Treatment of Functional GI Disorders With Psychotropic Medicines: A Review of Evidence With a Practical Approach

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Abstract: Functional gastrointestinal disorders (FGIDs) are complex in their physiology and clinical presentation. With no known biologic marker, investigators and clinicians use the Rome criteria to make a positive diagnosis. Psychosocial factors, although not part of these criteria, do contribute to illness presentation, severity, healthcare-seeking behavior and response to treatment. In this regard, psychoactive drugs are valuable in the management of FGIDs, particularly for patients with severe symptoms. The appropriate selection of antidepressants based on predominant symptom, side-effect profile, and psychological condition is an integral part of a successful management program.

Keywords
functional gastrointestinal disorders, psychoactive drugs, antidepressants, visceral analgesic effects, central effects

Functional gastrointestinal disorders (FGIDs) are defined by a variable combination of either persistent or intermittent symptoms arising from abnormal function of the GI tract in the absence of a clearly identified structural etiology. Because there is no biological marker that characterizes these disorders, they are often difficult to diagnose. The development and validation of symptom-based criteria by the Rome committees[1] have provided diagnostic consistency for clinical research and helped to make positive diagnosis in clinical practice with the use of red flags to limit unneeded investigation.

Current understanding of these disorders is based on a biopsychosocial model where biologic and environmental factors interact to produce the clinical syndrome and the illness experience.[2] One of the key elements to understanding the pathophysiology of FGIDs relates to dysfunction of the brain-gut axis regulatory system. This altered regulation, which involves central and enteric nervous system communication of motor function, sensation, and immune-inflammatory function, is multidirectional. The effects of these interactions have an impact on symptoms, illness behavior, and treatment efficacy. Thus, the various mechanisms of altered motility, changes in mechanoelastic properties, visceral sensation, and mucosal inflam-

mation,[3] though they are not sufficient for a diagnosis as they are nonspecific, lead to unique effects on individuals. In addition, genetic predispositions and stress reactivity act through the central thread of the brain-gut axis.

Because of multiple pathophysiologic mechanisms, it is difficult to target treatment with any single agent and successful treatment of these disorders has lagged behind the investigative effort. The current treatments are primarily symptom-based and marginally effective for only certain subgroups (eg, for predominant diarrhea or constipation).

For all these reasons, antidepressants are theoretically beneficial because of their overarching effects on the brain-gut axis, both centrally and in the gut. They also have a history of empiric use in different chronic somatic pain syndromes such as migraine and fibromyalgia, and their use in the treatment of FGIDs has been increasing. Although the newer, peripherally acting drugs are more aptly targeted at one particular symptom (eg, diarrhea or constipation), psychotropic agents have an advantage of being effective for most functional GI disorders because of their effect on nociception as well as associated central nervous system symptoms like anxiety and depression.

This article discusses the rationale, mechanisms, efficacy, and side effects of psychotropic agents and provides guidelines for their use in patients with FGIDs.

Rationale

Antidepressants, particularly tricyclic antidepressants (TCAs), used by experienced clinicians for many chronic painful conditions are increasingly used for treatment of the FGIDs. There are multiple reasons behind this approach. First, when used at full dosage, TCAs can treat major psychiatric disorders, and can therefore treat coexisting psychiatric disorders in patients with FGIDs. Second, they can treat stress-related exacerbations of GI symptoms, which are associated with hypervigilance and secondary anxiety, through their anxiolytic effect. Third, they possess central antinociceptive properties and facilitate central pain tolerance. Fourth, there is some evidence for peripheral analgesic effects associated with TCAs at the level of visceral mechanoreceptors and afferent nerve fibers. Finally, depending on the class of agent, TCAs can affect GI motility and secretion based on their serotonergic, noradrenergic, or anticholinergic effects. This is helpful in patients who have a predominant bowel habit (eg, diarrhea or constipation) in addition to pain symptoms.

Role of Psychosocial Factors

Psychosocial factors contribute to the predisposition to FGIDs, the precipitation of an acute flare of symptoms, and the perpetuation of the symptoms and illness experience and behaviors. Thus, they have direct effects on symptom severity, healthcare utilization, daily function, disability, and response to treatment.

