazepine also contributes to the severity. The taper of the benzodiazepine should be measured. A commonly utilized taper schedule is a 10–25% dose reduction every week. The rate of the taper may need to be decreased based on symptom severity, but should remain progressive and measured with the goal of discontinuation. Most individuals can be successfully withdrawn from a benzodiazepine over a period of 4–8 weeks.

Nonbenzodiazepine Hypnotics

The non-benzodiazepine hypnotics, zolpidem, zaleplon, and eszopiclone (commonly called the “z-drugs”), appear to impact only one of the GABA A subunits. This GABA A subunit appears related therapeutically only to sleep, not anxiety. Given the specific pharmacodynamic properties of

the z-drugs, they are indicated for the short-term treatment of insomnia.

Adverse Effects

This GABA A subunit receptor specificity may improve overall tolerability of the z-drugs when compared to benzodiazepines [24]. The most common side effects associated with this class of hypnotics include daytime sedation, memory and psychomotor impairment, and behavioral changes. Complex behaviors, such as sleep walking or even sleep driving, have also been reported. Similar to benzodiazepines the z-drugs should also be avoided in the elderly, due to a risk of falls, cognitive and motor dysfunction, as well as delirium [25].

Buspirone

Buspirone, a 5-HT_{1A} partial agonist, was the first nonbenzodiazepine anxiolytic developed for the treatment of generalized anxiety [26]. Buspirone is approved by the FDA for the management of generalized anxiety disorder. It is not indicated for the treatment of panic attacks or for anxiety disorder subtypes. Buspirone does not provide immediate symptomatic relief; rather, it takes up to 6 weeks to show equal efficacy with benzodiazepines [7]. Unlike benzodiazepines, buspirone is not sedating, it does not inhibit motor coordination, spontaneous motor activity, or psychomotor performance (either alone, or in combination with alcohol), and it has not been shown to adversely affect memory or cognition. Buspirone also lacks abuse potential [27]. For these reasons, buspirone is often an attractive alternative to benzodiazepines for chronic management of generalized anxiety symptoms. Buspirone must be dosed on a schedule (typically, 15–60 mg daily in divided doses) rather than "as needed" to provide adequate symptomatic relief.

Adverse Effects

The most common side effects documented are dizziness, drowsiness, nausea, headache, nervousness, fatigue, insomnia, light-headedness, dry mouth, and excitement [27]. Overall, buspirone is generally well tolerated and safe for long-term management of generalized anxiety disorders as well as mixed anxiety-depressive disorders.

Antipsychotics

Antipsychotics dramatically changed the treatment approach to persons suffering with psychotic disorders. Prior to the 1950s, people with schizophrenia and other psychotic disorders were confined for years to institutions and provided with supportive care, but little to no relief was available for psychotic symptoms. The development of antipsychotic medications allowed for many institutionalized patients to be discharged back to their communities.

Antipsychotics are best known for their use in acute and maintenance treatment of schizophrenia and schizoaffective disorders, but they also have other potential indications. These include the relief of psychotic symptoms associated with substance use, personality disorders, and mood disorders, as well as the provision of mood stability in both manic and depressive phases of bipolar disorder. Certain antipsychotics may also be utilized to augment the mood effects of antidepressants in major depressive disorder [28]. They can ameliorate tics associated with Tourette syndrome, as well as movements associated with Huntington's disease. They also provide relief for nausea, emesis, and hiccups.

Initiating

The literature favors initiation and maintenance treatment with an antipsychotic following a first episode of psychosis unrelated to substance use. Studies that have followed patients longitudinally after a psychotic episode have reported

relapse rates of almost 80% within 1 year of stopping antipsychotic treatment [7]. For patients with known affective disorders, adding an antipsychotic agent to a treatment regimen in the setting of worsening mood symptoms with psychotic features is indicated. The choice of antipsychotic should be made in close collaboration with the patient and with careful consideration of specific patient factors, such as medical comorbidities. As response and tolerability of these agents will vary widely among patients, there is no clear first-line antipsychotic agent. In terms of classes of medications, first-generation antipsychotics (FGAs) are more likely to precipitate extrapyramidal symptoms and tardive dyskinesia (Table 3.4). Second-generation antipsychotics (SGAs) are more apt to cause metabolic adverse effects (Table 3.5). All antipsychotic agents can lower the seizure threshold and may cause QT interval prolongation.

Table 3.4 First-generation antipsychotics

	Trade name	Formulations	Indications	Typical maintenance dose range (PO)
Chlorpromazine	Thorazine	PO[a] Suppository	Schizophrenia, nausea/emesis, acute intermittent porphyria, mania, tetanus (adjunct), intractable hiccups, psychosis	200–800 mg/day
Fluphenazine	Prolixin	PO IM[a] LAI[a]	Psychotic disorders	1–20 mg/day
Haloperidol	Haldol	PO IM IV[a] LAI	Psychotic disorders, tics in Tourette syndrome, schizophrenia	1–40 mg/day

(continued)

Table 3.4 (continued)

	Trade name	Formulations	Indications	Typical maintenance dose range (PO)
Loxapine	Loxitane Adasuve *(inhaled form)*	PO IM Inhalant	Schizophrenia, acute treatment of agitation associated with schizophrenia or bipolar disorder	60–100 mg/day
Mesoridazine	Serentil	PO IM	Management of schizophrenia that fails to respond adequately to other antipsychotics	100–400 mg/day
Perphenazine	Trilafon	PO IM	Schizophrenia, nausea/emesis	12–24 mg/day
Pimozide	Orap	PO	Suppression of motor and phonic tics in patients with Tourette syndrome	<10 mg/day
Thioridazine	Mellaril	PO	Management of schizophrenia that fails to respond adequately to other antipsychotics	200–800 mg/day
Thiothixene	Navane	PO	Schizophrenia	15–30 mg/day
Trifluoperazine	Stelazine	PO IM	Schizophrenia, nonpsychotic anxiety *(short-term, second-line)*	15–20 mg/day *(psychosis)*

From Stahl [43]

[a]Abbreviations: *PO* oral, *IM* intramuscular, *LAI* long-acting injectable, *IV* intravenous

Table 3.5 Second-generation antipsychotics

	Trade name	Formulations	Indications	Dose range (PO)
Aripiprazole	Abilify	PO[a] IM[a] LAI[a]	Schizophrenia, acute mania/mixed mania, bipolar maintenance, depression *(adjunct)*, autism-related irritability in children, Tourette syndrome	15–30 mg/day *(psychosis and mania)*
Asenapine	Saphris	PO	Schizophrenia, acute mania/mixed mania *(both monotherapy and adjunct)*	10–20 mg/day
Brexpiprazole	Rexulti	PO	Schizophrenia, treatment-resistant depression *(adjunct)*	2–4 mg/day *(psychosis)*
Cariprazine	Vraylar	PO	Schizophrenia, acute mania/mixed mania	1.5–6 mg/day
Clozapine	Clozaril	PO	Treatment-resistant schizophrenia, reduction in risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder	*Titrate to minimum serum level of 350 ng/mL*
Iloperidone	Fanapt	PO	Schizophrenia	12–24 mg/day
Lurasidone	Latuda	PO	Schizophrenia, bipolar depression	40–120 mg/day *(psychosis)*

(continued)

Table 3.5 (continued)

	Trade name	Formulations	Indications	Dose range (PO)
Olanzapine	Zyprexa	PO IM LAI	Schizophrenia, acute mania/mixed mania, bipolar maintenance, bipolar depression *(in conjunction with fluoxetine)*, treatment-resistant depression *(in conjunction with fluoxetine)*	10–20 mg/day
Paliperidone	Invega	PO LAI	Schizophrenia, schizoaffective disorder	6–12 mg/day
Quetiapine	Seroquel	PO	Schizophrenia, acute mania *(both monotherapy and adjunct)*, bipolar maintenance, bipolar depression, depression *(adjunct)*	400–800 mg/day *(psychosis)*
Risperidone	Risperdal	PO LAI	Schizophrenia, other psychotic disorders, acute mania/mixed mania *(both monotherapy and adjunct)*, bipolar maintenance *(both monotherapy and adjunct)*, autism-related irritability in children	2–8 mg/day *(psychosis and mania)*
Ziprasidone	Geodon	PO IM	Schizophrenia, acute mania/mixed mania, bipolar maintenance	40–200 mg/day *(psychosis and mania)*

From Stahl [43]

[a]Abbreviations: *PO* oral, *IM* intramuscular, *LAI* long-acting injectable

There are some general principles to consider when prescribing any antipsychotic agent. One should utilize the lowest possible effective dose of the medication to minimize adverse effects. If the patient is showing little to no response at 2 weeks post-initiation, the dose or the agent should be changed. For the majority of patients, monotherapy is recommended; there is little evidence that prescribing multiple antipsychotics, even in treatment-refractory disease, is ever effective. In general, antipsychotics should not be utilized "as needed" sedative agents.

Prior to initiation, baseline vital signs, as well as a complete metabolic panel, complete blood count, lipid panel, weight (including waist circumference), fasting plasma glucose, and electrocardiogram, especially in those with known cardiac disease or risk factors, should be documented [7].

Monitoring

As with any medication, one should monitor for adverse effects, adherence, and response. Follow-up is recommended within 2 weeks of starting an antipsychotic. If symptoms have not responded or only minimally responded, a dose change or change in medication is strongly recommended. The clinician should inquire about side effects such as excessive sedation and weight gain. Baseline cardiometabolic data as mentioned above should be monitored at regular intervals during treatment. Once a therapeutic maintenance dose has been reached, a repeat electrocardiogram should be repeated to ensure no changes in the patient's QT interval. A complete metabolic panel and complete blood count should be monitored annually as part of a routine physical health check.

Perhaps most crucial to the long-term health and well-being of patients suffering with psychotic disorders is the vigilant monitoring of physical illness by primary care clinicians. Studies have demonstrated a significantly decreased life expectancy (by up to 20 years) in patients diagnosed with schizophrenia, and patients suffering with schizophrenia frequently have limited or no access to appropriate health care [29].

Discontinuing

The decision to stop an antipsychotic regimen requires a thoughtful risk-benefit analysis. Typically, patients should be counseled that long-term treatment is generally required to prevent relapse. Abrupt withdrawal of treatment is not only associated with a discontinuation syndrome including headache, nausea, and insomnia, but has also been correlated with a higher incidence of relapse. Ideally, if an antipsychotic is to be tapered, it should be slowly weaned over the course of about 3 weeks [7]. If the patient wishes to discontinue treatment with an antipsychotic, involving the patient's primary support person(s) to discuss "warning signs" of relapse and when/how to seek urgent help is strongly encouraged.

First-Generation Antipsychotics (FGAs)

Also called "conventional" or "typical" antipsychotics, first-generation antipsychotics antagonize four major neurotransmitter systems in the central nervous system. These include the dopamine type 2 receptor family (D_2, D_3, and D_4), muscarinic cholinergic receptors (M_1), α-adrenergic receptors (α_1 and α_2), and histamine receptors (H_1). The targeting of the positive symptoms of schizophrenia (perceptual disturbances, delusions, disorganization of thought processes) is believed to be a result of D_2 blockade within the mesolimbic dopamine tract. Antagonism of all other above receptors manifests as side effects. Anticipated anticholinergic effects include dry mouth (xerostomia), blurred vision (mydriasis), constipation that can progress to paralytic ileus, urinary retention, drowsiness, and impaired cognition. Antiadrenergic effects include orthostatic hypotension, dizziness, sedation, and priapism. Antihistaminergic effects include weight gain and sedation. Dopamine antagonism in other tracts produces such effects as hyperprolactinemia (D_2 blockade within the tuberoinfundibular tract), blunting of cognition and avolition-apathy (D_2 blockade in the mesocortical tract), and

extrapyramidal symptoms or EPS (D_2 blockade within the nigrostriatal tract). High-potency FGAs, such as haloperidol, fluphenazine, and thiothixene will confer a higher risk of EPS and hyperprolactinemia, given their strong affinity for the D_2 receptors. However, these agents will have a much "cleaner" side effect profile otherwise. Lower potency agents, such as chlorpromazine and thioridazine, will confer a lower risk of EPS, but will have a higher incidence of anticholinergic, antiadrenergic, and antihistaminergic effects.

Second-Generation Antipsychotics (SGAs)

SGAs are also called "atypical" antipsychotics due to the early observation that these medications effectively treat the positive symptoms of schizophrenia while conferring a lower risk of extrapyramidal symptoms and hyperprolactinemia [15]. Their primary pharmacologic actions include serotonin 5-HT_{2A} receptor antagonism in addition to D_2 receptor antagonism. Whereas first-generation antipsychotics block dopamine receptors in the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular tracts, the effects of SGAs on postsynaptic 5-HT_{2A} receptors increase dopamine release in the nigrostriatal and tuberoinfundibular tracts, while still blocking the actions of dopamine in the mesolimbic tract. In this way, SGAs effectively mitigate the positive symptoms of schizophrenia while having a lower incidence of EPS and hyperprolactinemia. Similar to FGAs, SGAs may also exert effects on muscarinic, adrenergic, and histaminergic receptors as well.

Weight gain associated with antipsychotic use appears to result from a combination of increased appetite and decreased energy expenditure. Rapid weight gain in early treatment, defined as ≥5% above baseline weight after 1 month of treatment, has been shown to strongly predict long-term weight gain [7]. Metabolically adverse SGAs with a high or moderate risk of weight gain include clozapine, olanzapine, risperidone, paliperidone, quetiapine, and iloperidone. If rapid weight gain is observed early in the patient's treatment course, it is

prudent to switch medications to a more metabolically neutral option (such as ziprasidone, aripiprazole, lurasidone, asenapine, brexpiprazole, or cariprazine) in addition to encouraging lifestyle modifications. More recently, the addition of metformin to prevent, reduce, and reverse weight gain associated with antipsychotic treatment has gained favor [30]. It should be noted that clozapine is particularly effective in treatment-resistant schizophrenia but requires vigilant monitoring due to potential adverse effects including agranulocytosis, myocarditis, and constipation leading to small bowel obstruction. Clozapine is also notable for its role in reducing suicidality in high-risk patients [31].

Extrapyramidal Symptoms and Neuroleptic Malignant Syndrome

Though extrapyramidal symptoms (EPS) are most often associated with FGAs, they are possible with any antipsychotic. EPS may be acute or late in their onset. Medication-induced parkinsonism can occur after several weeks of treatment and can affect patients of any age, though it is more common in patients older than 40 [27]. Dystonias are painful, sustained muscle contractions that can affect the tongue, jaw, neck, back, eyes (oculogyric crisis), and larynx (can impair breathing and lead to death). Acute dystonias must be treated rapidly via IM or IV administration of diphenhydramine or IM benztropine. Akathisia, a subjective feeling of restlessness and the compulsive urge to move, is the most prevalent of the EPS and can occur at any time during the course of treatment. The classic presentation of late-onset EPS is tardive dyskinesia (TD), a syndrome involving involuntary choreoathetoid movements, typically of the perioral region. It generally takes at least 3–6 months of antipsychotic exposure to develop tardive dyskinesia, and it is often irreversible once it manifests. Neuroleptic malignant syndrome (NMS) is a rare, but potentially fatal, disorder of thermoregulation and neuromotor control [7]. Clinical presentation varies, but NMS is

generally characterized by muscular rigidity, hyperthermia, altered mentation, and autonomic dysfunction.

Mood Stabilizers

Mood stabilizers are agents used to prevent or treat manic or depressive episodes in patients with bipolar disorder and include lithium, antiepileptic drugs, and antipsychotic medications.

Initiating

Initiating a mood stabilizer requires careful screening for bipolar disorder, a diagnosis which is not uncommon, but is often unrecognized in the primary care setting. Some literature suggests that an estimated 20–30% of patients seen in primary care settings for depression and anxiety actually meet criteria for bipolar disorder [32]. One possible explanation for the challenge in diagnosing bipolar disorder is that most symptomatic periods of bipolar disorder are depressive in nature [33]. To meet diagnostic criteria for bipolar disorder according to DSM-5, a manic episode or hypomanic episode is required. To aid in diagnosis, careful history gathering is a necessity: a family history of bipolar disorder, psychosis, substance use, or suicide, as well as a personal history of frequent occupation changes and/or relationship instability should prompt further probative questioning [33]. Additionally, screening tools such as the Mood Disorder Questionnaire (MDQ) [34] or the Bipolar Spectrum Diagnostic Scale (BSDS) [35] may aid in diagnosis. Both of these tools can be effective at ruling out bipolar spectrum illness; however, they can lead to overdiagnosis of bipolar disorder by a factor of two to three [33], further emphasizing the importance of a careful clinical interview. Substance use, medical conditions, and medications that can present with symptoms resembling mania or hypomania must also be ruled out.

After a confident diagnosis of bipolar disorder is made, the major consideration in choosing a pharmacological intervention (whether an antipsychotic medication, antiepileptic drug [AED], or lithium) includes the determination of the current phase of illness and pattern of any historical episodes, as well as the patient's other medical comorbidities (Table 3.6). Prior to initiation of medication, baseline thyroid function, liver function, renal function and electrolytes, a complete blood count, lipid profile, blood glucose, weight, and electrocardiogram (if cardiac risk factors) should be collected and documented. The specific treatment choice dictates further monitoring.

Table 3.6 Mood-stabilizing agents in bipolar disorder and FDA-approved indications

Class	Medication	Maintenance	Mania	Depression
	Lithium	Yes	Yes	
Anticonvulsant	Carbamazepine XR		Yes	
	Lamotrigine	Yes		
	Valproate		Yes	
SGA[a]	Aripiprazole	Yes	Yes	
	Asenapine		Yes	
	Lurasidone			Yes
	Olanzapine	Yes	Yes	
	Olanzapine-fluoxetine			Yes
	Paliperidone		Yes	
	Quetiapine	Yes	Yes	Yes
	Risperidone		Yes	
	Ziprasidone		Yes	
FGA[a]	Haloperidol		Yes	

From Stahl [43]

[a]Abbreviations: *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic

Monitoring

In terms of monitoring mood-stabilizing medications, one should monitor for adverse effects, adherence, and response. Follow-up is recommended within 4 weeks of starting a mood stabilizer.

One special consideration, especially in the primary care setting, involves close collaboration with women of reproductive age to ascertain current or future plans for pregnancy and contraception. As lithium and many AEDs, especially valproate, have known teratogenic effects, women should ideally be on a reliable form of contraception while taking these medications. Additional considerations related to specific agents are described below.

Discontinuing

As with other psychiatric disorders, discontinuation of mood-stabilizing agents should be done only after a careful and thorough risk-benefit analysis. Intermittent treatment may worsen the natural course of bipolar illness, with a significantly increased risk of relapse. If a mood-stabilizing agent is to be discontinued, it should be done slowly over at least a month to mitigate the risk of relapse seen with abrupt discontinuation [7].

Lithium

As an element in the same group of the periodic table as sodium, the two are structurally similar; thus, lithium has the potential to alter any number of biological processes involving sodium. Lithium is minimally protein bound and renally excreted. Lithium is widely considered to be the “gold standard” of treatment for bipolar disorder. Studies have demonstrated lithium to be effective in treating both the acute manic and depressive phases of bipolar disorder, in prevent-

ing relapse in the maintenance phase of bipolar illness, as augmentation in treatment-refractory depression, and in reducing suicidality [27]. Optimal plasma lithium levels range from 0.6 to 1.2 mmol/L [7]. Most adverse effects of lithium are related to the dose and plasma levels and include GI distress, tremor, polyuria, polydipsia, edema, weight gain, and worsening of some skin conditions such as psoriasis and acne. Long-term treatment with lithium carries a risk of renal toxicity (especially at high plasma levels), irreversible nephrogenic diabetes insipidus, hypothyroidism, and hyperparathyroidism. Lithium toxicity reliably occurs at plasma levels >1.5 mmol/L and can present with prominent GI and CNS effects including nausea, diarrhea, muscle weakness or twitching, coarse tremor, drowsiness, confusion, and ataxia [7]. At plasma levels >2 mmol/L, one is at risk for seizures; levels >3 mmol/L are an indication to initiate dialysis. Major risk factors for toxicity include dehydration, drug-drug interactions, acute kidney injury, or significant changes in diet (e.g., starting a low-salt diet). In addition to baseline testing as previously described, ongoing monitoring for patients taking lithium should include plasma lithium levels, renal function, and thyroid function at least every 6 months. More frequent monitoring may be necessary in those with chronic kidney disease (CKD), those at risk for drug-drug interactions, and in elderly patients.

Antiepileptics

Valproate

Valproate is highly protein bound, and only the unbound drug is bioactive. For this reason, valproate should be dosed cautiously in patients taking other highly protein-bound agents, in those who have low serum albumin, and in women and elderly patients who have lower serum protein levels. Valproate is hepatically metabolized, and serum levels can increase if CYP enzymes are inhibited (e.g., erythromycin, fluoxetine, cimetidine). It is indicated as a first-line treatment

for acute mania and can also be utilized effectively as maintenance treatment in bipolar disorder. However, valproate should not be utilized—or only utilized in conjunction with reliable, long-term contraception—in women of child-bearing age given known teratogenic effects. Adverse effects may include gastritis, hyperammonemia, nausea, lethargy, weight gain, hair loss, and thrombocytopenia. In women, valproate can precipitate polycystic ovarian syndrome and menstrual disturbances. In addition to baseline testing above, ongoing monitoring should include weight, complete blood count, and liver function every 6 months [7].

Carbamazepine

The extended-release formulation of carbamazepine is FDA approved for the treatment of acute mania in bipolar disorder as well as episodes with mixed features [27]. Its side effect profile includes dizziness, diplopia, drowsiness, ataxia, nausea, headaches, dry mouth, edema, and hyponatremia. It also has the potential to cause leukopenia, and, far less commonly, agranulocytosis and/or aplastic anemia. Suggested ongoing monitoring includes weight, basic chemistry panel, liver function tests, and complete blood counts that are monitored at least every 6 months. Of note, if symptoms recur while the patient is managed on a previously effective dose, consider that carbamazepine can induce its own metabolism which will subsequently lower plasma levels. A dose increase may be warranted. One final special consideration: testing of Asian individuals should be conducted prior to treatment initiation to assess for genetic vulnerability for a serious exfoliative dermatological reaction to carbamazepine [27].

Lamotrigine

Lamotrigine is FDA approved for its use in the maintenance phase of bipolar illness, but despite expert consensus that it is effective for bipolar depression, the FDA has not approved

its use in the depressive phase of bipolar illness. Unlike many other anticonvulsant medications, lamotrigine is generally quite well tolerated and is weight neutral. It does have a known—but rare—propensity to cause Stevens-Johnson syndrome (toxic epidermal necrolysis), which is typically mitigated by a very slow, careful upward titration in dose. For women of reproductive potential, lamotrigine also represents a safer medication option than other anticonvulsant mood stabilizers. Studies of fetal lamotrigine exposure in utero have produced conflicting results regarding the possibility of increased risk of congenital anomalies, specifically cleft lip/palate. Longitudinal observational studies of children exposed to lamotrigine in utero have not demonstrated the same negative cognitive impact as seen with other anticonvulsant medication exposure [36].

Psychopharmacology in the Medically Ill

Renal

To provide safe and effective psychopharmacologic treatment to patients with chronic kidney disease (CKD), the provider must consider the potential for altered pharmacokinetic and pharmacodynamic parameters.

The presence of CKD may alter several pharmacokinetic properties of psychiatric medications. Renal failure may impact the distribution of the drug throughout the body as increased volume status may increase the volume of distribution of medications. As previously mentioned, most psychotropic medications are highly protein bound. Patients with CKD are at risk of decreased circulating proteins, thereby leaving more of the drug unbound and pharmacologically active.

The metabolism of most psychotropic medications is not seriously affected by renal disease, as most psychiatric medications are metabolized by the liver. However, drugs that are metabolized in the liver may represent a risk for patients with renal failure if pharmacologically active metabolites are

produced via hepatic metabolism that require renal excretion. If the renal function is impaired enough to reduce the excretion of the active metabolites, this may lead to an accumulation of those metabolites and toxicity, unless the dose is adjusted to account for the impaired renal excretion. Some psychiatric medications (such as lithium and gabapentin) are not metabolized by the liver and are excreted unchanged by the kidneys. As a result, it is imperative that doses are appropriately reduced when utilized in a patient with renal disease.

Cardiovascular

There are a couple of specific concerns related to the utilization of psychiatric medications in patients with pre-existing heart disease. The TCAs should be avoided in cardiac patients due to the potential for orthostatic hypotension, tachycardia, and conduction abnormalities. SSRIs are the most commonly utilized antidepressant agents in patients with cardiac disease due to efficacy and safety data. SSRIs, however, are associated with a modest risk of QT interval prolongation. It appears that among the SSRIs, citalopram and escitalopram are associated with the greatest QT prolongation although the clinical significance of this risk is unclear [37]. QT interval prolongation appears to be more of an issue with the antipsychotic class of medications. Thioridazine, a low-potency FGA, and ziprasidone, an SGA, appear to represent the largest risk of QT prolongation among the antipsychotics. Attention to the corrected QT interval (QTc) is important as prolongation of ventricular repolarization increases the risk of torsades de pointe (TdP). QTc prolongation has, therefore, become a surrogate marker to predict the risk of drug-related cardiac morbidity and mortality.

The prevention of QTc prolongation is an essential consideration of safe pharmacology. This is best accomplished by assessing the risk in each individual patient (Fig. 3.3). It is often the accumulation of multiple risk factors in a patient that represents the greatest risk for the development of TdP [38].

Genetic long QT syndrome (LQTS)
Age >65 years
Female gender
Circadian rhythm
Cardiovascular disease
Bradycardia
Electrolyte abnormalities • Hypomagnesemia • Hypokalemia
Pharmacologic • Pharmacokinetic • Pharmacodynamic

Figure 3.3 Risk factors for QT interval prolongation. (From Beach et al. [38])

Avoiding the addition of a medication known to potentially prolong QTc in a patient at risk of TdP is essential to avoid further exacerbating the patient's underlying risk of developing a potentially lethal ventricular arrhythmia.

The potential for drug interactions with cardiac medications is also an essential consideration when choosing a psychiatric medication. Thiazide diuretics increase lithium levels by 20–40%. The impact of other classes of diuretics and ACE inhibitors on lithium levels are varied. In the case of these medications, polypharmacy and medical comorbidities (such as pre-existing CKD) often play an important predisposing role in the induction of lithium toxicity. The metabolism of certain beta-blockers is accomplished via P450 2D6. This enzyme is inhibited by certain antidepressants, such as paroxetine and fluoxetine. The inhibition of the beta-blocker increases its plasma concentration, which has been shown to lead to a decrease in exercise-induced heart rate and blood pressure [39]. The co-administration of clonidine and mirtazapine may negate the antihypertensive effect of clonidine. Clonidine exerts its antihypertensive effect through agonist activity at central alpha-2 inhibitory receptors, while mirtazapine acts as an antagonist at the same alpha-2 receptors.

Mirtazapine may displace clonidine from the alpha-2 receptor and lead to the possible loss of antihypertensive effect.

Endocrine

Individuals with various psychiatric illnesses have a higher risk of diabetes, obesity, and dyslipidemia than the general population. Unfortunately, these conditions often go unrecognized and undertreated in patients with serious mental illness [40]. Adding to this disease burden is the fact that certain psychiatric medications may exacerbate this morbidity. Specific SGAs, such as clozapine and olanzapine, represent the greatest risk factor for worsening metabolic profiles and weight gain. In recognition of this risk, a consensus statement recommended that all patients receiving SGAs, regardless of indication, receive baseline screening and ongoing monitoring [41].

Hypothyroidism has been identified in 6–52% of patients chronically treated with lithium. Most commonly, it is subclinical in nature and occurs predominantly in women. As a result, baseline and annual testing of TSH is recommended when lithium is used to treat a patient.

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Chapter 4
Discussion on the Use of Psychiatric Medications: Questions by W. Harley Sobin MD Answers by Thomas W. Heinrich MD

Thomas W. Heinrich

1. Q: Most internists/gastroenterologists using antidepressants are using them to treat non-refractory depression, fibromyalgia, migraines, functional bowel disorders, etc. TCAs, in particular, are used much more to treat pain and functional symptoms, rather than depression by this group of non-psychiatrists. The doses used are generally much lower. Can you comment on the level of concern you would convey regarding the safety and risk of using TCAs in this clinical setting?

   A: Although there is a dose-response relationship to many of the adverse side effects of TCA, it still is worth

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respecting the potential for TCA to cause adverse events in susceptible patients (elderly patients, patients receiving polypharmacy, and with medical comorbidity). For example, given TCAs' classification as class 1A antiarrhythmics, they represent a risk for cardiac arrythmias in patients with a history of cardiac disease regardless of dose. Respect the medication.

2. Q: When choosing one of these drugs to treat depression and/or anxiety will you generally start with an SSRI if there is no pertinent personal history, family history, or painful syndrome?

   A: Yes. When I choose pharmacologic therapy to treat patients with uncomplicated major depression, I most often select an SSRI. They have proven efficacy across patient populations, are usually well tolerated and safe in overdose, relatively cheap, and once-a-day dosing can help improve adherence.

3. Q: In choosing an SSRI do you have any favorites, if you are dealing with a patient who has no pertinent exposure or family history. Who is basically a blank slate?

   A: My go-to SSRI is sertraline. It has minimal drug-drug interactions at lower doses and multiple therapeutic indications. It does not require dose adjustment in renal or hepatic dysfunction and has been demonstrated to be safe in patients with heart disease.

4. Q: If a patient doesn't respond to an SSRI, do you tend to go to a second SSRI or use a different class of drugs?

   A: It depends on the reason for the treatment failure. If it was due to intolerance that I can directly relate to the SSRI, I usually try to change class and avoid both SSRIs and SNRIs to avoid the risk of the patient experiencing the same adverse effects. If they had a partial response to the SSRI, I usually try to augment with a non-SSRI, trial another SSRI, or change to an SNRI.

5. Q: In choosing a drug to treat depression or anxiety, can you discuss which drugs other than SSRIs you tend to choose and in which setting?

   A: For patients experiencing chronic anxiety, pharmacotherapy starts with SSRIs. They are usually my first-line

pharmacotherapy for chronic anxiety as, when effective, they prevent future panic attacks or anxiety. For benzodiazepines to accomplish this, they have to be taken regularly on a scheduled basis, which raises the potential for the patient to develop tolerance, the need for escalating doses of medications, and the risk of withdrawal.

If a patient with depression or anxiety has comorbid pain, I may trial an SNRI as my first-line agent. Duloxetine is an excellent choice in this patient population as it has demonstrated efficacy for neuropathic and chronic musculoskeletal pain as well as fibromyalgia. If they have depression or anxiety comorbid with nausea or anorexia, I may elect to trial mirtazapine, although the evidence of mirtazapine and anxiety is less robust than for SSRIs and SNRIs.

6. Q: In choosing an SNRI, is there one you are more likely to use?

   A: When choosing an SNRI, it is important to recognize the fact that although they all inhibit the reuptake of both serotonin and norepinephrine, they do it to varying degrees. For example, at lower doses, venlafaxine is primarily a serotonin reuptake inhibitor. It is not until one achieves a dose of 150 mg/day or more that the norepinephrine reuptake inhibition becomes clinically meaningful. On the other hand, duloxetine exhibits uniform serotonin and norepinephrine reuptake across the dose range. In contrast, the newest SNRI, levomilnacipran, is a more robust inhibitor of norepinephrine reuptake than serotonin reuptake.

7. Q: Since sexual side effects are fairly common with SSRIs, do you tend to prescribe much sildenafil (or similar agents)?

   A: I have not utilized a phosphodiesterase type 5 inhibitor to treat antidepressant-induced sexual dysfunction. The data is quite poor. If a patient has had a good response to the SSRI or SNRI, but is experiencing sexual dysfunction, I will usually augment with bupropion. If that does not work, I would consider stopping the bupropion and replacing with amantadine, buspirone, or mirtazapine. If the SSRI

or SNRI was ineffective in treating the depression and causing sexual dysfunction, I would discontinue the offending medication and consider bupropion, mirtazapine, or one of the newer serotonin modular antidepressants.

8. Q: When you are using these drugs to treat patients who have underlying pain, do you tend to use TCAs more frequently or SNRIs?

   A: Given the propensity of patients with chronic pain to suffer from depression or anxiety, I tend to go straight for a medication that may address both of these conditions in the safest manner with the minimal risk of a large side effect burden. As a result, I tend to go with SNRIs in this patient population. Patients simply do not tolerate TCAs well at the doses it takes to achieve remission from depression or anxiety.

9. Q: Since most non-psychiatrists are not treating refractory depression, do you see MAO inhibitors being used by primary care doctors?

   A: No. They are really considered third-line agents.

10. Q: Primary care doctors are prescribing diabetic medications even though they are not endocrinologists and cardiac medications even though they are not cardiologists. Do you think it's equivalent to say the same for them prescribing psychiatric medications or do you think there is an inherent danger in that? In other words, do you think primary care doctors should be prescribing psychiatric medications without consulting with a psychiatrist? What are the biggest or most frequent mistakes made by primary care doctors in prescribing ADs?

    A: I may be biased as a family medicine physician and psychiatrist, but I think primary care clinicians are uniquely suited to address chronic conditions such as major depression and anxiety disorders. They often have the longitudinal relationship with the patient that allows them to identify a mental health condition. This could be through a population health approach, such as screening as recommended by the USPSTF, or through having a relationship with a patient and, thereby, knowing when

things are "off." This therapeutic relationship with the patient also improves adherence to treatment and likelihood of follow-up. In addition, it is not like we as primary care providers are not already seeing these patients as there simply are not enough psychiatrists nationally to address all the behavioral healthcare needs of the population.

11. Q: Are there any drugs that you encourage or discourage primary care doctors use in managing their patients with behavioral health problems?

    A: I usually recommend that primary care providers get comfortable with one or two medications from a given class of antidepressants. Of the SSRIs, I usually try and steer clear of paroxetine, as it has many drug-drug interactions and is quite anticholinergic. Fluoxetine also presents a risk of drug-drug interactions, so I tend to avoid it when polypharmacy is already an issue. Citalopram deserves a special mention given its FDA warning on risk of QT prolongation. As a result, I tend to avoid utilizing citalopram in patients with multiple risk factors for QT prolongation and/or torsades. If I am going to prescribe this medication to an at-risk patient, I will obtain a baseline and follow-up ECG to make sure the QTc interval is not prolonged.

Chapter 5
Cognitive-Behavioral Therapy for Irritable Bowel Syndrome

Melissa G. Hunt

Shelly is a 32-year-old woman who presented to your GI clinic with chronic abdominal pain and diarrhea. She is an elementary school teacher, married, with two young children of her own. Her difficulties began about 2 years ago when she experienced a severe episode of gastroenteritis that might have been viral or bacterial in origin. She is experiencing upward of 4–8 episodes of loose, watery stool daily, often accompanied by abdominal cramping and urgency. At the urging of her PCP and a nutritionist she consulted with, she tried various restrictive diets, including the low FODMAP diet, and several rounds of over-the-counter probiotics. She found that eliminating onions, garlic, wheat, cruciferous vegetables, and caffeine helped a little, and she still assiduously avoids them, which limits socializing and means she never eats out. Nevertheless, she is still quite symptomatic. A previous gastroenterologist completed blood work to rule out Celiac

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disease, stool tests to rule out a C-diff infection, and breath testing to check for SIBO, which came back marginally elevated. He recommended several rounds of Rifaximin. This gave her modest relief initially, but the pain and diarrhea quickly returned. He then recommended trials of first Bentyl (dicyclomine) and then Viberzi (eluxadoline). Bentyl caused mild dizziness and some tachycardia. She had several full-blown panic attacks while on the medication and elected to discontinue it. She found Viberzi helpful with abdominal pain and urgency, but blood work showed a very mild (and probably clinically insignificant) rise in ALT and AST, and she elected to go off the medication as she was terrified of liver damage. By the time she presents to your clinic, she is desperate. She has lost about 15 pounds over the last 6 months and now weighs a very slender 115 pounds at 5′4″. The weight loss is concerning enough that you decide to do a more thorough diagnostic workup. Fecal occult and fecal calprotectin are both normal. MRE is also normal. Her insurance approves a capsule endoscopy which also comes back normal, showing no signs of inflammation, ulcers, strictures, or other abnormalities. You are reluctant to complete a colonoscopy when there are no other alarm symptoms and no history of colon cancer or inflammatory bowel disease in the family, since it is very unlikely to uncover anything new. However, the patient and her husband are desperate for answers, and you reluctantly agree. The colonoscopy reveals one, very small polyp, which you remove and biopsy, but is otherwise completely negative for significant findings. At this point it seems clear that the patient's diagnosis is indeed IBS. She is tearful and upset in your office and seems very anxious and hopeless that anything will help. She has been living on Imodium and tells you that she often foregoes eating in order to avoid abdominal pain and the need to rush to the bathroom. She is seriously considering quitting her job since it is becoming almost impossible for her to remain in the classroom consistently without needing extended bathroom breaks. When she leaves your office to compose herself, her husband quietly informs you that she has experienced two episodes of fecal incontinence. He is desperately worried about her, and simply cannot

believe that there is not something seriously physically wrong with her. "Look at her!" he urges you. "She's wasting away in front of my eyes!" Having exhausted your diagnostic options, you feel you have little choice but to recommend a prescription for Lotronex (alosetron hydrochloride), which you have been cleared to provide, despite its high risk of adverse effects, though you suspect she will refuse to try it.