Patients with severe symptoms and who present to tertiary medical centers have a more significant contribution from psychosocial factors.[4,5] These factors include comorbid psychiatric disorders such as depression and anxiety, which occur in 50–90% of patients seeking medical care and about 18% of patients seen in community medical settings.[6,7] Other common stressors that either precipitate or contribute to symptoms range from daily stress and frustrations, to major life events, to sexual abuse.[8] In fact, severity of functional GI disorders is more highly correlated with psychological factors than physiological factors[5,9] and this also extends to poor physical functioning, poor quality of life, and greater healthcare utilization.[5]

Furthermore, patients without a specific psychiatric diagnosis may still react to GI distress with mood-related symptoms such as anxiety. This may relate to fear of serious disease and the development of maladaptive coping thought processes such as "catastrophizing." During stress, GI symptoms can worsen with enhanced gut reactivity (both sensory perception and motility) leading to further stress, resulting in a vicious cycle.[10-12] Continued symptoms coupled with negative work-up, lack of understanding by patients, and incomplete or ambivalent explanations from physicians can lead to constant worry, fear, and anxiety, thus perpetuating symptoms and influencing healthcare-seeking behavior adversely.[13]

The development of postinfectious irritable bowel syndrome (IBS) after a bout of gastroenteritis is related to mild inflammation and altered mucosal immune function, in association with significant life stressors at the time of infection. It is unclear whether this stress acts as a conditioning factor or it is a stress-mediated effect on inflammation.[14]

Mechanisms of Action of Psychotropic Medications

In addition to the known effects of antidepressants on psychiatric conditions, their multiple other visceral and nervous-system effects contribute to the clinical improvement seen in patients with FGIDs. These effects include central pain modulation, peripheral nociception, and GI secretomotor effects. Central pain modulation includes reduction of activation of emotional pain response centers in the brain, including the anterior cingulate cortex (ACC), augmentation of inhibition of spinal transmission of pain by descending spinal pathways, and central nociceptive actions from α-adrenergic blockade, sodium channel blockade, and an N-methyl-D-aspartate (NMDA)

antagonist–like action. Whereas peripheral nociception entails reduced firing of visceral receptors and afferents, both anticholinergic and direct effects on visceral smooth muscle and glands contribute to secretomotor effects.

Most of the antidepressants belong to three broad classes, the above-mentioned TCAs, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Comparison of the three classes is given in Table 1 and their effects are discussed in detail in subsequent sections.

General Approach to Prescribing Psychotropic Medications

Antidepressants, particularly TCAs, are considered first-line therapy for patients with severe and refractory FGIDs because of their pain-reducing effect. The analgesic effects of TCAs usually occur much earlier, are seen with lower dosages, and appear to be independent of their effects on depression, as this benefit can be seen even in non-depressed patients. The SSRIs are preferred in treating associated psychiatric conditions, including anxiety. This may be helpful to patients with FGIDs, despite the lack of demonstrable visceral analgesic effect. SSRIs are used at the same dosages for treating major psychiatric disorders and they have benefit for patients with anxiety, panic, and obsessional disorders, in which they also improve global well-being and quality-of-life scores. SNRIs, a relatively new class of drugs, have the visceral analgesic properties of TCAs without the accompanying anticholinergic side effects.

Choosing a particular drug for a particular patient depends on several factors: (1) the specific symptom that is being treated (eg, pain, diarrhea, or a combination), (2) the side-effect profile, (3) the cost of the drug, (4) the patient's previous experiences and preferences with antidepressants, and (5) the presence of co-existing psychiatric conditions.

The specific choice of treatment is based on the patient's symptom severity and degree of disability. Symptomatic treatment with nonantidepressant drugs may first be prescribed for mild, intermittent symptoms, whereas antidepressants are more frequently used for more severe symptoms and therapeutic benefit may not be achieved for 4–6 weeks. An initial lack of response may indicate either a suboptimal dose, patient nonadherence, or a delayed response, and should not lead to premature discontinuation of this class of drugs. Treatment response should be measured not only in terms of symptoms but also, more importantly, in terms of daily function, quality of life, and emotional well being.

The duration of therapy often depends on the particular reasons for use as well as the therapeutic response.

Table 1. Class Effects of Psychoactive Drugs

Effects	TCAs	SSRIs	SNRIs
Peripheral pain modulation	++	?	++
Central pain modulation	+++	? +	+++
Motility	++	+	?
Global well being	+++	+++	+++
Pain	+++	?	+++ (no studies yet on visceral pain)
Psychiatric comorbidities	++ (+++ full doses)	+++	+++

SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitor; TCAs = tricyclic antidepressant.

Generally, antidepressants are continued until a therapeutic response is seen and maintained at the lowest effective dose for at least 6–12 months. At that time, the patient and physician can agree mutually on dose modification or stopping the drug. Long-term therapy may be warranted in some patients.