Later in the week, you see Tom, a 57-year-old business man with a very high stress job in the financial sector. His chief presenting complaint is abdominal pain, constipation, gas, and bloating. He actually shows you a photo on his phone of his distended abdomen that does indeed look "5 months pregnant" as he describes it. He also has secondary complaints of heartburn and burping, especially first thing in the morning. Your first recommendation, that he try stool softeners and increasing his fiber consumption is met with angry disbelief. "You think I haven't tried all that? What do you take me for, an idiot?" He goes on to detail all the things he has tried with previous doctors, including Trulance (plecanatide) and Linzess (linaclotide) and insists that none of them are very helpful. He experienced more urgency and cramping pain on Trulance and insists that his gas was much worse on Linzess. He appears rigid, angry, and confrontational, and tells you that he simply doesn't agree with the last doctor's diagnosis of IBS. "This is NOT all in my head!" he insists. "There has to be something wrong." You agree to order an MRE and a motility study, just to be on the safe side. The motility study comes back normal, although the MRE does show evidence of significant quantities of stool in the descending colon. He continues to tell you that the abdominal pain he experiences (which he describes alternately as gas pains, cramping, a feeling of extremely uncomfortable fullness, and occasional urgency if he does give in and use a laxative) is ruining his life and that he is thinking about taking a leave of absence from his job because he's been taking so many sick days anyway. He simply can't focus on work when he's feeling sick. He can't even play golf or enjoy watching a football game with his friends. He can't understand why you can't find anything wrong when it is obvious to him that his

whole GI system is just "failing" and he fears that it will "stop working all together" if you can't fix it. You are considering a trial of Amitiza (lubiprostone) on the assumption that it might work for him since it is approved for chronic idiopathic constipation in men (although not for men with IBS-C). You offer him that option, but when he learns that nausea and diarrhea are common side effects, he refuses to try it. When you gently point out that chronic constipation seems to be his primary complaint, he retorts with "You're just trying to fix one problem by giving me other problems." By the end of the consult, he appears sullen, frustrated, and hopeless, and you are uncertain what to suggest next.

If you've been in practice for more than a year or two, you have probably encountered patients like Shelly and Tom. They can be very difficult to manage, and it can be worrisome and frustrating for caring, competent gastroenterologists to work with such individuals [1]. The good news is that cognitive-behavioral therapy has much to offer patients like these, and referral to a skilled cognitive-behavioral therapist is probably the best option with cases like these [2]. CBT has been tested rigorously in a number of randomized controlled trials, and typically results in substantial improvements in GI symptom severity *and* health-related quality of life, gains which are typically maintained and consolidated over time [3].

Why is CBT so effective for IBS? There are several reasons. First, many patients with IBS have psychiatric comorbidities that are complicating factors and may underlie, exacerbate, or prolong functional GI disorders. Indeed, as many as 65% of IBS patients overall suffer from psychiatric comorbidities, most predominantly anxiety and mood disorders [4]. In IBS patients who are actively seeking treatment, *upwards of 90%* may present with psychiatric comorbidity [5], including mood, anxiety, and trauma disorders. Second, IBS is primarily a disorder of central-enteric nervous system processing [6]. Even when there is no obvious psychiatric comorbidity, referral to a CBT provider will probably be the most helpful thing you can do. If you can find a good CBT therapist in your area who is also knowledgeable about GI specific issues, that's

even better. The fact is that IBS patients often show inadequate response to usual medical care and, therefore, empirically supported psychological treatments (including CBT and gut-directed hypnosis) should be considered in many cases [7]. Indeed, there is growing evidence that such complementary approaches typically result in far better treatment outcomes and improved quality of life for IBS sufferers over and above traditional medical care and dietary management [8].

This chapter will focus on the biopsychosocial model of IBS, and a review of the literature on mechanisms of action and efficacy of CBT for IBS, followed by illustrative case conceptualizations and treatment protocols for these two patients.

IBS is, of course, characterized by recurrent abdominal pain that is relieved by defecation, and is accompanied by abnormalities in the frequency and/or form of bowel movements (i.e., characterized by constipation, diarrhea, or an alternating mix of the two) [6]. The etiology of IBS is important to explain to patients, in part to get their "buy in" for the utility of psychological interventions. Unfortunately, patients with IBS often feel insufficiently informed and harbor numerous distorted, incorrect, and even catastrophic beliefs about IBS [9]. They understandably resent the suggestion that their problems are "all in their head," so referrals for psychotherapy consultation must be couched strategically.

One of the most important etiological processes in IBS is the development of *visceral hypersensitivity* [10], which is the end result of faulty central-enteric, or gut-brain processing. Visceral hypersensitivity refers to abnormal endogenous pain modulation and has been clearly identified as an underlying mechanism in IBS [11]. In sum, patients with IBS feel normal gut sensations that most people would be unaware of, and experience many of those sensations as more painful than healthy controls. Visceral hypersensitivity can be measured objectively with balloon distension (of the gastric fundus, descending colon, or rectum) and is clearly correlated with IBS symptom severity above and beyond symptoms of depression and anxiety [12]. While the underlying neurological mechanisms mediating visceral hypersensitivity are still

under investigation in both animals [13] and humans [14], the important point is that visceral hypersensitivity leads to a vicious cycle of vigilance, stress, increasing pain, and increasing vigilance. That is, anxiety about and hypervigilance toward visceral sensations exacerbate the underlying hypersensitivity [15, 16].

One metaphor I use with patients when discussing visceral hypersensitivity is an overly sensitive smoke detector. Pain is supposed to be a useful signal that damage is occurring or that something is wrong that needs to be addressed. A good smoke detector reacts to the presence of actual smoke (and fire) and alerts you that you need to take action. An overly sensitive smoke detector, however, might go off in the presence of water vapor – say steam from a shower or a boiling pot of pasta. At best, this is annoying. At worst, it would send the entire family fleeing the house every time they tried to bathe or cook dinner. I explain to patients that the pain sensors in their gut have turned into overly sensitive smoke detectors, and that they are spending a significant amount of time and energy reacting to sensations that are really benign. Pain receptors in the gut are supposed to tell us when we have a serious infection, an ulcer or fistula, and an obstruction or have eaten something dangerous. They are *not* supposed to overreact to benign foods, and they're certainly not supposed to overreact to environmental and psychological stressors.

Another metaphor that is often useful is the existence of phantom limb pain in amputees. Many people have heard that soldiers returning from war zones "feel" excruciating pain in limbs they no longer have. This is a compelling example of disordered pain processing, especially since marines, special forces operatives, and green berets are hardly the type to whine and complain. You can ask the patient, "So if the soldier feels like their right hand is on fire, but the right hand *isn't there,* where exactly is that pain being experienced?" It doesn't take most people long to figure out that the pain is being experienced *in the brain*, which is misinterpreting signals from the peripheral nerves. Which means that the pain is, in fact, all in the soldier's head, although it definitely does not

mean that they are making it up. IBS is the same. The pain is very real, but it is the result of the brain misinterpreting and magnifying signals from the gut.

Most patients with IBS have also noticed that stress clearly plays a role in the onset and maintenance of their IBS symptoms [17]. In fact, stress often precedes and subsequently exacerbates IBS symptoms [18]. In animal models, early life stress has been shown to induce visceral hypersensitivity in mice [19]. IBS patients have been shown to have sustained HPA axis responses to acute psychosocial stress, followed by an increase in problematic GI symptoms [20]. Moreover, *perceived* stress in IBS patients is correlated with self-reported average pain, worst pain, fatigue, and sleep disturbance, as well as overall health-related and mental health-related quality of life [21].

Given the role of stress (and the involvement of HPA axis dysregulation) in the onset and exacerbation of IBS, it is not surprising that low-grade inflammation has been hypothesized to play an etiological role [22]. Investigated mechanisms suggest a major role of hypothalamic corticotropin-releasing hormone (CRH – also known as corticotropin releasing factor or CRF) in stress-related pathophysiology of IBS and possibly in inflammation of the intestinal mucosa [23]. Stress may also reactivate previous inflammation when applied in conjunction with a small luminal stimulus. This reactivation triggers increased permeability and immune system alterations [24, 25].

Another important aspect of IBS's etiology is almost certainly the role of dysbiosis, or disruption in the normal balance of flora in the microbiome of the gut [26]. A recent surge of research has suggested that dysbiosis may underlie a wide range of health problems, including everything from depression to obesity, through neural, endocrine, and immune pathways [27]. Dysbiosis may thus help to explain the complex dysregulation of the central-enteric axis in IBS, and the links between chronic stress, psychiatric disorders such as depression, and IBS [28]. Indeed, there are clearly links between stress, the microbiome-gut-brain axis, and visceral pain [29].

Interestingly, treatment with probiotics has been found to improve global IBS symptoms and quality of life in some patients with IBS without adverse effects [30, 31].

Beyond the core symptoms of abdominal pain and altered bowel habits, individuals with IBS suffer from a host of related difficulties that substantially impair health-related quality of life and functioning. In particular, patients with IBS often develop catastrophic fears [32, 33] and attendant maladaptive coping strategies, most of which are designed to help them avoid visceral sensations, the possibility of needing to get to a bathroom urgently and not making it "in time," and public embarrassment or humiliation [34].

Fecal *urgency* and fear of fecal incontinence (FI) are significant concerns for many IBS patients, particularly those who suffer from diarrhea. Two recent population studies have examined the actual prevalence of fecal incontinence in IBS. One found rates of FI of more than once per month in approximately 20% of IBS patients, with even higher rates (43%) if patients with less frequent FI were included [35]. The other [36], found that about 60% of people with IBS reported experiencing at least one lifetime episode of FI, with just over half of those experiencing between 2 and 5 lifetime episodes. Not surprisingly, fear of FI (even in individuals who have never actually experienced it) has an adverse impact on quality of life, psychological symptoms and work productivity. Patients start to avoid many situations in which getting to a bathroom quickly and unobtrusively might be difficult. That includes numerous venues, such as malls, parks, stadiums, concerts, places of worship, and numerous situations, such as long drives, trains, planes, work environments that prohibit quick exits such as classrooms, reception, factory work, conference calls, and so on. These avoidance strategies can be so severe that they meet DSM 5 [37] diagnostic criteria for agoraphobia [38]. Indeed, panic patients with comorbid IBS (especially the diarrhea predominant subtype) are more likely to develop agoraphobia and avoid a greater number of situations and are more likely to develop a severe form of agoraphobia than panic patients without IBS [39, 40].

Bloating, gas, and flatulence also afflict many patients with IBS and can lead to significant physical discomfort, but also to embarrassment and fear of humiliation. Audible gut gurgles, belches, and farts are not socially acceptable in most settings, and patients with IBS fear that they will be viewed as inappropriate or even disgusting as a result. They will often go to great lengths to avoid exposing themselves to such public censure, such as timing their meals carefully around meetings at work. Indeed, there is evidence that IBS patients do not even talk openly with intimate partners and family members about their experiences with IBS for fear of embarrassment and humiliation. There is also evidence that communication apprehension and topic avoidance are correlated with more severe GI symptoms and pain [41]. Like many patients with social anxiety, they overestimate the probability that people will notice them, and are convinced that their burps or farts are far more obvious and repellant than they actually are. Many patients with IBS are surprised to learn how often normative farting occurs. They sometimes hold the mistaken belief that other people rarely or never fart.

Individuals with IBS often *believe* that they are intolerant of a number of foods and limit or exclude them from their diet, despite the fact that immune and malabsorption tests are generally negative [42] and that patient reported intolerance of specific foods does not correlate with the results of empirical food sensitivity testing [43]. Indeed, broad surveys of patients with IBS show that most strongly believe that IBS is caused by dietary habits and patients most often seek information about dietary changes to manage symptoms [9]. As a result, many patients with IBS also develop substantial fear of foods that they believe trigger their GI symptoms [44]. This in turn leads to trying various restrictive diets and to avoiding food and food-related social situations, which further reduces quality of life and contributes to isolation. Unfortunately, self-reported food intolerance and avoidance are associated with more severe symptom burden and reduced quality of life [45]. Indeed, fear of food is highly correlated ($r = 0.86$) with impaired quality of life in IBS [44].

There is empirical evidence that the low FODMAP diet, which first eliminates and then strictly limits all the short chain carbohydrates that are co-digested by symbiotic bacteria in the gut, can reduce symptoms in IBS [46, 47]. High FODMAP foods *do* reliably cause more gas and water content in the gut as a by-product of the fermentation process [48]. However, this is only problematic in the context of visceral hypersensitivity, and only IBS patients (and some inflammatory bowel disease patients) are particularly bothered by it [49]. There is mounting evidence that restricting high FODMAP foods does indeed reduce acute GI discomfort for people with IBS [50–52]. However, the long-term effects of this restrictive diet are concerning, particularly with respect to evidence that it increases dysbiosis by starving whole species of symbiotic bacteria such as bifidus [53]. Moreover, the diet is very difficult to maintain and difficult to get good nutrition on without the guidance of a specialized registered dietician [54]. Although patients do report significant IBS symptom relief on the diet, overall quality of life is generally *not* improved, [55] and the diet may not do much better than traditional dietary advice [56].

Many IBS patients take steps beyond dietary modifications to avoid experiencing visceral sensations or having to defecate at all during certain periods. For example, they will "pre-load" by taking multiple doses of anti-diarrheal medications before heading out for the day or by the simple expedient of *not eating* all day until they are back in the safety of their home. Some patients carry quick acting, dissolvable anti-diarrheal medication with them the same way panic patients carry clonazepam wafers "just in case" they begin to experience symptoms. Of course, both use of anti-diarrheals and fasting have adverse effects. While anti-diarrheal medications are quite safe, and do not typically promote tolerance, they *do* cause constipation. This can lead to straining, hemorrhoids, bloating, and more gas pain and may ironically require laxative medication to resolve, leading to a return of urgency.

Fasting is another strategy that many IBS patients feel is warranted. But if you told a patient that a new treatment had side effects including dizziness, nausea, headache, irritability, slowed reaction time, reduced concentration, memory impairment, and learning deficits, most would refuse it. Yet that is exactly what hunger does! While all of these subtle avoidance behaviors feel perfectly reasonable to IBS sufferers, they end up maintaining the cycle of visceral hypersensitivity, anxiety, and catastrophizing and thereby ironically tend to exacerbate symptoms and disability long term.

From a behavioral health perspective, the problem with all of these approaches is that they are, at their core, *avoidance strategies*. The goal of all of these restrictive dietary modifications, including fasting (and symptom-based pharmacological interventions for IBS such as anti-spasmodic, anti-gas, and anti-diarrheal medications), is to minimize or eliminate visceral sensations. From the psychotherapeutic perspective, experiential avoidance almost always backfires. This gives the feared sensations, thoughts, or feelings greater salience and exacerbates the underlying hypervigilance towards, anxiety about and reactivity to them [57]. While avoidance strategies attempt to eliminate sensations that people with IBS are hypersensitive to, psychotherapy attempts to reduce the hypersensitivity itself.

Thus, there are a number of targets for psychotherapy in IBS. Psychiatric comorbidities can be directly addressed. Patients can be taught effective strategies for stress management and relaxation, which will reduce HPA axis reactivity and minimize the impact of stress on GI symptom exacerbation. Catastrophic, distorted cognitions that magnify stress and thus exacerbate GI symptoms can be corrected. Maladaptive avoidance can be reduced. Most importantly, exposure therapy can actually reduce visceral hypersensitivity and can begin to normalize central-enteric pain processing. There are several different empirically supported psychotherapeutic approaches to IBS, including gut-directed hypnotherapy, mindfulness, and cognitive-behavioral therapy [58].

Gut-directed hypnotherapy, originally developed by Whorwell and colleagues [59, 60], has been tested and reviewed and found to be an efficacious treatment for IBS [61] with reasonable, but not robust, long-term follow-up efficacy [62]. In a typical protocol, hypnotic induction (including arm levitation) is followed by basic psychoeducation about the functioning of the gut, and guided imagery of a smoothly functioning gut while the patient places their hands on their abdomen. A typical course of treatment is 7–12 sessions, delivered over 2–3 months. Outcomes include not only reductions in abdominal pain, constipation, and diarrhea but also improved quality of life, which highly restrictive diets typically do not afford. Overall, hypnosis appears to reduce rectal hypersensitivity and psychological distress in response to visceral sensory perception [61]. The most recent review [63] found strong support for hypnotherapy as highly efficacious in reducing bowel symptoms and providing relief to IBS patients. The question of mechanism of action remains. During hypnotic induction, various aspects of GI functioning are altered in measurable ways. For example, hypnotic suggestions for reduced pain sensation in the gut can suppress evoked viscerosensory brain potentials [64] and also slow GI smooth muscle activity, reducing cramping and urgency [65]. Moreover, hypnosis appears to normalize visceral discomfort thresholds [66]. It seems plausible that gut-directed hypnotherapy combines the benefits of relaxation training (which will quiet HPA axis activity) with the benefits of mild exposure to and reinterpretation of feared GI sensations, which will break the cycle of experiential avoidance that was paradoxically maintaining visceral hypersensitivity.

Another psychotherapeutic approach to IBS that emphasizes decreasing experiential avoidance is mindfulness. Mindfulness training typically involves helping people to attend to present-moment experience in a non-judgmental way and was developed by Kabat-Zinn and colleagues to treat a variety of chronic pain conditions [67]. Mindfulness-based interventions (or MBIs) have been applied to IBS with considerable success. For example, Gaylord, Palsson, and

Garland et al. [68] found that mindfulness training had a substantial effect on bowel symptom severity, relative to a support group, and improved health-related quality of life and reduced distress. Similarly, Zernicke, Campbell, Blustein, et al. [69] also found that a mindfulness-based stress reduction (MBSR) program resulted in significant improvement in symptom severity, compared to a waitlist control. In addition, there was significant improvement in quality of life, and overall mood, that were maintained 6 months following treatment. Bridging the gap between mindfulness and CBT with its explicit exposure component, Ljótsson and colleagues [70, 71] delivered a combination of mindfulness and exposure to IBS patients via the Internet. Even with very limited interaction with therapists, the intervention resulted in significant improvement in IBS symptoms, quality of life, and anxiety related to GI symptoms. Gains were generally maintained over a year later.

While hypnotherapy and mindfulness are clearly efficacious approaches to IBS, the psychological approach to IBS with the most empirical support is cognitive-behavioral therapy [2]. CBT has been tested rigorously in a number of randomized controlled trials, and typically results in substantial improvement in GI symptom severity *and* health-related quality of life, gains which are typically maintained and consolidated over time [3]. A number of protocols delivering CBT for IBS have been developed and tested in randomized controlled trials. They typically include substantial psychoeducation about the brain-gut axis, the role of stress and arousal in exacerbating GI symptoms, relaxation training, the role of visceral hypersensitivity, and the degree to which experiential and behavioral avoidance maintain and exacerbate disability and distress. Some focus primarily on interoceptive exposure [72]. Others combine mindfulness and acceptance with interoceptive and in vivo exposure [70]. Still others combine interoceptive and in vivo exposure with explicit cognitive restructuring to reduce catastrophizing about IBS symptoms. For example, Moss-Morris, McAlpine, Didsbury et al. [73] developed a manualized self-management

intervention incorporating modules on recognizing and managing unhelpful thoughts and reducing perfectionism and all-or-nothing thinking. Hunt, Moshier, and Milonova [74] developed a brief CBT treatment with modules that teach patients to challenge negative automatic thoughts and GI-specific catastrophizing. The efficacy of CBT for IBS has been shown to be partially mediated by reductions in visceral sensitivity [34, 74, 75] and by reductions in maladaptive, illness-related cognitions [76] and GI-specific catastrophizing [77]. Exposure to IBS symptoms and related situations seems to be a core component of effective treatment [78] and works in large part by reducing gastrointestinal specific anxiety [79].

Despite the efficacy of CBT for IBS, one of the main barriers to dissemination remains the lack of sufficient numbers of practitioners knowledgeable about both GI processes and CBT [2]. Many groups have tested variants of CBT for IBS with limited or distance (e.g., via email) therapist involvement [70, 71, 74] and typically obtain robust effect sizes. Several treatment manuals and self-help books are available that detail the CBT treatment approach. One (*Cognitive-Behavioral Treatment of Irritable Bowel Syndrome: The Brain-Gut Connection*; Toner, Segal, Emmott & Myron, 2000) is a manual written for clinicians. Another (*Controlling IBS the Drug-Free Way: A 10-Step Plan for Symptom Relief*; Lackner, 2007) was written for consumers. The third (*Reclaim Your Life from IBS;* Hunt, 2016) was also written for consumers, and is unique in that it was actually tested as a stand-alone, self-help therapy with no therapist guidance, in a randomized, controlled clinical trial [77]. Participants had 6 weeks to work through the book, at which point posttreatment assessments were completed. Treatment completers showed statistically and clinically significant improvement on GI symptom severity and health-related quality of life, mediated by substantial reductions in both visceral sensitivity and GI-specific catastrophizing, with effect sizes in the large to very large ranges. Gains were typically maintained at 3-month follow-up. Thus, there are a number of resources

available to interested clinicians and patients that can be used as stand-alone self-help treatments or in conjunction with in person work with behavioral health specialists.

Let's return now to Shelly and Tom, the complex, treatment refractory IBS patients we met at the beginning of the chapter. Here's how a cognitive-behavioral therapist might work with each of them.

Case 1: Shelly

Session 1

Recall that Shelly has lost a significant amount of weight and has been unable to tolerate or unwilling to continue with several different medications. In the first session, a CBT therapist takes a thorough history, including eliciting information about family of origin, social and academic development, and history of psychiatric symptoms and diagnoses in the family and in Shelly herself. She reports that her mother has always had "bad nerves" and that her father, who works as an actuary, has always been very risk intolerant. She admits that she has had a number of panic attacks in her life, many of them prior to the onset of the IBS symptoms, and she dreads having them. She worries about her health and often seeks reassurance from her husband, her primary care doctor, or the Internet when she experiences a new symptom. Although she has continued working as a teacher, she has been avoiding almost all other activities. Her husband has been doing the errands and the grocery shopping and taking their two children to their weekend activities. She is terrified of being in the car, or in line at the supermarket or at a soccer field and being unable to get to a bathroom in time. They have not eaten out or had friends over to dinner for months. In fact, she has been calling in sick from work frequently, and is seriously considering taking an FMLA leave or applying for disability. It becomes clear that Shelly meets criteria for panic disorder with agoraphobia, in addition to IBS.

The therapist explains how anxiety exacerbates all the different physical symptoms Shelly experiences through sympathetic nervous system arousal and assures Shelly that although these sensations are extremely uncomfortable, they are not dangerous. In fact, it is the body reacting normatively to a perceived threat. If the threat were a saber-toothed tiger, the body's reaction (increasing respiration and heart rate, secreting adrenalin and cortisol, converting glycogen to glucose, and shutting down digestion) would be quite adaptive! The therapist then teaches Shelly deep diaphragmatic breathing to show her that she has some control over sympathetic versus parasympathetic arousal. Shelly's homework is to practice deep breathing 3–4 times a day for 1 minute at a time, at a rate of 4 breaths per minute. The therapist also suggests that Shelly purchase and start reading a CBT self-help book for IBS, such as *Reclaim Your Life from IBS* (Hunt, 2016) or *Controlling IBS the Drug-Free Way* (Lackner, 2007).

Session 2

Session 2 begins with a review of the homework. Shelly reports that she practiced the deep breathing a few times a day. Sometimes it feels quite helpful, but other times she's not even sure she's doing it "right" and starts to feel lightheaded, which scares her. The therapist watches her breathe and corrects her technique, encouraging her to slow down and hold her breath for a second or two at the top of each inhale. Then, to show Shelly that she need not fear physical sensations, they do an interoceptive exposure therapy exercise, first intentionally hyperventilating together, and then switching to slow diaphragmatic breathing. Shelly is amazed to discover that she can feel dizzy, and experience rapid heart rate and tingling hands without having a panic attack. She notes that it wasn't scary because she was in the therapist's office and the therapist was doing it too, so she knows it can't be dangerous.

The therapist then proceeds to help Shelly identify the many catastrophic beliefs she entertains about physical

symptoms and sensations, and about GI sensations in particular. The therapist guides Shelly to understand that these thoughts and beliefs make her feel far more anxious and distressed and exacerbate her GI discomfort. The therapist asks Shelly explicitly if she is afraid of experiencing fecal incontinence, and if she has ever actually experienced it. She admits that yes, she is terrified of it. She has experienced two episodes. One happened at home in the morning. She was in the kitchen making tea and thought she needed to fart. She was appalled when a small pile of slimy, wet feces plopped onto the kitchen floor. The second time it happened she was in the supermarket. She was experiencing cramping and urgency, and the only available public restroom was occupied. By the time she got in to the bathroom, there was feces in her underwear. She has not gone shopping since. In fact, she has been too afraid of it happening again to do much of anything, including making love to her husband. Every time they start to be intimate, she has images of being incontinent in bed, and it upsets her so much that she has to stop. She grows quite tearful at this point, and says she is afraid she is going to lose everything because of her GI issues – her job, her marriage, her ability to function as a parent. The therapist empathizes with her distress but insists that together they will help her reclaim her life. Then the therapist encourages Shelly to try a behavioral experiment at home. When she feels the urge to defecate, the therapist encourages her to "hold it" for 1 minute. If she is able to do that successfully, then she can extend the time to 2 minutes, or 5 minutes, or even 10 minutes. She can try to use deep breathing to see if it will relieve the cramping.

Session 3

Shelly is pleased to announce at the beginning of the session that she has the hang of deep breathing now, and that she has been able to "hold it" for a full 10 minutes at home. On one occasion, at school, she was able to use deep breathing so

effectively that the cramping stopped, and she continued with the lesson without needing to go to the bathroom at all! She is amazed by this but is still quite fearful of tackling her avoidance of other areas, including activities where a bathroom might be hard to find, and eating foods she has been avoiding. They also discuss why Shelly has been refusing to eat out or to eat at a friend's house or even invite friends over. Shelly acknowledges that this has limited her contact with friends considerably, and that her husband is growing increasingly frustrated with her. Together they explore Shelly's catastrophic beliefs about what her friends would think if she asked them to cook special food, or if she had to leave the dinner table for 10 or even 15 minutes to go to the bathroom. She admits that if a friend asked her for similar accommodations, she would be sympathetic and happy to oblige them, and she admits that she has been assuming her friends would think she was pathetic or disgusting or selfish if she asked them to help her out. In fact, it turns out she has not told *any* of her friends or co-workers about her recent difficulties. Her homework assignment for the week is to pick one trusted friend and tell them about her IBS in a straightforward, factual way.

Session 4

Shelly is pleased to report that she told a close friend about her IBS and the friend was not only sympathetic, she was pleased that Shelly had shared the truth with her. The friend had been worried that Shelly was angry at her, or didn't like her anymore, and was actually very relieved to learn that Shelly missed her and had simply been too embarrassed to tell her the truth. The friend in turn shared that she herself had been struggling with depression and anxiety and marital problems, and Shelly had the opportunity to connect with her friend in an intimate, genuine and reciprocal way. She tells the therapist that now she feels stupid for having kept her IBS secret so long. The therapist assures her that many people do

just that and encourages her to widen the circle of people she tells, including her principal at work, and the co-teachers in her grade. Rather than considering an FMLA leave or disability, they conclude that it would make far more sense to ask for help. For example, Shelly reasons that since her classroom shares a door with the classroom next door, if she really needs to step out to go to the bathroom, the teacher in the adjoining room could keep an eye on her pupils for a few minutes. She could also talk to the principal about mentoring a student teacher for the rest of the year. That individual could also manage the class if she has to step out.

In light of this progress, the therapist begins to encourage Shelly to stop using so many subtle avoidance strategies, including skipping breakfast and lunch and using so much anti-diarrheal medication. The therapist has Shelly consider the effects of hunger on her mood, concentration, and energy. Indeed, she gets Shelly to acknowledge that when her pupils or her own children are irritable, reactive, distractible, and tired, it is often because they are hungry! Shelly agrees to try eating a small "safe" breakfast of soluble fiber-rich oatmeal and a few blueberries or half a banana.

Session 5

Shelly is pleased to report that her principal has agreed to let her mentor a student teacher in the second half of the year, and that the other teachers on her team have agreed to watch her class if necessary. Now that she is less anxious about the possibility of having to step out, she is actually finding that her gut acts up far less frequently during the day. She does report that her stomach gurgled very loudly one day in the middle of a lesson, and all the kids heard it and giggled. She notes that she was a little embarrassed but was able to make a joke out of it, and the kids really just thought it was funny. She is still anxious about passing gas or feeling an urgent need to move her bowels during faculty/staff meetings, and she is very anxious about the upcoming parent-teacher conferences, which

meet back to back for 3 hours without a break. The therapist encourages her to identify her catastrophic thoughts, and then replace them with more realistic, benign beliefs. Shelly does report that she finally got up the courage to eat breakfast on a school day and was pleased to discover that she felt less fatigued and was able to concentrate better throughout the day. She admits that she also took several Imodium that day, however. The therapist encourages Shelly to eat breakfast without using any anti-diarrheal medication during the upcoming week.

Session 6

Shelly reports that she has been eating breakfast every day and is no longer using Imodium "just in case." She is growing more confident about her ability to breathe through her cramps, and to hold it if she needs to. She got through the parent-teacher conferences successfully and notes that she was so busy and focused on what she needed to convey about each child, that she actually didn't think about her gut at all. She is still not doing much outside the house, however, other than going to work. She also raises the issue that her husband's sister is getting married the following weekend, and that she is terrified of flying out of state and getting through the entire ceremony and reception. She has always been a nervous flyer, but now the thought of being trapped in her seat on the airplane and then standing up with her sister-in-law as the matron of honor with all eyes on her is making her feel like she should just cancel the whole trip. She loves her husband's family, but she is terrified that she will have a panic attack on the plane or during the ceremony. Even if she doesn't have a full-blown panic attack, she is afraid her gut will start spasming during the wedding, and she will have to flee to the bathroom, ruining the ceremony, bringing humiliation down on herself and making everyone in the family hate her.

The therapist reviews her negative beliefs about flying and about her husband's family. Together they complete an imaginal exposure exercise in which the therapist walks her

through an entire flight in imagination, including using the tiny airplane restroom, some turbulence, the seat belt sign being turned on, and the bumps and deceleration of landing. They also talk through the "worst case scenario" for the wedding and think through how to talk to her sister-in-law in advance. The therapist agrees that, perhaps, just for the wedding ceremony, taking an Imodium might not be a terrible idea. But Shelly also agrees to be honest with everyone in the extended family and realizes that it is highly unlikely that anyone in the family would "hate" her, even if she did have to step away just before or even during the ceremony.

Session 7

Shelly skipped a week of treatment, since she was out of town at her sister-in-law's wedding. She is pleased to report that the whole trip went off without a hitch. She was a little nervous standing in the security line at the airport on the trip out, but once she was on the plane, she stayed occupied entertaining her kids and reading a magazine and even took a short nap. She didn't need to get up even once. The wedding itself was lovely, and she realizes how silly she's been thinking everyone would notice every little thing about her. She did excuse herself from the rehearsal dinner to go to the bathroom, but it was no big deal, and she doesn't think anyone even noticed. She got a little nervous about the drive from the ceremony to the reception. Her husband was driving his mom and dad and an elderly relative, and she had to drive with another member of the wedding party. It was the first time she had driven with anyone other than her husband since her IBS started. She felt a few twinges of cramp on the drive, but she was able to breath and tell herself it was no big deal, and the cramps went away. Even if she had had to ask the driver to pull over at a gas station or convenience store so she could go to the bathroom, she realizes it would have been fine. She is thrilled that the flight and the wedding went off so successfully. Her confidence is growing, and she now feels ready to tackle other things she's been avoiding, like the supermarket

and her kid's soccer tournaments. Shelly and the therapist agree that she can wait 2 weeks for her next session and that she will tackle some of the places she has still been avoiding in the meantime.

Session 8

Shelly reports that, overall, she is pleased with how things are going. She went with her husband and kids to an afternoon movie, and the following day she went with them to a large, multi-field soccer tournament. She admits a little sheepishly that she scouted out where the porta potties were, but also identified a nearby convenience store that had good ratings on a bathroom finder website. The therapist encourages her to simply use porta potties and shares their own experiences with camping at relatively rough campsites. Shelly laughs and says the therapist may be willing to use stinky, gross out houses, but she is more civilized. Hotels with beds and proper toilets are more her style. She does acknowledge that she had a slight setback when she tried to go to the supermarket. As soon as she got inside, she remembered her panic and the desperation of not being able to access the public restroom. She felt so overwhelmed that she turned around and left the store without buying anything. However, when she got home, she was so ashamed of giving up, that she determined to go back that very afternoon and buy at least a few items. She was able to return to the store later in the day and completed a small shopping. It felt like a victory, and she was proud of herself for going back. The therapist praises her courage and persistence and helps Shelly understand that even when setbacks occur, she now has the skills and understanding to overcome them on her own. Shelly shyly acknowledges that she and her husband also made love for the first time in months. She had a few concerning thoughts that she might fart or actually pass some stool, but she refocused her attention on the experience of intimacy and was able to keep herself in the moment. Her husband was tender and grateful and she is thrilled to have that part of her life back.

Toward the end of the session, the therapist reviews with Shelly everything she has learned and confirms that her IBS is now under far better control. She still has up to three loose bowel movements a day, but the cramping pain and urgency have lessened considerably, and she is no longer terrified of experiencing incontinence. Moreover, she now understands that her catastrophic thoughts about what other people would think were distorted and foolish. She is socializing again and has tackled most of the places she had been avoiding. She is eating more regularly and has gained back a healthy 7 pounds in the time she's been in therapy. She is still a little nervous about expanding her diet to include more high FODMAP foods, but she is willing to give it a try. With the therapist's reassurance that if she feels she needs more support in the future, she can always come back, Shelly decides to terminate therapy and tackle the rest of her issues on her own. She asks the therapist if she can have a hug, and thanks them fervently for "giving me my life back."

Case 2: Tom

Session 1

Tom arrives at his first session of therapy with a chip on his shoulder. He informs the therapist at the outset that he's not sure he believes in all this therapy mumbo jumbo and he still thinks there is something truly wrong with his GI system. However, since the gastroenterologists haven't been able to help him "at all," he's decided to give this a shot. Rather than diving in to taking a history, the therapist decides to address Tom's skepticism right off the bat. First, the therapist acknowledges that Tom is absolutely right – there *is* something truly wrong with his gut. The therapist then explains enteric-central nervous system miscommunication, the microbiome, and how stress has a direct, biological effect on the functioning of the GI system. The therapist uses the example of phantom limb pain. Tom's father was a marine, and he knew many veterans growing

up, so this explanation makes sense to him. Somewhat mollified, Tom asks how on earth talking is going to fix any of this. The therapist points out that "talking" affects how we think and what we believe – basic functions of the brain. By changing the way the brain interprets signals from the gut, and by changing the messages the brain itself is sending in response to threat and stress, Tom will actually be able to change the way his gut feels and works. Relaxing somewhat, Tom admits that that might make sense, and agrees to "go along" with what the therapist suggests "for now."

The therapist then takes a psychosocial and family history. Tom reports that his father was demanding, disciplined, and somewhat harsh but that Tom always respected him. Tom's father insisted that the house be kept spotless and would grow irate if things were out of place, or if Tom wore dirty shoes into the house, or broke some other rule. Tom learned to keep everything in his life clean and in perfect order. Although Tom's mother did most of the cooking, Tom's father always did the dishes, and had complicated rules for disinfecting the kitchen counters and the sink. Upon reflection, Tom realizes that some of his father's rules were extreme and probably didn't make sense. The therapist wonders out loud whether Tom's father might have had an obsessive-compulsive spectrum disorder. Tom bristles initially, but then admits that even for a military family, his Dad seemed particularly rigid about cleaning, order and doing things the "right" way. "It was his way or the highway," Tom comments "and God help you if you broke the rules." Upon further questioning, Tom describes his father's rules in more detail. Hands had to be washed with soap and scorching hot water for three full minutes after using the bathroom and before eating. Raw meat and eggs were kept strictly separate from all other food stuffs, and counters and cutting boards had to be disinfected with boiling water and bleach. If a utensil or a milk cap or jar lid fell on the floor, it had to be soaked in bleach for at least 10 minutes and then washed. Tom reports that he himself has maintained some of these rules, and uses hand sanitizer after touching doorknobs, using public restrooms or shaking someone's hand. The therapist suggests that

all this compulsive sanitizing may actually have compromised Tom's microbiome and he might want to take a probiotic. Finally, the therapist teaches Tom deep diaphragmatic breathing. Tom is, as always, skeptical about this. The therapist is able to show Tom how his heart rate accelerates during an inhale and decelerates during a lengthy exhale, and assures him that those same parasympathetic processes will work on his gut as well. Tom agrees to try it over the course of the week. The therapist also sends him home with an OCD symptom checklist to complete, to ascertain the degree to which he might himself meet criteria for OCD.