Although most side effects diminish within 2 weeks, follow-up consultations within the first week and again 2–3 weeks later help to address persistent side effects and improve patient adherence. If side effects do emerge during the course of treatment, dose adjustments or switches to a different drug in the same or different class can be made with mutual patient-doctor consent.

General issues that need to be addressed with patients before starting treatment with antidepressants are listed in Table 2. An important issue is the impact on the patient of their GI symptoms. Often, the recurrent nature and unpredictability of their symptoms create a sense of apprehension and helplessness, which can lead to feelings of frustration. This may be compounded by the physician not explaining the basis of their illness from a biopsychosocial rather than a traditional biomedical perspective. This may lead patients to continue to seek additional evaluations and treatments hoping for an organic diagnosis or a cure, all of which perpetuates the sense of hopelessness and despair.[13]

The physician needs to elicit and address the patient's concerns regarding the use of antidepressants before prescribing them. Societal stigma associated with the use of antidepressants for psychiatric conditions and negative feedback from family and friends might negatively influ-

Table 2. General FGID Treatment Guidelines

Therapeutic Principles
• Foster empathy and trust • Provide validation and reassurance • Make a confident diagnosis • Pay attention to the patient's specific concerns such as fear of cancer • Educate and explain consistently with patient belief system, using biopsychosocial model • Identify psychosocial factors and make a mental health referral when needed • Address unrealistic expectations of cure, emphasize coping versus cure • Set treatment goals and negotiate the treatment plan • Base treatment on symptom severity and the degree of disability • Individualize drug therapy • Maintain regular follow-up • Help the patient take responsibility • Address false beliefs and concerns regarding antidepressants • Monitor and manage side effects
Antidepressant Treatment Plan
• Choice of drug depends on the type of symptoms, side effect profile, cost, and previous experience, as well as associated psychiatric conditions • Start with a low dose and gradually increase to lowest, most effective dose • Keep patients on medication to achieve beneficial effects, which may take up to 4–6 weeks • Recognize that most side effects diminish within 1 to 2 weeks. If persistent, best to continue same or lower dose before switching to another medication, preferably in the same class • Follow up within 1st week and then 2–3 weeks later to help maintain adherence o Gauge treatment response by improvement in daily function, quality of life, and emotional state o Choose a combination of drugs based on predominant symptom and side-effect profile

Modified from Longstreth and Drossman[13] and Chang and Drossman[17]

ence the patient's decision to take them or lead to poor treatment adherence. They may be told that the problem is "all in their head." An explanation of the independent effects of antidepressants on pain and bowel symptoms is a critical component of the treatment plan.

Physicians should address patient expectations for treatment and keep in mind that patients may hold unrealistic expectations for cure. This is addressed by negotiating a treatment plan and seeking reasonable, attainable goals for improvement. Involving patients in treatment decisions empowers them, provides a sense of control over symptoms, and leads to a better physician-patient relationship.

Lastly, the physician needs to address possible side effects prior to administration of the drug. Side effects may be more prominent during the initial two weeks of treatment but tend to improve over time. Patients with FGIDs often report symptoms later attributed to side effects even before starting desipramine, a TCA.[15] These non–drug-related symptoms do not worsen during the course of therapy, may improve, and are predicted by a general tendency to report somatic symptoms.[16] Close monitoring and active management of side effects in order to achieve optimal therapeutic dose, is similar to the therapeutic approach in the administration of interferon and ribavirin for hepatitis C infection.

Tricyclic Antidepressants

Efficacy

TCAs are used for many chronic pain conditions including the FGIDs and are most often used in patients with severe symptoms who fail conventional therapy. They are also used when patients have disruption of daily function and associated psychiatric comorbidities. Both uncontrolled and controlled studies have shown efficacy with TCA therapy. One large uncontrolled series showed symptomatic improvement and complete remission in 89% and 61% of IBS patients, respectively, using antidepressants of both TCA and SSRI classes.[18] A small but well-designed double blind crossover study comparing desipramine, atropine to control for anti-cholinergic properties of desipramine and placebo established the efficacy of desipramine in diarrhea-predominant IBS patients, independent of anticholinergic properties.[19]

One meta-analysis shows that TCAs are effective in a variety of FGIDs and the summary odds ratio for improvement was 4.2.[20] In another analysis, the number needed to treat (NNT) was 3 in comparison to other therapies such as antispasmodic drugs (NNT, 4.1).[21] However, a number of methodologic considerations limit interpretation of these trials and restrict their generalization.

Data from a recent large, high-quality, double-blind randomized, multicenter, controlled trial by Drossman and associates[22] showed the benefit of desipramine (73%) versus placebo (49%) for moderate to severe FGIDs. Although intention-to-treat analysis did not reach statistical significance as the number of dropouts was relatively high at 28%, per-protocol analysis was statistically significant, and this effect was more robust if patients with nondetectable levels of desipramine were excluded. These results underscore the importance of careful monitoring of dosage and side effects by physicians, along with ongoing patient support to improve compliance.

Despite methodologic difficulties due to different outcome measures and lack of uniform improvement[22-27] in many trials of antidepressants for FGIDs, the overall

trend is towards improvement in global improvement rather than actual symptom relief. This is consistent with patients' clinical reports that: "the pain is still there but I'm dealing with it better." Thus, the drug appears to work primarily on central emotional centers rather than on central nociception. However, further studies are needed.

Interestingly, improvement appears to be independent of changes in anxiety or depression scores. In the Drossman study, subgroup analysis showed that improvement was better in patients with moderate rather than severe symptoms and with no depression. Because the effect of these antidepressants on the key pathophysiology of visceral hypersensitivity is less convincing and the effect is independent of psychiatric comorbidity improvement, it is possible that these benefits may primarily come from the effect of TCAs on the affective components of bowel symptom perception. Individual symptom improvement may have been from the drugs' effects on transit, motility, and the cholinergic nervous system.

Mechanism of Action

Although the somatic analgesic effects of TCAs have been extensively studied, their visceral analgesic properties are less clear. The main mode of action lies in the inhibition of reuptake of both norepinephrine and serotonin at the presynaptic level. Anticholinergic and antihistaminic properties account for the major side effects. Their peripheral analgesic effects are due to reduction in the firing of primary afferent sensory nerves to the spinal cord from the somatic structures or viscera. TCAs consistently reduce pain sensitivity on chronic neuropathic animal pain models and they are more potent than purely serotonergic SSRIs.[28] Attenuation of responses of pelvic nerve afferent fibers innervating rat's colon to noxious colorectal distension by TCAs attests to their visceral peripheral analgesic actions.[29]

Action on peripheral serotonin (5HT) receptors may also play a role in the nociceptive effect of TCAs, as they have moderate affinity for $5HT_3$ and act on second messengers of $5HT_4$ receptors.[30] Activation of the ion channel–coupled $5HT_3$ receptors on primary afferents produces brief pain and $5HT_2$ receptors enhance the effects of other inflammatory mediators such as prostaglandin E2 and bradykinin.[31]

The analgesic properties of TCAs are likely also contributed to by alpha-adrenergic blockade, sodium channel blockade, and an NMDA antagonist–like action.[28,32] Selective reduction of pain threshold without a concomitant change in sensation threshold, lack of antinociceptive effect of antidepressants produced by lesions in the descending pathways, and potentiation of morphine analgesia by antidepressants as demonstrated in some animal studies suggest that modulation of descending serotonergic, noradrenergic, and opioid pathways from brain stem by antidepressants as a potential mechanism of their central pain modulation.[28,33-36]

Because studies of effects of TCAs on visceral perception in human volunteers have been mixed, studies on the FGIDs are less compelling. Although one study showed increased pain thresholds associated with imipramine therapy without a concomitant change in esophageal tone or visceral sensation, another study did not find any effects on visceral sensory perception and compliance with amitriptyline, albeit reduction in both innocuous and noxious somatic pain stimulation was found in healthy volunteers.[33,37] Two studies reported significant improvement in visceral symptoms in patients with FGIDs without a change in sensory perception or motility, one with functional dyspepsia and the other with noncardiac chest pain[38,39] but an unblinded study reported improvement in both rectal hypersensitivity and GI symptoms with 25 mg of amitriptyline in IBS patients.[40] Whether this relates to the underlying need for visceral hypersensitivity, as in patients with FGIDs, in order for TCAs to show an effect, is unclear.