Session 2

Tom begins session 2 by telling the therapist that deep breathing is helpful in the moment, when he's doing it, but hasn't had any effect at all on his overall symptoms. His constipation, heartburn, belching and gas are as bad as ever. He did complete the OCD symptom checklist and says "I can't believe some of the crazy crap on this list. People really think this stuff?" He denied most obsessive symptom clusters (e.g., religious, sexual, violence, and harm-related themes), but did endorse perfectionistic checking and doubting, as well as a number of contamination fears and cleaning rituals. Although he says he's never had a particularly bad GI infection, he is terrified of contracting one that might make his symptoms worse. He thinks that would push him "right over the edge." His obsessions and compulsions are pervasive and time consuming enough that he meets criteria for mild OCD. He also says he ordered a probiotic and started taking it 3 days ago but is disappointed and frustrated that it hasn't helped. The therapist assures him that probiotics, like therapy, take time to take effect and that he shouldn't expect anything to be a "magic bullet" that will eliminate his troublesome symptoms overnight.

The therapist must now choose between initiating treatment for the OCD (which is undoubtedly adding to Tom's stress and exacerbating his dysbiosis) versus continuing to address Tom's

distressing GI symptoms directly. Working collaboratively, the therapist lays out the choice directly to Tom and asks him what he would rather work on first. Tom makes clear that although he is intrigued by this whole OCD thing and glad to hear treatment is possible, it's really the GI symptoms that are making him miserable. The therapist agrees to focus the next several sessions on GI symptom management but notes that it will make sense to return to the OCD relatively soon.

The rest of the session is spent exploring Tom's catastrophic beliefs and language about his GI symptoms. He shares the fear that his whole GI system will just "shut down completely" and confides that when he is experiencing GI pain, he gets so worried about it that he can't focus on anything else. He is particularly bothered in the morning when he first wakes up. He might feel okay for a minute or two, but as soon as he stands up, he almost always becomes aware of heartburn and vague nausea. This leads him to think to himself, "Oh no – here we go again. This day is shot. I just can't catch a break." The therapist suggests elevating the head of the bed by 2–3 inches as a partial solution and explains that simple gravity will help keep stomach acid from pushing against the esophageal sphincter, thus reducing his morning heartburn. He reports that his gastroenterologist suggested this and insists he tried it and it didn't help. On further questioning it is clear that he has tried propping himself up on pillows instead. The therapist stands firm that elevating the head of the bed is more likely to be both comfortable and successful. Tom agrees to try it. They then work on combating his catastrophic beliefs that his GI system will shut down and that he cannot have a productive or enjoyable day if he is experiencing GI discomfort. The therapist encourages Tom to elevate his bed, continue with deep breathing, and to reframe his GI symptoms as uncomfortable, but not dangerous or catastrophic.

Session 3

Tom reports that elevating the head of the bed has helped "a little" with his morning heartburn but that he is still very bothered by gas, bloating, and constipation. At the time of the

session, he notes that he hasn't defecated in 3 days. "If I could just go like a normal person my life would be fine." The therapist reviews his diet and encourages him to add more soluble fiber and to drink more water. Tom usually has a cup of coffee for breakfast. The therapist encourages him to try oatmeal or granola with fruit. Tom always thought oatmeal was "binding" and is interested to learn about the distinction between insoluble and soluble fiber. He is still resistant to the notion that simply relabeling his symptoms as "uncomfortable sensations" rather than pain will do any good. "You can call it whatever you want, but I know it's pain," he insists.

The therapist then asks Tom about his job. It is demanding, fast paced, and his work is often carefully scrutinized by his managers and the VP of the company. Tom notes that he usually double and triple checks everything he does to ensure accuracy. He notes that the turnover rate in the profession is very high and that one of his colleagues recently retired early due to high blood pressure. When the therapist asks if he would ever consider changing careers, he says no. He makes excellent money. He also notes that when he is healthy, he loves the intensity and the high stakes decisions he is asked to make. It's just now that his gut is acting up it makes it hard to focus and makes him doubt himself. He worries that he will make a mistake – a mistake that could cost the company millions of dollars. He has always checked his work multiple times, but now he's rarely satisfied. He has even started checking emails he sends multiple times to be sure there are no typos or errors in them. The therapist points out that his IBS and his OCD seem to be intersecting. When he is at the top of his game, he can triple check everything (as his OCD demands) and be assured that he is doing a good job. But when he isn't feeling well, the OCD makes him especially doubtful that he hasn't made a mistake. This is extremely anxiety provoking and leads to his feeling overwhelmed at work. At this point, Tom actually starts to become tearful. "I really want to be excellent at my job – the best," he says. "I just don't know if I can keep doing it through all this pain." The therapist points out the irony that Tom's intensity and distress are leading him to consider taking a leave from work that is lucrative and that he loves and suggests that targeting

the OCD and health anxiety may well enable him to function effectively again. Tom expresses hope that that would work. For homework, the therapist encourages Tom to alter his diet to include more soluble fiber (and water) and to start keeping track of how often he doubts his work and double and triple checks himself.

Session 4

Tom starts the session by announcing that he has defecated every day this week but once, and that oatmeal is fantastic. The therapist is pleased that Tom is feeling better but cautions him against concluding that oatmeal was the "magic bullet." Eating breakfast, especially with some soluble fiber, probably helps, the therapist explains, but it would be good to mix it up and try other foods as well. Tom *is* feeling better, but is still concerned about gas and bloating, and still feels very overwhelmed at work. One morning he didn't feel the urge to defecate until he got to work. Too embarrassed to use the men's room on his floor (where his managers and peers might hear and smell the results) he made a point of going down two floors to another department entirely and used the rest room there. The therapist takes this opportunity to talk about social anxiety and how fear of embarrassment can exacerbate IBS symptoms. The therapist asks if his coworkers ever defecate in the bathroom. Tom admits that they do and the therapist encourages Tom to just use the restroom on his floor in the future. The therapist also discusses experiential avoidance more generally and points out that all of his efforts to avoid discomfort have actually made his problems worse. The therapist lists the many things Tom does to avoid anxiety around contamination and the possibility of making mistakes, to avoid embarrassment, to avoid work when his gut is uncomfortable, and to avoid visceral sensations all together. "How's that workin' for ya?" the therapist asks. Tom admits that his quality of life and productivity have been getting worse and worse over the last year, and that it may be time to try a new strategy.

The therapist now introduces the notion of exposure therapy, which will be helpful for both OCD and for reducing visceral hypersensitivity. The therapist has a small mandarin orange on their desk, which they peel and divide into multiple sections. The therapist asks Tom how uncomfortable it would make him to eat a piece of orange that had touched the coffee table, or the carpeted floor, or his shoe. He looks at the therapist as if they are crazy. "Who in their right mind would eat something off a shoe!?" he asks. "Well, I would," the therapist replies, "if it will help you overcome your OCD. I will never ask you to do anything I wouldn't do." The therapist places a segment of orange on the top of their shoe and encourages Tom to eat a piece of orange that has touched the table, then a piece that has touched the arm of the couch. This makes him extremely uncomfortable, but he is willing to try it. The therapist then eats a piece of orange that has been on the carpet, and finally eats the piece that has been resting on their shoe. Tom sits with the discomfort and says "If I get really sick tonight I'll know who to blame!" The therapist praises his courage and willingness to engage in exposure and moves the conversation on to homework. Tom agrees to use the bathroom on his floor at work, to go to work even if he isn't feeling well, and to try to stop washing his hands so frequently and to throw out the hand sanitizer. At the end of the session, the therapist asks how anxious he is feeling about having eaten the orange slices. He admits that he had actually stopped thinking about it, and is no longer uncomfortable with it.

Session 5

Tom returns for session 5 very agitated and distressed. He says he was doing fine until 2 days ago, at which point he experienced terrible gas pains and GI discomfort that lasted a full day and night. He stayed home from work, trying multiple times to defecate. It got so bad, he convinced his wife to take him to the ER at 3 am, as he was convinced he had developed an intestinal blockage. After an imaging study

revealed simple constipation, the ER doctor suggested he try miralax and an enema and sent him home with 1 mg of alprazolam to help him sleep. He stayed home the next day as well. Tom is exhausted, tearful, and angry. "I thought this was supposed to be helping me, but it's just as bad as ever!" The therapist empathizes with his distress and says "It sounds like you were really scared and at your wits end that night." "Yes," Tom replies. "I really thought I might die. It was terrifying." The therapist then guides Tom to think through how his vivid catastrophic thoughts that night led to an increase of cramping, pain, and spasms in his pelvic floor muscles. The therapist reminds Tom about the effects of sympathetic arousal on the entire GI system and points out that catastrophizing almost certainly exacerbated the pain and panic and made the problem much worse. Exhaustion and sleep deprivation also didn't help. Tom is also angry at the ER doctor, whom he felt was dismissive and rude. "He treated me like I was crazy," Tom complains. The therapist gently guides Tom to consider the possibility that the ER doctor was also tired and busy and may have been brusque and unsympathetic because they had so many other patients to take care of. The therapist also encourages Tom to consider that he was engaging in catastrophic distortions about his symptoms, which made his pain worse. The evidence is that he was simply constipated and gassy, which was definitely uncomfortable, but not dangerous in any way. Had he simply eaten some oatmeal, drunk his coffee, and gone to work, his day probably would have gone much better.

The therapist encourages Tom to try to go to work every day and to remind himself that constipation is *uncomfortable and annoying* but not dangerous. The therapist also asks Tom about his exercise regimen and explains that exercise is one of the best ways to burn off stress and to get the GI system moving. Tom was a football player in high school and college and tells the therapist that he used to enjoy running and playing tennis, but that ever since his GI problems started, he has felt too worn down to work out. The therapist encourages Tom to start working out again by going for a brisk walk or

jog several times a week and maybe hitting some balls with his wife at the tennis club. The therapist and Tom have a good laugh that a military kid who played football and never complained would let a little gas slow him down. Tom admits the irony and agrees to start exercising again.

Session 6

Tom reports feeling much better this week. He has defecated about every other day but is trying hard not to catastrophize or panic on mornings when he doesn't defecate. He has gone to work every day. He did use the restroom on his floor once, although he wasn't happy about it. He acknowledges that if someone else is defecating, it bothers him a bit, and he doesn't like the smell. He is always quick to leave the room before the other person emerges from their stall in order to save them both the embarrassment. The therapist praises Tom for the strides he is making and admits that no one "likes" the smell of poop. However, the therapist encourages Tom to stay in the bathroom long enough to make eye contact and engage in casual banter with other people from time to time. Tom also notes that he went running twice, although he and his wife haven't been to the tennis club yet. He is dismayed to discover that he is so out of shape. He used to be able to run a 5k in 18 minutes. Now it takes him over 20 minutes to cover two miles and he was winded and sore. The therapist praises Tom for starting to exercise again and reminds him to take it slow and not expect himself to jump back in at the same level of fitness he had previously. Tom says that although he was frustrated with how slow and out of shape he is, he remembers why he loved running and admits that he felt calmer and more centered after each run.

The therapist then inquires about handwashing, hand sanitizing, and use of antiseptic and antibacterial products around the house. Tom admits that it is hard for him to change old habits, but that he understands why it might be important. "We never used to have hand sanitizer," he admits. "I followed

Dad's rules at home, but when I was with my friends we just ate right after practice, mud, sweat and all, and I never got sick." This insight helps him commit to exposing himself to more things without engaging in cleaning compulsions. In session, he agrees to put his hands on the floor, and then rub them on his clothes. The therapist models rubbing their hand on the bottom of their shoe and then touching their hair and face. Not to be outdone, Tom takes off one shoe and, with a grimace, touches the sole to his cheek. "There, you happy?" he asks the therapist with mock belligerence. For homework, Tom agrees to continue exposing himself to possible "contamination" at home. He notes that if he eats something off the floor, his wife will be shocked but thrilled. She has always thought his rules about cleanliness were excessive.

Session 7

Tom continues to make good progress with both his contamination-focused OCD symptoms and his IBS. However, he is still bothered by his GI symptoms at work and is now fixated on the possibility that he will belch or fart during a meeting or will have to leave a meeting to go the bathroom. He has never confided in any one at work about his difficulties and is appalled when the therapist suggests sharing that he has IBS with a few key people. "Are you kidding!?" he asks. "I would never talk about this stuff at work – it's disgusting and pathetic. I don't want people pitying me or worse thinking I'm off my rocker. You show weakness in my line of work, and your head is on the chopping block." The therapist helps Tom unpack all the negative, catastrophic distortions and beliefs embedded in this. GI problems do not make a person "disgusting and pathetic" or "off their rocker." Acknowledging a health problem is unlikely to get him fired. Moreover, Tom need not frame it in a way that evokes pity or makes him look weak. Rather, the therapist suggests that Tom say simply "Hey, just wanted to let you know I've been experiencing some chronic GI issues. I'm handling it and getting it treated, but I

may need to excuse myself from meetings every so often to hit the men's room." Tom admits that when it is framed that way, it doesn't sound so bad, and agrees to tell his direct manager.

The therapist also jokingly suggests that Tom intentionally drink a carbonated soda during a meeting so he can burp on purpose. "Should I bring a whoopee cushion too?" Tom asks. Laughingly, the therapist agrees that that would be an excellent exposure. In all seriousness, however, the therapist suggests that Tom pay attention to how often *other* people discreetly burp during meetings. The therapist also assures Tom that other people are farting around him all the time. He expresses skepticism about this and the therapist educates him about normal rates of flatulence. He is surprised by this and admits that he has been trying hard not to fart *at all* in the last year. The therapist suggests that passing gas is normal and healthy and that suppressing farts, especially by clenching the buttocks and anal sphincter, may have contributed to his bloating and to tight pelvic floor muscles that make defecation more difficult. The therapist encourages Tom to fart whenever he feels the urge but acknowledges that doing so discreetly is more polite.

Session 8

Tom reports that he did tell his direct manager about his IBS as planned. His manager was relieved to know that whatever was going on it was being handled. He had been concerned about all the sick days Tom was taking and was worried that there was something more seriously wrong, or that Tom was actually using the days to interview at other firms. The manager was pleased that Tom had let him know, and assured Tom that he was a valued member of the team and could take whatever time he needed. He even offered to let Tom work remotely a day or two a week if that would help. While the therapist is pleased the experience of confiding in his manager went so well, they discourage Tom from taking up the offer to work remotely for now. It is more important to get

himself into the office on a regular basis. Ironically, now that Tom knows it wouldn't be a big deal to step out of a meeting, he has not felt the urge to do so.

Tom was also surprised to realize how many people were discreetly burping, coughing, suppressing yawns, excusing themselves from meetings for various reasons, scratching their ears or noses, checking their phones, and generally engaging in far more "impolite" behavior than Tom had ever realized, including, he assumes, farting. He has been so focused on his own experience and his fear that other people were watching him, that he realized he never actually observed anyone else. The irony of this is not lost on him, and the therapist points out that most people feel like there is a "spotlight" on them and that everyone notices their behavior far more than they actually do. Tom is quite relieved by these observations, and decides he is going to stop worrying about burping and even farting. He has been feeling less gassy this week overall. "Better out than in I guess," he says.

Overall, Tom's IBS is much better, and the remaining symptoms (defecating approximately every other day, occasional gas, bloating, and mild belching) are bothering him far less. He is no longer convinced that something is "really wrong" with his GI system and has accepted that stress was exacerbating his symptoms and making them much worse. He still has work to do on his OCD and may well continue in therapy for several more months to bring that under better control, but overall he is pleased with his progress, and admits that "all this talking" did somehow make his gut work better.

Shelly and Tom are representative cases of how a cognitive-behavioral therapist might work with a distressed IBS patient. It is noteworthy that both individuals had a psychiatric comorbidity. Shelly suffered from panic disorder and agoraphobia, while Tom suffered from obsessive-compulsive disorder. In both cases, the psychiatric problem predated the onset of the IBS, but interacted with the IBS in ways that made the person's disability and distress far worse.

A prototypical course of CBT for chronic GI disorders would follow something like the protocol below.

Session 1

- Review of differential diagnosis and medical history.
- Unless the patient was referred by a known and trusted gastroenterologist, ensure that the patient has had appropriate medical rule outs (e.g., celiac disease and inflammatory bowel disease) and does not currently experience alarm symptoms.
- Educate the patient about the impact of stress and arousal on GI function via multiple mechanisms and pathways, including cortisol, adrenaline, sympathetic arousal, and the microbiome.
- Educate the patient about the role of visceral hypersensitivity in maintaining and exacerbating symptoms. Have patient complete the VSI (included in Appendix A).
- Teach effective relaxation strategies, including deep diaphragmatic breathing (which optimizes intestinal motility and activates the parasympathetic nervous system), muscle relaxation, and imagery. Some GI patients have difficulty with breathing and muscle relaxation because it focuses them on and in their body and heightens visceral awareness. If they feel like their body has become their enemy, getting the body to do what they want may seem impossible. In that case, start with imagery, but come back to other strategies later in treatment.
- Encourage adding probiotics to their diet, since research does suggest that dysbiosis is often an underlying factor in IBS.

Sessions 2–3

- Introduce the basic cognitive model of stress management, including negative automatic thoughts, and the link between thoughts and both emotions and physical reactivity. Teach the basic principles of cognitive restructuring. Use all components of classical cognitive therapy including identifying situations, thoughts, and outcomes (feelings and behaviors), learning to generate benign alternatives, and examining the evidence for competing beliefs.

- Begin to explore any GI-specific catastrophic beliefs and distortions, especially those that overlap with panic disorder (such as catastrophic misinterpretation of benign bodily sensations) and social anxiety disorder (such as the "spotlight effect," and catastrophic beliefs about how others both notice and judge one's behaviors negatively).
- Have patient complete the GI-Cog and FFQ (included in Appendices 2 and 3) to gauge catastrophizing and fear of food. Be sure to explore the actual experience of and fear of fecal incontinence, as many patients are acutely embarrassed by this topic and will not spontaneously report it. IBS patients may fear it despite never having experienced it. Some patients may be justified in their concern about the probability of FI, but may still have exaggerated, catastrophic fears of the implications of it (e.g., a patient who states unequivocally that if she ever experiences incontinence at work, she would have to quit that day and never return is probably catastrophizing in a maladaptive way).