Lack of substantive human data on peripheral visceral analgesic properties of TCAs suggest a more prominent role for their central effect on pain perception. Ascending visceral sensation, including pain, is processed at the level of the cortex, which prominently includes the insular cortex (the "sensory cortex" of the visceral system) and other areas involved in the emotional experience of pain: the ACC and midcingulate cortex, thalamus, and hypothalamus, which in part comprise the limbic system. The rostral or perigenual portion of the ACC is involved in the affective component of pain, whereas the more caudal (posterior-dorsal) region of the cingulate cortex, otherwise known as the cognitive division of the ACC, is involved in cognition.[38,41,42] The ACC has direct neural connections with the limbic system, brain areas involved in pain modulation, arousal, and autonomic activity.[41]

Functional MRI imaging and regional blood flow analysis by PET scan have demonstrated alteration in the regional brain activation of these areas, especially the anterior ACC, in response to colorectal distension in IBS patients compared to healthy volunteers.[42,43] Psychological factors also influence this activation, as demonstrated in a case report.[8] Activation of the anterior ACC is attenuated by amitriptyline during stress in response to colorectal distension, indicating a central pain-modulating role for TCAs[44] and these effects are thought to be from alteration of neurotransmitter levels in the relevant parts of the brain.[38,44]

The anticholinergic actions of TCAs prolong intestinal transit and reduce intestinal secretion resulting in constipation. TCAs slow both small bowel and colonic transit and also slow the progression of MMC in the small intestine as measured by manometric and transit studies.[45,46]

In conclusion, TCAs act at various levels of the gut and brain. They reduce visceral hypersensitivity by reducing the firing of ascending sensory neurons from the periphery or, alternatively, by abolishing the enhancement of effects of other anti-inflammatory mediators through 5HT receptors. This may only happen in patients with underlying heightened visceral sensitivity as suggested by studies showing lack of analgesic effect on healthy subjects.[37] They may facilitate or enhance the effects of central, opioid, or serotonergic- or noradrenergic-mediated descending inhibitory pain-modulating pathways on ascending spinal sensory pathways that carry visceral pain. By acting on the affective component of the pain-processing center of brain, the ACC, and the insular cortex, they reduce the visceral pain experience and possibly also the perception of pain. Because of their effects on motility and secretion, they may improve bowel symptoms when properly selected. Finally, their mood effects contribute to the improvement in overall general well being, quality of life, and improvement of psychiatric comorbidities, particularly if high enough doses are used.

Dosage and Side Effects

To minimize side effects, treatment with TCAs should start with low doses (10–25 mg) and gradually be titrated to the lowest most effective and tolerated dose. Often medication is given at bedtime to minimize, or take advantage of, the sedation that occurs. This is particularly helpful in patients with FGIDs, who have fragmented sleep; poor quality of sleep has been associated with increased symptoms the following morning.[47,48] As TCAs have varying dose-ranging effects, gradual escalation of dose is the way to identify the optimal effective dose while minimizing adverse effects.

Better efficacy for diarrhea due to their anti-cholinergic effects make TCAs ideal for diarrhea-predominant IBS patients.[22] In contrast to tertiary amine TCAs such as amitriptyline and imipramine, secondary amine TCAs (desipramine and nortriptyline) are associated with less sedation and constipation, presumably because of their lower antihistaminic and anticholinergic properties. Secondary amine TCAs could be used in patients with concerns of sleepiness or who do not typically experience sleep disturbances. Desipramine could be used in patients with constipation for abdominal pain while simultaneously treating constipation with other agents.

Selective Serotonin Reuptake Inhibitors

Efficacy

SSRIs have not been as well studied as TCAs for use in FGIDs. The existing evidence suggests that their effects are mainly on overall well-being and some aspects of quality of life, in addition to their anti-anxiety effects. In some studies, this response was still seen even after controlling for effects on mood. Although some animal studies have shown visceral analgesic effects from SSRIs, human data thus far show either no effect or marginal improvement of individual symptoms of IBS.

A recent double-blind, placebo-controlled trial by Tabas and associates concluded that paroxetine (Paxil, GlaxoSmithKline) improved overall well-being and improved quality-of-life scores in the emotional well-being domain only, in IBS patients, without a significant change in abdominal pain and bloating. The therapeutic gain persisted even after controlling for depression.[25] However, the study was limited because of small sample size and selection bias. Smaller studies showed improvement in global well-being, individual symptoms, or both with different SSRIs.[49-51] A relatively large UK study comparing individual psychotherapy, paroxetine, and usual care failed to show any difference in primary outcome of abdominal pain severity, despite a decrease in the number of days with pain in the paroxetine group and improvement in the physical component of quality of life in both groups.[23] This study evaluated only patients with severe IBS and almost half of them reported a psychiatric disorder.

Although there is not enough evidence in the literature to support efficacy for SSRIs in the treatment of FGIDs, they have been shown to improve overall well-being of these patients and may be useful in a subset of patients with FGIDs.

Mechanism of Action

SSRIs act by selectively inhibiting reuptake of serotonin and by blocking the serotonin transporter protein at the level of presynaptic nerve endings, thus increasing the synaptic exposure to a higher concentration of serotonin.