Session 4

- Educate the patient about the role of experiential avoidance in maintaining and exacerbating impaired quality of life (because of missed experiences) and in contributing to visceral hypersensitivity and GI symptoms, including pain.
- Encourage the patient to identify avoidance behaviors in their own life and begin to make an anxiety hierarchy of situations they typically avoid.
- Explain the principles of graded exposure, and agree collaboratively on some relatively easy homework assignments they can try. For example, if an IBS patient fears fecal incontinence, and believes that they must always be no more than 30 seconds away from a bathroom, have them try to delay defecation by 1 minute in the safety of their own home. If they are able to do that successfully, increase the delay to 2 minutes, or three or five. This both provides exposure to feared GI sensations, and also gives people a sense of mastery. If the patient has become agoraphobic about travel, have them sit in their car in the driveway or garage for half an hour. When that is easy and

boring, have them drive around the block multiple times, so that they are never more than a minute away from home. This follows all the basic principles of graded exposure therapy, but applies them specifically to GI-specific feared sensations, situations, and outcomes.

- If a patient has been avoiding public places like the mall or the movie theater, agree on graded exposures they can try to achieve mastery. For example, they could look up the mall online, figure out where the bathrooms are, and then shop for half an hour in a store close by.

Sessions 5–6

- Continue reviewing reinterpretation of experiences and beliefs using thought records.
- Continue in-session exposure (e.g., have an IBS patient wear tight clothing that presses on the abdomen) and discussion of out of session exposure assignments.
- Begin to explore whether an IBS patient is engaging in *subtle* avoidance (e.g., prophylactic use of anti-diarrheal medication, fasting, food rituals, scoping out bathrooms in advance, preferential seating near exits). Encourage patient to begin curtailing subtle avoidance. Patients will often insist that it is perfectly rational and sensible to use these strategies, but further probing will often reveal that they are using them in maladaptive ways that perpetuate the cycle of anxious avoidance. For example, if the person knows they have a stressful day coming up at work, they may take one or two Imodium before they even leave the house *just in case*. While anti-diarrheal medications are quite safe, they can cause constipation and bloating and also perpetuate further avoidance and distress and maintain maladaptive beliefs. For example, people can become convinced that needing to poop unexpectedly is a catastrophe to be avoided at all costs. It turns out that getting people to stop using these medications on a regular basis is an important part of reducing GI-specific catastrophic cognitions and visceral sensitivity, and ultimately it actually leads to *reductions* in abdominal discomfort and urgency.

- Encourage continued acceptance and reinterpretation of visceral sensations as uncomfortable but not dangerous or illness-related.
- Encourage the patient to begin experimenting with eating a wider range of foods, including foods they have been avoiding for fear of triggering GI sensations and symptoms.

Sessions 7–8

- Explore any remaining catastrophic beliefs and explain the concept of behavioral experiments. This is good time to explore whether shame and secrecy play a role in experiential avoidance. Many GI patients believe that others in their lives would be disgusted or repulsed if they knew the "truth" about their GI issues, and therefore take great pains to disguise their issues, make up excuses for absences or for avoiding social gatherings, and so on. A good behavioral experiment to encourage is having the patient choose one trusted person in their life and tell them the truth about having chronic GI issues. Since the vast majority of people are actually compassionate, curious, and concerned, patients are typically very positively surprised.
- Continue to encourage curtailing avoidance and engaging in life fully, including eating a variety of healthful foods and participating in activities that involve food or situations in which getting to a bathroom instantly might be difficult. For example, send the patient to a movie theater or house of worship, have them sit in the very back, and *count* how many people actually get up at some point to leave and then come back. They will be surprised by how often this happens and how little most people react.
- Remind patients that even if they experience some GI symptoms, their quality of life will still be far better if they engage in life rather than giving in to the urge to avoid. Honesty, humor, and problem-solving go a long way toward reducing the shame, embarrassment, and social isolation IBS can cause.

- End with relapse prevention and planning. Remind patients that *everyone* experiences occasional GI discomfort, episodes of diarrhea or constipation, gas, and flatulence. Encourage patients to normalize those experiences, rather than catastrophize them.

Summary

Patients with IBS are troubled by recurrent abdominal pain, and altered bowel habits, but also by urgency, bloating, flatulence, and fear of fecal incontinence. Many patients engage in substantial avoidance behavior that can meet criteria for agoraphobia and IBS patients are at increased risk for comorbid psychiatric disorders, especially anxiety disorders and depression. Many develop substantial fear and avoidance of food, and restrict their diets considerably, leading to loss of social opportunities and hedonic pleasure, and, in some cases, compromised nutrition and/or increasing dysbiosis.

Unfortunately, traditional medical management is often unsatisfactory in IBS, and IBS patients (and their gastroenterologists!) are at risk for greatly reduced health-related quality of life, even when the GI doc is delivering highly competent medical care. Fortunately, psychosocial, behavioral health treatments have been developed that are quite effective for IBS. Hypnotherapy, mindfulness-based interventions, and cognitive-behavioral therapy in particular are all evidence-based treatments for IBS that have considerable empirical support for their efficacy. All three approaches discourage experiential avoidance and teach patients to approach and think about their symptoms in less catastrophic ways.

Ideally, gastroenterologists will develop collaborative relationships with GI informed cognitive-behavioral therapists in their area. The growing field of psychogastroenterology focuses on the application of scientifically based psychological principles and techniques for the alleviation of digestive symptoms and disease burden and improving HRQL. The importance of the role of gastroenterologists in

the promotion of integrated psychological care cannot be overstated [80]. Unfortunately, there are still not enough GI informed cognitive-behavioral therapists available. Fortunately, CBT protocols for IBS have been modularized and adapted as self-help workbooks which can be used as stand-alone treatments, or as adjunctive bibliotherapy in work with a therapist. This should increase the dissemination of such treatments and make it easier for healthcare professionals from various disciplines (psychology, counseling, social work, nurse practitioners) to incorporate GI informed psychotherapy into their work with GI patients. It also makes it easier for gastroenterologists to provide their IBS patients with truly effective, empirically supported treatment.

Reclaim Your Life from IBS: A Scientifically Proven Plan for Relief Without Restrictive Diets is a self-help book that makes the entire CBT protocol available to IBS patients as a stand-alone treatment. It was tested in a randomized controlled trial and was shown to be quite effective, even without direct therapist support [77]. Given how much we know patients can benefit from complimentary approaches to reduce pain and improve quality of life, it is my fervent hope that together gastroenterologists and therapists can increase access to effective treatment and improve outcomes for these challenging patients.

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Chapter 6
Exposure Therapy for Functional GI Disorders

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One of the most frustrating patient encounters a physician can have is when the patient looks to the doctor for a medical cure and the physician knows that no medical cure is forthcoming. The primary problem with functional GI disorders is that although the patient's health is intact, they misperceive their ability to cope and believe activities of daily living are impossible without the complete removal of the symptom. Additionally, any observant physician will realize that many other patients with severe GI disorders that result in similar or more extreme symptoms are seemingly able to live their lives fully and with great grit. For example, an irritable bowel syndrome patient might complain and refuse to attend work for fear of bowel urgency and cramping, while an ulcerative colitis patient might attend all business meetings and travel extensively for work or vacation without complaint. Furthermore, many physicians attempt to allay the apparent fears of patients with functional GI disorders by ordering

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repeat testing in a vain attempt to reassure patients that all is well or to search for a rare possibility that something organic is at play because reasonable medical interventions have failed to diminish nausea, pain, bowel urgency, vomiting, or diarrhea. The dilemma for everyone is that the treatments that are most likely to help are not the ones likely to be mentioned in medical training.

Fortunately, there is a great deal that can be accomplished to help patients with functional GI disorders overcome their anxiety, physical symptoms, and difficulty engaging in activities of daily living. The solution is to apply the science from psychological interventions that have been shown to be most effective for anxiety, that is, *exposure with response prevention therapy* (ERP) [1–4].

Many physicians who treat patients with functional GI disorders have correctly realized that anxiety is a major component of the patient's profile. The problem occurs when the treatment provider accidentally chooses interventions that worsen the patient's ability to manage their anxiety. Here is an example of this unfortunate process.

Case vignette: Allen, a young adult male white-collar professional seeks Dr. Smith's help to get rid of recent onset repeated nausea and occasional vomiting that occurs every time the patient has to give presentations. Dr. Smith's initial exam reveals no significant findings, and he prescribes an antiemetic medication and antacid tablets for the patient to take before presentations. The patient returns 3 weeks later complaining of the same symptoms despite taking the medication as prescribed. Dr. Smith asks the patient if he is anxious about giving presentations, and the patient insists that he enjoys public speaking but hates the thought of feeling nauseated and distracted or of having to leave a meeting to vomit. He has an apparently successful career and denies any previous history of anxiety. Dr. Smith, perplexed and wanting to help the patient feel better, conducts an upper GI and several other studies and finds only a healthy gut. Dr. Smith then wonders if the patient has any food intolerances but fears that any tests for food allergies or intolerances will similarly

come up negative. Meanwhile, the patient has more episodes of nausea and vomiting that appear to be worsening in frequency and intensity and have resulted in some missed days of work.

The aforementioned case vignette is all too common with more testing, more medications and no improvement being the likely outcome. Taking a different approach that assesses the presence of anxiety and the functional relationship between anxiety and behavior in the patient provides great promise. The reason for the improvement in outcome is because the greatest problem for a patient with functional GI disorders is their worry about the occurrence of their symptoms and their worry about the significance of their symptoms. It is their dread of GI symptoms, and avoidance of situations they believe will provoke their symptoms, that creates the biggest obstacle. This is why one patient with an ileostomy may be seeking your advice about how to become a distance runner and another patient with unexplained nausea is unable to attend work and frequently seeks new medication. Understanding the nature of anxiety, and the role that reassurance seeking and avoidance plays in cementing anxiety in place, helps to explain the apparent contradiction between these two types of patients. It also explains why a physician's attempts at unnecessary testing and repeated attempts at medication can make things worse.

The Nature of Anxiety

Anxiety is best understood as the general fight, flight, or freeze response that humans experience when they misperceive danger. The perception of real danger is called a fear response. The body does not distinguish between a real or misperceived threat when it generates a physical and mental response to a trigger. For example, a driver spinning on black ice feels the same physical and mental distress as does a bee phobic when they hear buzzing. Most people who experience anxiety quickly recognize that their anxious response is a

false signal and they explain away their symptoms to a benign cause. For example, a professional athlete who is not prone to clinically significant anxiety might experience strong anxiety, symptoms of shakiness, increased heart rate, and loose stools prior to a game but thinks, "Of course I am hiked up. It's a game. Once I start playing I always feel better and get past it." On the other hand, someone prone to developing an anxiety disorder responds with alarm and the assumption that what they feel is both dangerous and unmanageable, "Oh no! I feel terrible! This should not be happening to someone as experienced I am at sports. I am a professional. What if this messes up my game today? What if I cannot focus on the game? What if I have to go to the bathroom in the middle of a play?" This is why one patient with cyclic vomiting syndrome might continue to work and maintain a job despite knowing that they will have severe bouts of predictable nausea and vomiting and another patient, the anxiety prone one, stops working and stops doing chores at home and appears to be completely disabled. The anxiety-prone patient is worrying about what will happen, fears the occurrence of their symptoms, and is desperately seeking a quick escape from their GI symptoms instead of tolerating them.

The Role of Negative Reinforcement

When patients try to escape the triggers of their anxiety to obtain quick relief, it is called negative reinforcement. It is adaptive to use the fight, flight, or freeze response in the face of real danger. However, giving in to the urge to avoid, escape, or seek reassurance in the presence of anxiety reinforces anxiety and makes it worse in the long run. Negative reinforcement works in the following manner. A patient with irritable bowel syndrome worries about getting bowel urgency when driving in heavy traffic. They decide to avoid driving at rush hour and on expressways for fear that they will need to use the restroom. Each time they opt to avoid the expressway and choose instead to drive an inconvenient residential route

they reinforce the likelihood that seeing an expressway or traffic jam will result in feeling unwanted belly sensations. This will then rapidly increase the belief they cannot drive unless they stay on "safe" residential roads. Additionally, thinking about expressways or driving in rush hour traffic becomes classically conditioned to the occurrence of belly sensations. This is like Pavlov's dogs that drooled to the sound of a bell after they had repeatedly eaten meat powder after hearing a bell ring. Negative reinforcement can take myriad forms, including patients asking for testing, procedures, and additional consultations with multiple providers (Table 6.1).

Here is how negative reinforcement works. A patient experiences anxiety and believes that they cannot tolerate the sensation of nausea, cramping, vomiting, belly pain, or diarrhea. They misinterpret the experience as being dangerous instead of benign. They then attempt to escape the situation. Once they escape the situation by using avoidance, reassurance seeking, or ritualistic reassurance, they get quick relief. The problem is that this quick relief reinforces everything that happened prior to the quick escape. This guarantees that the next time the patient encounters a similar sensation or

Table 6.1 Examples of negative reinforcement

Repeatedly asking for reassurance that "nothing is seriously wrong"
Repeated visits to the doctor or ER
Repeatedly researching symptoms on the Internet. The doctor's explanation is never enough
Asking for more tests or repeat testing
Avoiding work, school, chores, exercise, travel, socializing when symptoms occur, or when the patient fears they might occur
Avoiding activities unless the patient has their medications even when the medications are not working
Avoiding activities unless the patient carries an emesis bag, wears a diaper, or takes antacids
Repeated doctor visits and requests for tests to find out "what is really wrong"

worried thought, they will feel greater anxiety, a greater desire to avoid, and feel more incapable of tolerating their symptoms. They will also likely experience stronger sensations of their symptoms. Ouch!

Contrast this with what patients do who are not prone to developing anxiety. They experience nausea, cramping, vomiting, diarrhea, or bowel urgency, and they interpret the experience as something unpleasant but manageable. They assume they can cope. They do not worry about what will happen. Instead, they allow their symptoms to occur and to subside of their own accord. They instinctively, or through observation, realize that anxiety is self-limiting and will decrease on its own without the need for escape. They also increase their self-confidence about managing their symptoms while engaging in normal daily activities of living.

There is a process in which neuroreceptors become saturated with anxiety-related molecules then remain at steady state. After a while, there is a decrease in the anxious physiological response. This process is called habituation. Habituation occurs when any steady-state stimulus is maintained and the body is allowed to get used to the situation. For example, if you fear roller coasters, then what do you think would happen if you rode a roller coaster a hundred times in a row? You would undoubtedly feel very anxious the first three or four rides, but by the twentieth ride you might feel less anxious and then by the fiftieth ride you might feel mildly entertained. After one hundred rides, you would surely feel bored and no longer fear riding the roller coaster. This is habituation. We all have the capacity to benefit from habituation when anxiety overcomes us because it is built in to our neurophysiology.

Additionally, when habituation occurs, it inspires patients to reframe the experience of anxiety as something they can master. They have a real-life experience that convinces them that anxiety will not spiral out of control and will gradually decrease to a comfortable level. The type of therapy that takes advantage of the process of habituation and reversing negative reinforcement is called exposure with response prevention therapy

(ERP). The idea of exposure with response prevention is not a new one. You may have heard the type of advice that people who instinctively understand the principle of exposure with response prevention tend to give. They tell people in an automobile accident to be sure to drive as soon as possible after the accident to avoid becoming fearful of driving.

Exposure Therapy with Response Prevention Applied to Functional GI Disorders

The protocols for treating panic disorder, agoraphobia, and generalized anxiety disorder have components that can readily be applied to the treatment of functional GI disorders [5]. These anxiety disorders each have symptoms that mimic what happens in patients with functional GI disorders, such as being intolerant and worried about physical sensations, avoiding activities of daily living for fear that these activities might bring on feared physical sensations, and intolerance of uncertainty such as not knowing whether or not symptoms will return or when they will end. Additionally, patients with these groups of anxiety disorders are also at high risk of seeking medical intervention for their symptoms despite medical reassurance that they are in good health.

The basic principle of exposure therapy is to engage the patient in facing the situations that he or she fears and avoids while remaining in the situation until their anxiety naturally decreases. Refraining from negative reinforcers is called response prevention. Successful exposure also includes refraining from avoidance behaviors, reassurance seeking, compulsive checking, and using safety maintaining rituals as part of the response prevention. Successful treatment means simultaneously decreasing and banning the patient's negative reinforcers, applying response prevention, while encouraging the patient to gradually practice facing the situations, sensations, and thoughts he or she fears.

Safety maintaining rituals are referred to as safety signals. For example, a patient who fears vomiting may use the

following as safety signals: sucking on ginger lozenges, wearing anti-nausea bands, keeping a bottle of water nearby at all times, and looking in the mirror to see how peaked he or she looks. Another patient who fears GI cramping and pain might avoid eating foods with fiber or that are gas producing, might avoid eating when outside of their home, and wear a thermal bio-dot to try and maintain a constant state of relaxation that they falsely believe will prevent cramping.

Avoidance behaviors might include avoiding commercials that mention GI symptoms, avoiding exercise, avoiding doing things too vigorously, avoiding drinking carbonated beverages, avoiding eating certain foods, and believing they have food intolerances despite lack of verification. Avoidance of work and school and leaving the house are common avoidance behaviors.

Patients can engage in compulsive checking as a form of negative reinforcement. This might include examining each stool, repeatedly going to the bathroom, trying to completely empty their bowel for lengthy periods of time, and repeatedly scrutinizing belly sensations. Compulsive checking might also involve repeatedly asking the doctor for their opinion or seeking additional medical consultation that is unnecessary.

Research on exposure with response prevention therapy shows that patients who are seen in the emergency room following panic attacks and receive instructions to do exposure and response prevention fare better than patients who are told that they are in good health and need to seek treatment for anxiety [6]. This is because patients are more likely to attempt exposure practice and to improve response prevention when an authority explains how to implement a therapeutic intervention even though they do not provide the intervention. This means that whether you choose to provide advice on how to conduct self-directed exposure and response prevention therapy with referral to a mental health professional or you choose to directly guide your patients to complete exposure with response prevention therapy, you will be doing them a great service. The mistake you want to avoid is

to just provide reassurance that their body has no identifiable symptoms of disease and to consider mental health counseling. Patients feel invalidated because their symptoms are indeed real, including their symptoms of anxiety. Offering a helpful explanation and advice for how to better manage symptoms, which includes exposure with response prevention therapy, can be immensely comforting in the light of no physical findings, for a patient with a functional GI disorder. Here is an example of how a physician might conduct exposure with response prevention therapy.