SSRIs may have effects on pain sensitivity in animal somatic pain models, though it is weaker than with TCAs.[28] Enhancement of opioid descending spinal pathways may also play a role in their analgesic effect as they are devoid of noradrenergic properties.[35,36] Although individual SSRIs may have differential effects, overall, the data on visceral perception thresholds in healthy volunteers is equivocal and there is a paucity of studies for the FGIDs. Although both paroxetine and sertraline (Zoloft, Pfizer) failed to show any difference in gastric perception thresholds,[52,53] citalopram (Celexa, Forest) did decrease esophageal sensitivity. It did not, however, change colonic sensitivity in normal, healthy volunteers.[54,55] One small study showed efficacy of fluoxetine on visceral pain only in a subgroup of IBS patients with rectal hypersensitivity, suggesting a possible peripheral action by this class of drugs.[24]

Effects on intestinal compliance in healthy volunteers showed no difference in gastric compliance with sertraline, a small change on postprandial gastric compli-

ance with paroxetine, and increased colonic compliance with citalopram.[52-55]

Central nociceptive effects of SSRIs have not been studied and some SSRIs seem to possess motility effects as shown by paroxetine, which shortens orocecal transit time by accelerating the progression of phase III contractions of MMC as well as increasing the frequency of MMC in the small intestine.[37,46,56]

Dosage and Side Effects

Treatment with SSRIs is usually started with lowest conventional doses for psychiatric conditions (eg, 20 mg/daily of fluoxetine). They can be started at a once-daily dose, either in the morning or in the evening, depending on their induction of drowsiness. The dose is increased only occasionally as most of their therapeutic effects are usually seen with the starting dose. Lower doses may be needed for elderly patients, patients with liver disease or renal disease, or patients on concomitant TCA therapy.

The common side effects for the SSRIs are nausea, vomiting, insomnia, diarrhea, diaphoresis, dizziness, sexual dysfunction, anxiety, and agitation. Paroxetine has strong anticholinergic properties and can be used in patients with diarrhea. Sertaline, citalopram and its isomer escitalopram (Lexapro, Forest) are reported to have drug interactions. Because of their effects on the Cytochrome P450 system, particularly for paroxetine, careful attention needs to be paid when prescribing combinations of TCAs and SSRIs and the dose of SSRIs needs to be reduced appropriately. Paroxetine, which has a short half-life, is associated with withdrawal syndrome when discontinued abruptly. Fluoxetine has the longest half-life of all drugs in this class and is usually not associated with withdrawal syndrome.

Serotonin Norepinephrine Reuptake Inhibitors

Efficacy

No randomized trials have evaluated the efficacy of SNRIs in patients with FGIDs. However, these drugs could potentially provide efficacy similar to TCAs, due to their dual blockade of reuptake of both norepinephrine and serotonin, without the side effects commonly associated with TCAs. Venlafaxine (Effexor, Wyeth) and duloxetine (Cymbalta, Eli Lilly) are the two SNRIs currently available.

Exploratory analysis from the three pivotal safety and efficacy trials of duloxetine in the treatment of depression showed it improved somatic painful symptoms (abdominal pain was not evaluated) in patients who were not preselected on the basis of significant baseline levels of pain.[57,58] Part of this effect was attributable to a direct effect of duloxetine when compared to associated improvement in the depression score.[57] However, duloxetine also improved pain symptoms in depressed patients with baseline pain scores of at least moderate intensity, even without a significant change in depression scores.[59] Duloxetine has also been shown effective in the treatment of fibromyalgia and it is approved for treatment of diabetic peripheral neuropathy.[60,61]

Mechanism of Action

Venlafaxine, at low doses, blocks mainly serotonin. At higher doses it bocks reuptake of both serotonin and noradrenaline. It is also a mild inhibitor of dopamine reuptake. Duloxetine blocks reuptake of serotonin and norepinephrine at all doses and lacks affinity for muscarinic, histamine-1, alpha-1 adrenergic and dopaminergic receptors, thus avoiding the unwanted side effects of these actions associated with TCAs.

Both SNRIs attenuate somatic pain response in animal models of persistent pain and neuropathic pain whereas their effect is minimal in acute nociceptive pain.[62,63] Duloxetine appears more potent with regard to pain reduction than venlafaxine and amitriptyline. In healthy volunteers, venlafaxine increased somatic pain tolerance thresholds after electrical stimulation[32] as well as increasing postprandial gastric compliance without affecting symptoms, gastric emptying, or small bowel and colonic transit at a dose of 75 mg/daily.[64] Though this dose has mostly serotonergic effects, target-organ sensitivity may also differ at this low dose.