Exposure Therapy for a Patient Disabled by Belly Pain

Cecilia is a 32-year-old married female who complains of frequent belly pain that makes it difficult for her to stay at work or to do activities at home. Her internist referred her after being unable to find a physical cause for her symptoms. She wonders if she has gastroparesis, something she read about on the Internet. She has negative findings for food allergies and food intolerances and has normal bowel movements. She has lost weight due to fear of eating too much food and is very thin. She has been given multiple trials of various medications, all of which have failed. She continues to take these medications for fear that she will get worse if she stops them. She avoids gluten and fears she has undiagnosed celiac disease despite a negative test for celiac sprue. She calls the gastroenterologist's office frequently, asking for new medications and complaining of disabling belly pain. She is reluctant to seek psychotherapy because she believes that all will be well if she could only get rid of belly pain. She keeps a daily diary of all of the fluctuations in her symptoms, what she eats, when she defecates, and the quality of her stool. She has stopped all exercise. She fears that if she exercises, this will precipitate belly pain, nausea, increased heart rate, and breathlessness, sensations typically felt during an anxiety attack. She stays home from work or leaves work early and

goes to bed when she has belly pain, which can happen four to five times per week.

- Case formulation: Cecelia is caught in a cycle of negative reinforcement that has been exacerbating her belly pain and making it difficult to work and enjoy her life. In particular, she has several areas of concern that should be addressed.
- Avoidance behaviors: Avoiding eating gluten, avoiding eating normal quantities of food, leaving work when she has pain, avoiding exercise, and staying in bed.
- Reassurance-seeking behaviors: Checking stool, monitoring belly sensations, calling the doctor's office, taking medications that do not work, and searching the Internet for information about her symptoms
- Worries: That something serious is wrong, that she will never get better, and that a medical cure is her only way to a better life
- Treatment goals: Decrease avoidance of work, increase time out of bed, increase eating of normal quantities of food, eat foods containing gluten, begin daily exercise, stop compulsively recording symptoms, stop examining stool, and decrease calls to the doctor's office unless the doctor has given explicit directions to call

Beginning Treatment: Explain to Your Patient the Following Information

"I know that you have been suffering and you must be really frustrated that we have not been able to find a medication that helps rid you of your symptoms. I, too, wish that I had a pill that could make it all go away. The good news is that there is still a lot that we can do to help you get your life back and to feel less worried about your belly pain. Scientific studies on the treatment of functional GI disorders suggest that your body has gotten stuck in a pattern of sending the wrong signals to your gut and your gut in turn sends wrong signals to your body. We know that when people react to their symptoms with alarm, worry and avoidance of situations that might trigger their symptoms, they accidentally create a cycle

of negative reinforcement of the very symptoms they want to avoid. Negative reinforcement occurs when someone tries to rapidly escape an unpleasant sensation. Rapid escape feels good but reinforces all the symptoms that came before the moment of relief. It is like when someone picks up a baby who cries and then the baby accidentally learns to cry more often and more loudly in order to get picked up. The parents then continue to pick up the baby more and more until they carry the baby everywhere all the time and the baby cries as soon as a parent puts them down.

The best treatment to get rid of this vicious cycle of negative reinforcement is exposure therapy. Exposure therapy helps to reverse the process that your belly pain accidentally started. Exposure therapy can help you get your life back. The one trick is that you will have to focus on stopping negative reinforcement and practice doing the things that belly pain has made you fear, regardless of whether or not you feel pain. We also know that when you repeatedly practice exposure tasks your mind will learn to refocus on things besides your belly pain. This will lessen your anxiety about belly pain and make belly pain easier to tolerate and even lessen your pain. We know that anxiety about pain makes the pain worse. So, we need to identify some targets for exposure practice and some targets for response prevention, or stopping the negative reinforcement cycle. What do you think of this idea?"

If the patient disagrees with the idea of exposure therapy or tells you that they cannot improve because of the pain, then reply with empathy and pointing out how the more the patient has sought intervention, the worse she has gotten. For example, "I wish we could get rid of your pain right away, but everything that you have tried to help your symptoms has failed to help and your test results show that you are in good health. Your biggest problem is breaking the cycle of negative reinforcement that has cemented your symptoms in place and learning how to get your life back despite the presence of pain or the possibility of cramping. I know that sounds harsh, but medical science does not have a medication for a body that is essentially healthy but sending wrong signals at the

wrong time. The best treatment for this is exposure with response prevention therapy. What is the worst thing that could happen if you try this? Doing what you have been doing is not helping and things have been getting worse because of negative reinforcement. How about we work together to see if this can help you?"

It might help to draw a diagram of the cycle of negative reinforcement with the patient's symptoms to better illustrate their problem. See the diagram (Fig. 6.1) below that illustrates how leaving work, scrutinizing symptoms, avoiding food, laying down, etc. make things worse for the patient.

FIGURE 6.1 Cycle of negative reinforcement with patient's symptoms

Defining Targets for Exposure

Make a list with the patient of all the possible targets for exposure practice. Have the patient identify how difficult they believe each task might be using the SUDS (Subjective Units of Distress Scale) from 0 to 10, with 0 equivalent to the patient's calmest most peaceful moment and 10 equivalent to their worst moment with their worst symptoms. SUDS ratings can help you and your patient determine where to start practice and makes it easy to track practice as the patient's SUDS ratings change during practice. Keeping track of SUDS ratings helps the practitioner identify whether or not an exposure practice is effective. Initially, exposure practice that is working well should increase a patient's SUDS ratings. Early on the patient will experience more anxiety. But as time goes on, the hallmark of successful exposure therapy is that the patient's SUDS ratings will decrease for the various exposure tasks on their practice list. This is called *between session habituation*. Between session habituation is your indicator that treatment is working. Patients who fail to report between session habituation are almost always engaging in negative reinforcement despite doing exposure practice. You should inquire about this if your patient claims not to experience any habituation in spite of doing exposure practice.

The goal of treatment is to learn to tolerate things that elicit a higher SUDS rating rather than trying to avoid the experience of distress entirely. Patients often confuse progress (being able to tolerate higher SUDS without avoiding, seeking reassurance, or using safety signals) with not getting anxious in the first place. This is incorrect. Success means being able to deliberately provoke an increased level of anxiety and discomfort and to endure it without avoiding it or quickly escaping it. An exposure practice list might look like the list below (Table 6.2).

Making Exposure Therapy Successful

Effective exposure therapy has to have two important elements. Effective exposure needs to provoke anxiety and distress and the patient has to stick with it until their anxiety

Table 6.2 Exposure practice list

SUDS 3 Not eating ginger lozenges at work or on the way to work
SUDS 4 Walking at a normal rate around the block
SUDS 5 Not checking stool and flushing toilet before looking at my stool
SUDS 5 Not writing down my symptoms
SUDS 6 Not researching GI disorders on my phone or laptop
SUDS 6 Not seeking other medical consultation, not talking to other doctors about my symptoms
SUDS 7 Not calling the doctor's office when having symptoms while waiting until the next scheduled appointment to talk to the doctor
SUDS 7 Walking rapidly for 10 minutes
SUDS 8 Not telling others when I have symptoms, not talking about it with friends
SUDS 9 Eating until I feel full
SUDS 9 Repeating these phrases until SUDS drops by half "What if I have something seriously wrong that no one can cure? What if I get worse by doing this therapy? What if I can never go back to work?"
SUDS 10 Eating small amounts of foods containing gluten
SUDS 10 Jogging in place for 5 minutes
SUDS 10 Staying at work for a half day with no antacids or other medications
SUDS 10 Not taking medications when I think I might get symptoms
SUDS 10 Going to work and staying for a half day no matter which symptoms occur

decreases by about half. This requires empathy and a gentle firmness to help the patient be willing to attempt tasks that they habitually avoid. It is helpful to remind yourself of the times that you have had to do similarly difficult things, such

as give a speech that made you anxious, sit in your seat on an airplane during severe turbulence, or demonstrate a physical exam on a patient in front of your instructor. The patient's anxiety and distress are real and not imagined. Your ability to validate their anxiety with empathy while encouraging them to do something difficult will make is easier for them to be courageous and willing to cooperate. It is much easier for the patient to do difficult things when they feel deeply understood and supported.

Using a gradual approach to beginning exposure with response prevention practice is very helpful. Patients can develop confidence in treatment and in their ability to manage their symptoms when they start with easier lower-level SUDS exposure tasks that allow for quicker and more readily accomplished success. It is best to ask patients which exposure task they would be willing to start as practice and to suggest that they begin with their lowest level SUDS rated exposure tasks.

Most patients will have a range of SUDS ratings for their exposure task list. Unfortunately, some patients will report that all possible exposure tasks are a 10 level of SUDS rating. This can be challenging because everything will feel very difficult for this patient. This often means that the patient's ability to tolerate distress in general is impaired. It can also mean that the patient has extreme self- critical thoughts about their inability to cope that compounds their distress each time they experience symptoms. Reminding the patient that their anxious reaction is completely understandable and nothing to feel ashamed of is helpful in this situation. Additionally, helping the patient break down the exposure tasks into smaller chunks can result in some lower SUDS items that are easier for the patient to imagine tackling. For example, if a patient who fears going anywhere without antacids and rates this task as a SUDS = 10, then ask them if they would be willing to travel with fewer antacids in their pocket. Once they can accomplish this, ask them to travel with a single dose, then a half dose tablet and then to go for a short period of time without carrying antacids. The patient might then be more willing to begin exposure tasks and work their way up to attempting to go all day without carrying antacid tablets.

When patients begin practicing their exposure tasks, they need to overcome the urge to avoid, seek reassurance, or to do rituals that reduce anxiety. Addressing these negative reinforcers is critical for success. There are ways to troubleshoot accidental attempts on the part of the patient to engage in negative reinforcement. Here are examples of typical ways that patients accidentally undermine exposure practice by avoiding the response prevention component of successful treatment.

Dilemma: The patient keeps asking for reassurance that their gut is healthy and that they do not have a serious disease.

Helpful response: "It looks like your anxiety is making you seek reassurance. This is an example of negative reinforcement that keeps your symptoms in place. I want to help you get better at managing your anxiety. Therefore, I am not going to say anything."

Dilemma: Everything the patient puts on their target list for practice is rated a SUDS of 10.

Helpful response: Break down the items into shorter, smaller, or easier doses of exposure. For example, if the patient cannot imagine spending half a day at work or a full hour in class, then ask if they can practice going to work and staying for a shorter period of time before leaving. Ask them to sit near the back of the class and stay for half of the class. Have the patient commit to a predetermined amount of time so their anxiety does not determine when they leave. Then gradually build up the amount of time the patient does the difficult task. This can be readily accomplished for avoidance of feared foods (take a small taste and then spit it out, taste and hold in mouth for 3 seconds, then taste and hold in mouth for 10 seconds, etc.), fear of activities that might cause symptoms such as exercise (do a few minutes of mild exercise, then a few more minutes, then gradually increase the intensity of exercise, etc.), or stopping prescribed medications and over-the-counter medications (cutting the pill in half, then cutting it in quarters, then spacing out dosages, then skipping several days of pills, etc.). It also helps to advance the level of difficulty slowly and gradually by asking the patient when they

feel ready to take the next challenge while reminding them that every exposure task will make them feel anxious. It helps to reinforce them for being courageous.

You could give the patient a graduated list of exposure tasks and ask them to do the lowest level every day for a week and then advance to the next step when they notice that it is less anxiety provoking to do the initial task. Some patients will be able to increase the level of difficulty every few days and some may take several weeks of practice on one task before being able to advance to the next level.

Dilemma: The patient tells you that exposure practice will not work because they have already tried this on his or her own.

Helpful response: "I know that you have tried really hard to get your life back. You would not be in my office if that were not the case. The problem is that you were accidentally leaving the scene too soon, or getting reassurance or using rituals to help you manage. This is an example of unintended negative reinforcement of your symptoms. This negated the effect of your attempts at exposure. I am sure that if we plan to practice in a gradual fashion, and help you avoid your negative reinforcers, then you will get better. You have nothing to lose by trying, since nothing else we have done has been helpful."

Dilemma: The patient fears that doing exposure will make their symptoms worse.

Helpful response: "That might be true in the short run because we are deliberately practicing situations that will make you anxious. However, if you practice long enough, you will habituate to these situations and your body will lose its ability to respond with GI symptoms and anxiety. The situations you avoid have become classically conditioned to your GI symptoms. That means that when you do things your body has associated with your symptoms; these situations acquire the power to trigger symptoms. Doing exposure with response prevention practice will help reverse this process."

The duration of each exposure practice must be sufficiently long to allow the patient to learn that they can manage their

anxiety and to learn that their anxiety or GI symptoms will not continuously worsen just because they are doing something they once avoided. A good rule of thumb is to practice exposure tasks until the SUDS decrease by half, or until the patient reports that it no longer disturbs them as much as it did at the start, or when they report that they can accept and tolerate the exposure. Discontinuing the exposure task while the patient has peak anxiety will result in fear conditioning, the opposite of the desired effect. This means that if you are practicing with a patient, or instructing the patient to do exposure practice, you must coach them to keep going until it gets easier despite the relative increase in SUDS. The rate at which various patients' SUDS ratings drop is highly individual and can vary in speed and intensity. *The most important skill patients must learn is that regardless of their discomfort level, they can tolerate and manage their GI symptoms and anxiety in any situation.* This necessitates real-life practice to become skilled and confident.

Dilemma: You have prescribed a low FODMAP diet for your patient to help decrease their gut symptoms and they are terrified to eat any foods that might be high in FODMAPS. Alternatively, your patient has gluten sensitivity and you have prescribed a gluten-free diet and your patient is terrified to eat foods containing gluten. This may not seem like a dilemma, but it is because the patient is worried and anxious about experiencing any GI sensations. People without anxiety who have the same problems do not worry about accidental or deliberate exposure to small amounts of foods that create gas or other symptoms. They are able to adapt and be flexible. For example, they may go to a friend's house for dinner and realize too late that the main dish could cause gut symptoms. Their solution would be to eat a normal or small amount of the main dish and willingly suffer the consequences without worry and without comment or explanation to the entire dinner party. Anxious patients on the other hand would worry ahead of time, go into lengthy explanations to the host and dinner party, and then avoid eating altogether for fear of cross contamination

of foods. Exposure with response prevention, therefore, is necessary to help the patient learn to deal with accidental real-life exposure to feared foods, and other situations in which it is more convenient to break a strict adherence to a prescribed diet. This guideline is specific to functional GI disorders and not intended for those patients whose physical wellbeing is dependent upon strict dietary adherence such as celiac patients.

Exposure to Worry

Sometimes the most frightening symptom for a patient is what they imagine in their mind when they are worrying, as opposed to the experience of the actual symptoms. For example, an irritable bowel syndrome patient with significant worry might have constant worry about when they will next experience pain, constipation, diarrhea, or cramping. They may repeatedly seek your reassurance about whether or not they will get constipated or have diarrhea. They may worry that their medications might fail and they will someday need an ileostomy. They may even self-administer enemas prior to going to work, because of severe worry about being constipated. Then when they take laxatives, they panic about having diarrhea and worry that they may get chronic diarrhea. This patient may spend lots of time asking you about how severe their constipation is compared to other patients and ask you to predict whether or not they might someday experience an impaction, chronic diarrhea, or need an ileostomy. This is despite having received patient education and despite your reassurance that IBS patients do not typically require ileostomies or colostomies. They might also worry about diarrhea and be afraid to take stool softeners or other medications even though they have severe complaints about constipation. Their greatest problem is the impact of worry on their behavior. They end up trying to solve the imagined frightful problems suggested by their worry instead of being able to enjoy their relative good health in the present.

Worry occurs when someone thinks or implies a "What if…." statement that is about the worst-case scenario. For example, "What if I lose control of my bowels while I am giving a presentation?" or "What if I never feel good again and become crippled by the pain?" are typical worries a patient might experience. Worry is a response to the perception of uncertainty in a person who is intolerant of uncertainty. They select a "better safe than sorry" strategy and reduce uncertainty by narrowing the field of all possible outcomes down to the worst-case scenario, so they can feel prepared for the worst. The patient falsely assumes that it is better to focus on the worst-case scenario than to assume that all is well until something truly unpleasant happens. People who worry have worry supporting beliefs that maintain their worry. They believe that their worry protects them against danger and is a way to be responsible, caring, or loving. You may have heard worriers express these beliefs when they say things like "It is a parent's job to worry," "Better to worry now than to get caught by surprise," or "Someone has to worry about my health!" Another belief common to all worriers is the belief that they could not cope with their symptoms or the worst-case scenario if it occurred in reality. They falsely believe that they must know and be well prepared ahead of time in order to cope. This causes problems because preparation for every event in our lives is impossible. Self-confidence is built on the knowledge that you can learn how to cope in the moment, rather than on trusting that you have expertise in every aspect of life.

Worry creates its own set of problems. Chronic physical arousal occurs because the brain is unable to detect the difference between real and imagined frightening situations. This results in sleep problems, sore muscles, headaches, GI symptoms, irritability, and restlessness. Worry also drives patients to seek reassurance. They do this by researching symptoms on the Internet, grilling their doctors about symptoms repeatedly, and then relentlessly talking to others about their symptoms, to do a comparison to figure out what the future might hold. Since worry is the negative reinforcer for intolerance of uncertainty, then exposure to worry is the treatment of choice. This may seem counterintuitive if you do not recognize that the trigger to worry is fear of intolerance.

Application of exposure to the treatment of worry also allows the patient to emotionally process the imagined feared situation and increase their awareness that they can indeed cope.

Worry exposure involves setting up a list of worry thoughts graduated by SUDS. This is similar to the way you construct an exposure practice list, with the target being anxiety-provoking thoughts instead of anxiety-inducing situations. In this instance, anything that triggers worry becomes the target of exposure. This can include saying words associated with anxiety, writing tragic stories about disabling symptoms, or reading or watching media that reminds the patient of the content of their worry. These worry exposure targets can be graduated in lower to higher SUDS rating to make it easier for patients to participate in worry exposure. Worry exposure may take longer for patients to acquire mastery. Worry exposure sessions usually need to last 20–30 minutes per topic at the start of worry exposure practice. SUDS can be identified and tracked for each worry thought just as for real-life situations. Here is a sample of a worry exposure practice list for a patient with irritable bowel syndrome (Table 6.3).

Table 6.3 Worry exposure practice list

SUDS 1 Saying the word constipation or diarrhea over and over
SUDS 3 Looking at photos of Depends diapers and saying, "What if I have to wear these?" over and over
SUDS 5 Hearing my doctor tell me that I might have a serious disease over and over without getting reassurance
SUDS 8 Writing a story about how I get severe untreatable diarrhea and have to wear diapers and then get an ileostomy
SUDS 10 Looking at photos of people with ileostomies and colostomies
SUDS 10 Watching a youtube.com video of someone changing their ileostomy bag
SUDS 10 Writing a story about getting feces all over myself in a board meeting
SUDS 10 Saying aloud, "I am going to end up with an ileostomy and be very sick and die an early death" while my doctor agrees that this will happen to me.

It may take some ingenuity to think of useful worry exposures. It is easier if you always imagine what the worst-case scenario might be for the patient given their concerns and symptoms and if you let their avoidance guide you. It is easiest to start with single words or phrases that provoke worry and then to work up to developing a worry story about a worst-case scenario. It also helps to be willing to be as extreme as the patient's worry and to include topics such as disability, terrible suffering, dying, and death.

Exposure to Uncertainty

Exposure practice to uncertainty is very helpful for patients with worry. Many patients with functional GI disorders fear uncertainty. They go to great efforts to be prepared by calling ahead to find the location of toilets, recovery spaces, or quick exits should they get symptoms. They may always carry lozenges, medications, or over-the-counter medications, in case they need them, spare clothing in case of an accident, and avoid going places without a person who they deem to be supportive and knowledgeable about their symptoms. They may avoid vacations to foreign or more rural destinations because they fear not having access to medical care or quick availability of support staff who might make them feel safe. They may avoid visits to large, unfamiliar venues. For example, a patient decides to go to a professional baseball game, and then searches on the Internet for a layout diagram of the location of public restrooms and buys his tickets based on proximity to the restrooms. Another example of intolerance of uncertainty is the patient who had a negative colonoscopy and then calls several times a month to vividly describe the changes in color, texture, and volume of her stool fearing that she has bowel cancer.

Many physicians misunderstand or experience intolerance of patient's uncertainty and the resultant worry and reassurance seeking. They believe the patient is being difficult, or controlling, or simply unwilling to trust them. But, in actuality,

Table 6.4 Uncertainty exposure practice list

SUDS 2 Leaving antacid tablets and TUMS at home when leaving the house
SUDS 3 Not checking your supply of antacid medications and TUMS and letting them run out before you purchase more
SUDS 6 Only buying one bottle each of TUMS and Prilosec
SUDS 7 Not going to the bathroom to empty your bowel before you leave for work
SUDS 8 Going to a new place without researching where the restrooms and parking are located
SUDS 9 Getting hair colored and cut at a salon and staying the entire time without going to the bathroom beforehand
SUDS 10 Flying on a plane to visit your family without getting a seat near the restroom
SUDS 10 Traveling to visit family without having backup bottles of TUMS and Prilosec

it is not the physician they are trying to control. It is their fear of uncertainty.

Setting up exposure practice to uncertainty is similar to the way you set up exposure practice to situations and worry. It involves identifying the situations that provoke a feeling of uncertainty and feeling unprepared. Uncertainty exposure pushes the patient to practice doing things and going places without being well prepared ahead of time (Table 6.4).

Length of Treatment

The duration of treatment will depend on how often the patient does exposure practice on his or her own outside of your office. The more often you can meet with the patient to encourage, support, and even practice with them, then the more rapidly they will progress through their list of exposure tasks. This process may take months or longer. You need to give your patient the message that they can recover using

exposure with response prevention and that you have faith in their ability to do the assigned home practice.

Avoiding Being the Negative Reinforcer

Hopefully, you now understand that ordering more tests in order to reassure the patient is an accidental form of negative reinforcement. Many physicians make this mistake because they correctly detect the patient's anxiety and they offer comfort. Unfortunately, this is only true for patients who do not get caught in worry. It is a mistake to believe that another negative finding will help the patient stop worrying and accept their diagnosis of a functional GI disorder. Because of their worry, they will misinterpret your orders for an additional lab or procedure to indicate either that you really are worried about their physical health or their worst-case scenario that they are the unlucky patient who had a false-negative test, missing the critical diagnosis of a terrible disease. This means that you will need to redirect your compassion to help by giving the patient the news that repeat testing is unnecessary and even unhelpful. You can then take the point of view of a surgeon. They have the secure knowledge that even though surgery necessitates pain, it leads to great good. The same is true for exposure with response prevention therapy.

You might be reading this chapter to better understand exposure therapy and its role in functional GI disorders, but do not plan to attempt this type of therapy on your own. In this case, you need to know how to locate and refer a patient to a mental health provider who is familiar with exposure-based therapies. There are several good sources for finding therapists skilled in exposure-based treatments. These therapists have training in cognitive behavioral therapy and typically work with anxiety disorders, obsessive-compulsive disorder, and behavioral medicine. There is a list of mental health providers who are specialists in the treatment described in this chapter located in the Appendix.

Summary

This chapter was written to explain new treatment tools that you might add to your toolkit of intervention for functional GI disorders. It was also written to excite and inspire you to reframe your expectations of patients whose anxiety about their disorder poses obstacles to recovery. These conditions are highly treatable when you approach them from the perspective of identifying and taming the anxiety that prevents acceptance of symptoms, adaptive coping, and worry-free living. Simply telling the patient that all is well and that they should no longer worry is inadequate to help these patients because their anxiety makes this impossible. Your willingness to understand and explain the nature and appropriate treatment of your patient's anxiety will be more likely to inspire your patients to attempt therapeutic exposure-based learning than any negative test result or heartfelt reassurance. Your willingness to adapt new interventions, such as exposure with response prevention therapy, will improve your effectiveness with this often-difficult patient population of functional GI disorders.

Appendix

Referral Sources for Mental Health Professionals Specializing in Anxiety

Anxiety and Depression Association of America – has national and international listing of mental health professionals at adaa.org

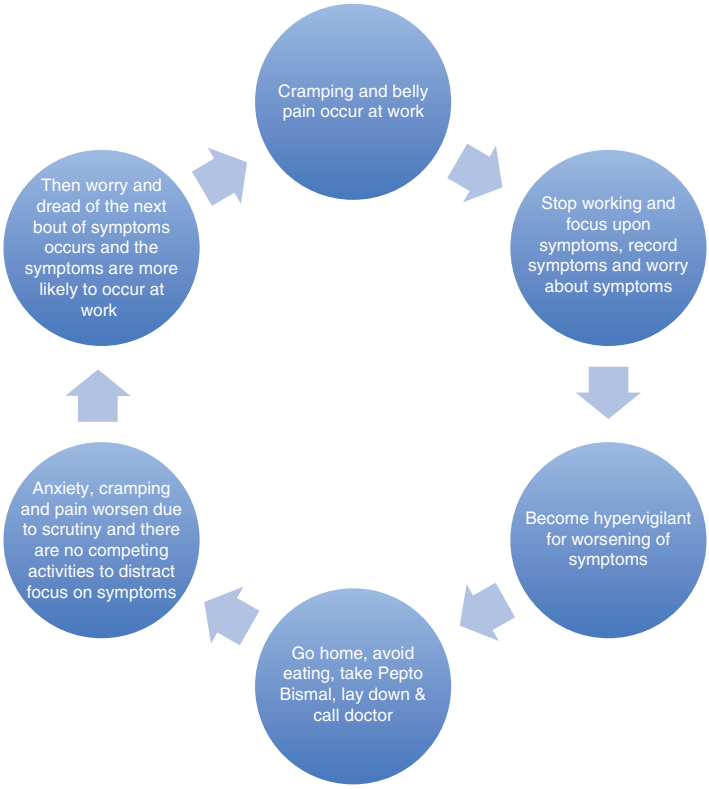
International Obsessive Compulsive Foundation – has national and international listing of mental health professionals, support groups, and regional patient advocacy groups at iocdf.org.

Association for Behavioral and Cognitive Therapies – has national and regional listing of specialists in cognitive behavioral therapies at abct.org

Society of Behavioral Medicine – has national and international listing of mental health and medical professionals who specialize in working with patients who have medical conditions that challenge their coping, functional conditions, or chronic pain at sbm.org

Patient Handout

Diagram of the Cycle of Anxiety and Negative Reinforcement



Patient Handout

Explanation of the Role of Anxiety, Negative Reinforcement, and Exposure Therapy for Functional GI Disorders

Even though you have been frustrated by lack of progress with your GI symptoms, there is good news! There is a lot that we can do to help you get your life back and to help you feel less worried about your symptoms. Scientific studies on the treatment of functional GI disorders suggest that your body has gotten stuck in a pattern of sending the wrong signals to your gut and your gut in turn sends wrong signals to your body. We know that when people react to their symptoms with alarm, worry, and avoidance of situations that might trigger their symptoms, they accidentally create a cycle of negative reinforcement of the very symptoms they want to avoid.

Negative reinforcement occurs when someone tries to rapidly escape an unpleasant sensation. Rapid escape feels good but reinforces all the symptoms that came before the moment of relief. It is like when someone picks up a baby who cries and then the baby accidentally learns to cry more often and more loudly in order to get picked up. The parents then continue to pick up the baby more and more until they carry the baby everywhere all the time.

The best treatment to get rid of this vicious cycle of worry about symptoms and accidental negative reinforcement is exposure therapy. Exposure therapy helps to reverse the process that your symptoms accidentally started. Exposure therapy can help you get your life back. The one trick is that you will have to focus on stopping negative reinforcement and practice doing the things that your symptoms have made you fear, regardless of whether or not you feel your symptoms. We also know that when you repeatedly practice exposure tasks your mind will learn to refocus on things besides your symptoms. This will lessen your anxiety about your discomfort and make it easier to tolerate and even lessen your discomfort and symptoms. We know that anxiety about pain

and symptoms makes the pain and symptoms worse. So, we need to identify some targets for exposure practice and some targets for or stopping the negative reinforcement cycle.

Patient Handout

Exposure Task List

Rate each item from 0 to 10 SUDS (Subjective Units of Distress Scale). O = total peace and calm, best day ever, and 10 = worst symptoms and anxiety ever.

SUDS Task Sample: 1 Not looking at my stool when I go to the bathroom Sample: 5 Not researching treatment for irritable bowel syndrome

Patient Handout

Worry Exposure Task List

Rate each item from 0 to 10 SUDS (Subjective Units of Distress Scale). O = total peace and calm, best day ever, and 10 = worst symptoms and anxiety ever.

SUDS Worry Sample: 3 Saying aloud, "What if I vomit?" Sample: 7 Writing a story about vomiting at work on my desk in front of everyone

Patient Handout

Uncertainty Exposure Task List

Make a list of things that you are afraid to do without feeling prepared or without making special preparations for fear that you will get symptoms. Rate each item from 0 to 10 SUDS (Subjective Units of Distress Scale). O = total peace and calm, best day ever, and 10 = worst symptoms and anxiety ever.

SUDS Task Sample: 2 Going to someone's home I do not know well Sample: 4 Going to a concert and standing near the back so I can be close to the restrooms Sample: 10 Going to work without taking extra clothes and leaving my antispasmodic medication at home

Patient Handout

List of Negative Reinforcers

Make a list of all of the situations or things you avoid, leave quickly, or the things you do to get rid of anxiety about your symptoms.

Negative reinforcers Sample: Calling my doctor every time I get symptoms Sample: Avoiding walking fast or exercising Sample: Avoiding foods that might give me symptoms

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Chapter 7
A Personalized Approach to the Patient Requiring Central Therapies

W. Harley Sobin

Does every patient with DGBI (disorders of gut-brain interaction) previously known as FGIDs (functional gastrointestinal disorders) require central therapies?

The answer is no. Most cases will respond to changes in diet, and "routine" GI drugs, or simply improve once the patient is assured there is no significant pathology. But many "complicated" patients will require those therapies that act more on the gut-brain connection.

Which patients are these? Patients who remain symptomatic in spite of aforementioned dietary interventions and peripherally acting GI drugs, who suffer significant impairment in their work and private lives. Many of these patients suffer considerable anxiety about their symptoms. Some have depression.

When I first meet with the patient and review the history and any antecedent tests and treatments, I am part detective:

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(a) Is there an organic diagnosis that might have been missed?
(b) Are there any dietary factors that might not have been addressed?
(c) Are the symptoms possibly adverse side effects of medications that have been used?

I am also interested in learning:

(d) Are there situational factors that might have been missed?
(e) Is there apparent associated anxiety, is there significant depression that is not being addressed?

If the patient is not responding to simple therapies and the answers to a, b, and c are negative, the patient may fit the "complicated" category. It is with these patients that I will address the use of the central therapies. Generally, I will propose the use of a central neuromodulator (CN). For some, I may propose referral to a psychologist. I think the involvement of mental health specialists is invaluable. As outlined in this text, CBT and exposure therapy, as well as other psychological therapies, can be enormous adjuncts in managing patients. One of the obstacles is the resistance of some patients to seeing mental health specialists, and the other is availability of people trained in these fields.

When I broach the idea of these central therapies, it is often necessary to address the patient's defense mechanisms. The patient may ask if "I think it's all in their head." No, I do not. I let them know about the gut-brain connection. I teach them about activated neural pathways that might lead to exaggeration of what are normally innocuous signals. I inform them that central therapies may help when peripheral therapies don't. I'll mention that CNs that happen to be antidepressants have also been used outside of GI to treat pain, migraines, symptoms of menopause, fibromyalgia, and neuropathy. If a patient appears to be more severely disturbed, I will try to enlist the aid of a psychiatrist.

Assuming the patient is willing to start using a CN, the next challenge is to have him stay on the drug and not aban-

don it prematurely. It's necessary to tell patients they should expect to get side effects immediately. They should also expect the drugs to take weeks, or a month or longer, before they are fully operational. Patience is absolutely necessary. A short-term follow-up with the patient is needed to go over concerns and discuss side effects that may arise. It is also essential to educate patients not to discontinue their meds abruptly. They need to inform us if they are planning on stopping their drugs, to avoid the discontinuation syndrome.

If after a month or two the patient is tolerating the drug but their clinical response is limited, we may increase the drug dosage. We may consider augmentation therapy using a second medication. Addition of a second CN can enhance the benefit of the first one in some cases.

There is undoubtedly more effort that goes into the therapeutic relationship with these "complicated" DGBI patients. It is necessary to allot more time for these visits to allow patients to convey their concerns. It is necessary to listen to what the patient is trying to communicate. There may be a number of defense mechanisms at work. One needs to address the patient's expectations, but then to confront the patient with how realistic those expectations may be. Patients may be expecting magic, but, unfortunately, we are not magicians. Setting realistic expectations of perhaps 25% or 50% improvement in symptoms will help avoid disappointment. Describe a process of collaboration, working together to find the treatment that will most benefit the patient. There may be trial and error. There may be tinkering. But convey your own willingness to persevere with the patient if he/she is willing to stick it out.

Some patients will resist, or abandon, attempts at central therapy. Others will be vigilant, and some of these may experience dramatic relief of their intractable symptoms. These results are what makes this difficult work fulfilling.

Is it necessary for a gastroenterologist prescribing psychiatric medications to go through a psychiatry residency? The answer is no. Psychiatrists are not specifically trained to use CNs to help manage symptoms of DGBI, and we

gastroenterologists are not using psychiatric medications to manage schizophrenia or major depression. We have our different interests, our different training, our different niches. It is also not necessary for a gastroenterologist to take a training program in psychology and psychologic counseling. Our training programs in gastroenterology should certainly focus on teaching trainees the art of listening to patients, but, we should not try to substitute for the practice of well-trained psychologists.

In managing our GI patients, we have a duty to rule out organic disease. But, common sense comes into play, and not every patient with abdominal pain warrants an EGD, colonoscopy, and CAT scan. Once we have ruled out organic disease to our satisfaction, it becomes an issue of managing symptoms. Some patients will likely respond to our initial suggestions and peripheral therapies, while others will likely be recalcitrant. Indeed, in our initial interaction with our patients, we can generally glean if the problem is more "gut than brain, or brain than gut" [1]. A useful tool can be the Multidimensional Clinical Profile (MDCP) for Functional Gastrointestinal Disorders [2] developed by the Rome Committee. This tool includes biopsychosocial aspects of the patient's life in evaluating a patient's illness. The first part of the MDCP is the "Categorical Diagnosis." The diagnosis is currently based on Rome IV criteria, i.e., Chronic Nausea and Vomiting Syndrome. Part 2 consists of "Clinical Modifiers," i.e., is pain continuous or episodic, frequent, or sporadic and is there coexisting nausea or bloating. Part 3 looks at the "Impact of the Illness On Daily Activities," none, mild, moderate, or severe. The fourth category, which is quite pertinent to the discussion, is "Psychosocial Modifiers," which includes DSM diagnoses, either past or present, major life stressors, and Rome IV psychosocial flags. These flags are meant to be an indicator of which patients most warrant a referral to a mental health professional. They include frequent anxiety, moderate or severe depression, suicidal ideation, abuse and trauma history that causes distress, intimate partner abuse, severe bodily pain in the past 4 weeks, distress over associated somatic symptoms, pain or impairment that frequently interfere with daily life, or using excessive alcohol, prescrip-

tion drugs for nonmedical reasons, or illegal drugs on a frequent basis.

The final category relates to "Physiological Modifiers of Function and Biomarkers," which can be diagnosed by manometry, radionuclide testing, etc.

It is sensible to get comfortable with using a few central neuromodulators. I have my own favorites that I tend to turn to. For functional nausea, I prefer mirtazapine. For the choice of a tricyclic antidepressant for pain or IBS-D, I prefer nortriptyline. In choosing an SNRI, I prefer duloxetine. Sometimes duloxetine is not covered and then I will prescribe venlafaxine. For functional dyspepsia-PDS type, I prefer buspirone. For an SSRI, I prefer escitalopram. If that's not covered, I prefer citalopram in a young patient without heart disease or sertraline otherwise. Although escitalopram does not carry the same FDA arrhythmia risk assigned to citalopram there may be some QT prolongation. Therefore, it should also be avoided in patients at risk of QT prolongation or who had a recent MI. For the choice of an augmenting agent for pain, I prefer low-dose quetiapine.

Because some of these patients may be challenging, it is possible they will be resistant to central neuromodulators. Some of them may benefit from consultation with a mental health professional, if not yet done. Others may benefit from referral to a tertiary care center that focuses on the care of patients with complex DGBI (FGIDs). I would encourage use of the Rome Foundation web site, or the International Foundation for Functional Gastrointestinal Disorders (IFFGD) web site for referral sources to enlist aide for more recalcitrant patients.

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