Venlafaxine also reduced colonic tone during fasting as well as postprandially while improving colonic compliance without a statistically significant change in the sensation thresholds in healthy subjects.[65] Although the precise neurotransmitters involved are unclear, there is some evidence to suggest both neurotransmitters are involved and that noradrenergic effects are mostly mediated through alpha-2 receptor activity.[65] The effects of venlafaxine and duloxetine on visceral sensory perception in FGID patients have not yet been studied.

Dosage and Side Effects

The treatment approach with SNRIs is similar to that of SSRIs. Venlafaxine can be started at 37.5 mg or 75 mg daily and gradually titrated up to the maximum tolerated effective dose. The most common side effects are nausea, dizziness, nervousness, insomnia, and constipation. Venlafaxine has also been associated with mild increases in blood pressure.

Duloxetine can be started at 30 mg daily and increased to 60 mg over the course of several days. In patients with early side effects, a 20 mg starting dose may be better tolerated. The most common side effects are nausea, dry mouth, and constipation. Other side effects include

diarrhea, vomiting, insomnia, dizziness, somnolence, and sweating. Sexual side effects occur but are thought to be less common than with SSRIs. Approximately 1% of patients who participated in the depression and diabetic neuropathy trials had abnormal elevation of transaminases and none of them were fatal.[66]

Miscellaneous Psychotropic Agents

Mirtazapine

Mirtazapine is a tetracyclic, dual serotonergic and noradrenergic drug, which acts independently of reuptake transporter mechanisms at the level of the central nervous system by its presynaptic alpha-2 adrenergic antagonistic effects. It is also a potent antagonist of $5HT_2$ and $5HT_3$ serotonin receptors and H1 histamine receptors and a moderate peripheral alpha1-adrenergic and anticholinergic muscarinic antagonist. In theory, it can be useful because of its dual action on these neurotransmitters and it has been shown to be effective for FGIDs in a case report.[67] Because of its anticholinergic and antihistaminic effects, it can be used in patients with poor sleep, inability to gain weight, and diarrhea. It may be particularly beneficial for treatment of nausea because of its $5HT_3$ blocking properties.[68,69]

Buspirone

Buspirone is an anxiolytic agent that is often used alone for anxiety or as adjuvent therapy with SSRIs for treatment of anxiety and depression. It is nonhabit-forming and acts via nonbenzodiazepine GABA receptors. The actual mechanism of action for buspirone is not known but it has strong affinity for $5HT_1$ and $5HT_2$ receptors and moderate affinity for dopamine D_2 receptors. Buspirone can be used in patients with functional dyspepsia or in patients needing augmentative therapy with SSRIs.

Because of its $5HT_1$-receptor agonist properties, buspirone relaxes the gastric fundus and improves gastric compliance; it can theoretically improve symptoms of functional dyspepsia.[70] Despite differences in both dosing and the method of gastric volume measurement, two studies showed buspirone to improve both symptoms and gastric accommodation to a meal in patients with functional dyspepsia[71] and improved symptom scores in healthy volunteers without a change in postprandial gastric compliance.[64] The effects of buspirone on colonic tone have been inconsistent, with one study showing reduced tone and another showing no effect.[65,72] Additionally, it has been shown to inhibit CRF and stress-induced cecal motor response in rats by acting on $5HT_1$ receptors.[73]

Combination Therapy With Multiple Psychoactive Drugs

The combination of different classes of drugs is often used for augmentation of incomplete therapeutic response in the treatment of depression. This approach is helpful for patients with severe complaints or side effects to multiple drugs. The combination should be based on several factors: the presence of comorbid psychiatric conditions, the most severe symptom for which treatment is sought, anticipated or actual experience of a particular side effect, and a particular drug's target organ of action.

Because SSRIs address primarily the psychiatric comorbidities over the abdominal pain, there may be benefit for the combination of an SSRI with a low dose desipramine or duloxetine, especially if abdominal pain is the predominant symptom. In patients with diarrhea predominance, a small dose of a TCA may balance the diarrhea producing side effect of SSRIs. Similarly, buspirone could be added to augment SSRIs when treating anxiety. Buspirone with a SSRI may also be used in patients with nonulcer dyspepsia or chronic nausea because of its effects on gastric compliance. Obsessive-compulsive features and hypochondriacal tendencies suggest the need for an SSRI. Delusional thinking or agitation may require addition of an atypical antipsychotic along with psychiatric consultation. In select patients, while waiting for the therapeutic response, it is prudent to aggressively treat side effects. For example, patients with constipation-predominant IBS are better treated simultaneously with a TCA for the pain component and either a regimen of laxatives or tegaserod (Zelnorm, Novartis) for constipation.

This approach of using a combination of medications often requires sound knowledge of the therapeutic class of drugs and clinical wisdom. It is preferred for patients who have multiple or more severe symptoms along with psychiatric comorbidities and also to help reduce healthcare seeking behavior. Combination therapy also helps to minimize the side effects of different drugs as it allows for lower doses to attain the therapeutic response.

Combined Psychotherapy and Pharmacologic Therapy

The combination of antidepressants and psychological therapy can be synergistic. Refractory patients often need multimodalities of treatment. Such an approach has been shown to be very effective in the treatment of depression, tension headache, and fibromyalgia.[74-78] Psychological therapies such as hypnotherapy have durability of response

Table 3. Antidepressant Receptor Effects

Drug Class		Daily Dose	NE	5HT	Histamine	ACh	Patient Indications, Efficacy Profile
TCA	Amitriptyline	10–150 mg	+++	+++	++++	++++	Highly sedative
	Doxepin	10–150 mg	++	+++	++++	++	Highly sedative
	Desipramine	10–150 mg	+++	++	+	+	Most empiric evidence for efficacy, less sedation and constipation
	Nortriptyline	10–150 mg	+++	+	++	++	Least sedative
SSRI	Citalopram	10–40 mg	nil	++++	nil	nil	Fewer side effects and drug interactions
	Escitalopram	10–20 mg	nil	++++	nil	nil	Fewer side effects and drug interactions
	Fluoxetine	20–60 mg	nil	++++	nil	nil	Long half-life, less withdrawal effects
	Paroxetine	20–40 mg	nil	++++	nil	nil	Short half-life, more likely withdrawal effects, Greater anticholinergic effects, use in diarrhea-predominant patients
	Sertraline	25–150 mg	nil	++++	nil	nil	Less drug interactions, requires dose ranging
SNRI	Venlafaxine	37.5–225 mg	++	++	nil	nil	Similar to SSRIs
	Duloxetine	20–60 mg	+++	+++	nil	nil	No anticholinergic effects, use in pain-predominant patients
Other	Mirtazapine	15–45 mg	++	+++	++	+	Has $5HT_3$ antagonist properties and can be used for nausea, and patients with poor sleep, weight loss, and diarrhea
	Buspirone	15–30 mg	–	+	–	–	$5HT_1$ agonist, antianxiety effects, can augment treatment with TCAs and SSRIs, useful in functional dyspepsia

ACh=acetylcholine; 5HT=serotonin; NE=norepinephrine; SNRI=serotonin-norepinephrine reuptake inhbitor; SSRI=selective serotonin reuptake inbhitor; TCA=tricyclic antidepressent.

Modified from Chang and Drossman.[17]

and may even correct visceral hypersensitivity.[79] This combined approach may be appropriate for patients with severe symptoms or comorbid psychological conditions.

Summary

Antidepressants are commonly used for chronic non-malignant pain conditions including the FGIDs. Both older and the newer antidepressants can be used but with different expectations and effects based on the class of agent used: TCAs, SSRIs, SNRIs, and miscellaneous psychotropic agents. The main mode of action is thought to be central pain modulation although some of these drugs do have peripheral actions such as peripheral pain modulation and effects on sensorimotor function of the GI tract. The relative effects of all classes of antidepressant drugs are shown in Table 3.

The evidence for efficacy and the low cost of TCAs make them attractive, but their side effects need to be monitored and treated. By actively managing the side effects, one can improve adherence to treatment. The SSRIs and SNRIs are better tolerated and have a lower side effect profile but they are more expensive. While their efficacy has not been proven by controlled studies, available evidence suggests that they improve quality of life in these patients and are particularly helpful in patients with psychiatric comorbidities.

Selecting an appropriate drug often depends on type and severity of symptoms, patients' previous experience with the drug, cost, side-effect profile and presence of psy-

chiatric co-morbid conditions. With any antidepressant, partnership with patient in managing symptoms as well as side effects is of paramount importance. In patients with refractory symptoms, a clever combination of different class of drugs to maximize therapeutic benefit while minimizing side effects or a combination of psychotropic drugs with psychological therapy might be beneficial because of synergistic or additive effects.

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