



Antidepressants and Functional Gastrointestinal Disorders

By: Kevin W. Olden, M.D., F.A.C.G.
St. Joseph's Hospital and Medical Center

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Antidepressants are commonly prescribed for the treatment of functional gastrointestinal disorders; they are unique drugs, which have a number of properties that make them particularly useful. In order to fully understand their usefulness in functional gastrointestinal disorders, three areas should be understood.

The first is the mechanism of action of antidepressants, how they exert their effect. The second is the relationship between the brain and the gut, the so-called "brain-gut axis." Finally is the role of antidepressants in treating the various symptoms of functional gastrointestinal disorders. The purpose of this article is to review all three of these topics to help put the use of antidepressants in functional gastrointestinal disorders in perspective, and to help the reader participate more fully with their physician in deciding whether this would be an appropriate course of treatment for them.

History

Antidepressant drugs first appeared in the early 1950's. It was noted by a number of physicians who were treating patients with tuberculosis using the drug Isoniazid that some of the patients, who had symptoms of depression, tended to have improvements in their mood and sense of well-being when they received the drug. This led to speculation that there was an "antidepressant" property to this anti-tuberculosis drug. Researchers found that Isoniazid had a tendency to inhibit an enzyme called monoamine oxidase (MAO), which is involved in the breakdown of norepinephrine (adrenaline). This led, in the early 1950's, to the development of a number of drugs specifically designed to maximize this tendency to inhibit MAO. These so-called *MAO inhibitors* (MAOIs) were shown to be effective for the treatment of depression. However, the drugs were problematic in that they interacted with a number of other chemicals in the body. One of these was tyramine, a substance found in many foods including most nuts, chocolate, wines, and other foods. When a patient ingested foods containing tyramine, the MAOI's would impair ability to metabolize this substance and lead to elevated blood levels of tyramine; this can cause dramatic and dangerous elevations in blood pressure. The need to adhere to a strict diet when taking the MAOI's led to a search for other, easier-to-use agents.

In the 1950's and 1960's the *tricyclic* antidepressants were developed. These drugs have a chemical structure consisting of three chemical rings, hence the name "tricyclic."

The first of these drugs was amitriptyline (Elavil). This was followed subsequently by imipramine (Tofranil), desipramine (Norpramin), and others. [Table 1] Although these drugs belong to the same family, they have different properties. Some of them tend to be more anticholinergics – they block the activity of the nerves responsible for gut motion, salivary production, and in part, heart rate control. These medicines are more likely to produce dry mouth, constipation, and a feeling of dizziness upon arising, which is called *orthostatic hypotension*. Other drugs, such as doxepin, tend to be more antihistaminic and thus tend to stimulate appetite, and promote sleep.

The tricyclic antidepressants have been shown to be, by and large, quite safe. However, if taken in overdose, they can produce changes in heart rhythm, which can be quite serious and occasionally fatal. The drugs, when prescribed under a physician's direction, in doses used for depression (*or in lower doses, as is common in treating gastrointestinal disorders*) are rarely associated with any serious adverse consequences.

In the 1970's and 1980's, newer drugs were developed which were not tricyclic antidepressants but were unique in their structure. These are the so-called *atypical* antidepressants. Trazodone (Desyrel), bupropion (Wellbutrin), and more recently nefazodone (Serzone) best represent this group.

The latest addition to the therapeutic store has been the *selective serotonin reuptake inhibitors* (SSRIs), the prototype of which was fluoxetine (Prozac). The growing list of drugs in this category is outlined in Table I. The SSRIs tend to have a lower side-effect profile than the tricyclic antidepressants, and do not cause constipation, blurred vision, orthostatic hypotension, or cardiac arrhythmias. For this reason they are seen in Psychiatry as a major advance. Numerous studies have shown that the SSRIs per se have shown no real advantage over the tricyclics in terms of *treating* depression. However, the drugs are better accepted both by patients and physicians because of their tendency to have fewer side effects. Nevertheless, like any drug, these drugs are not completely free of side effects. SSRIs tend to produce headaches, GI upset (particularly diarrhea), nausea, and occasionally vomiting, as well as a "caffeine-like" effect with tremors and increased anxiety. Patients not infrequently experience impaired sexual function, particularly inability to have an orgasm. This latter side-effect has been particularly annoying for patients and may lead to discontinuation of the drug.

There are some very rare but dangerous neurologic conditions associated with use of SSRIs, particularly when used in combination with other psychiatric medications. The best known of these, the so-called “serotonergic syndrome,” can be life-threatening and is characterized by seizures, very high fevers, and cardiac arrhythmias. This syndrome has been reported only in very ill psychiatric patients taking multiple medications of a psychiatric nature. It has never been reported in a patient taking SSRIs for a functional gastrointestinal disorder.

TABLE 1

Classes of Antidepressants

I. Tricyclic Antidepressants

Amitriptyline (*Elavil*)
Clomipramine (*Anafranil*)
Desipramine (*Norpramin*)
Doxepin (*Sinequan*)
Imipramine (*Tofranil*)
Nortriptyline (*Pamelor*)

II. Selective Serotonin Re-Uptake Inhibitors

Citalopram (*Celexa*)
Fluoxetine (*Prozac*)
Fluvoxamine (*Luvox*)
Paroxetine (*Paxil*)
Mirtazapine (*Remeron*)
Sertraline (*Zoloft*)

III. Antidepressants with Unique Properties

Nefazodone (*Serzone*)
Trazodone (*Desyrel*)
Venlafaxine (*Effexor*)
Bupropion (*Wellbutrin*)

The Brain-Gut Axis

How do these drugs work? Simply stated, the major antidepressant effect of these drugs comes from their ability to block the reuptake of either norepinephrine (NE) or serotonin, which is also known by its chemical name, 5-hydroxytryptamine (5-HT). It is felt by brain researchers that an impaired ability for the brain to utilize NE and 5-HT results in depleted levels of these chemicals in the brain cells and subsequent development of the clinical syndrome we know as depression.

Interestingly, these drugs have also been shown to be very helpful for many anxiety disorders, including panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and generalized anxiety disorder. The drugs of all classes – MAOIs, tricyclics, atypical antidepressants, and SSRIs – share most of these properties. However the SSRIs have no ability to affect the uptake of norepinephrine, which is why they are called selective serotonin reuptake inhibitors.

It has been recognized for some time that the enteric nervous system of the gut, beginning in the esophagus and extending all the way into the anorectal area, is richly innervated with nerves that contain large amounts of norepinephrine and serotonin. Indeed, the largest amount of serotonin is not found in the brain and spinal cord, but rather in the gut. This fact led a number of investigators to begin using tricyclic antidepressants for the treatment of functional gastrointestinal disorders. The initial studies were done treating irritable bowel syndrome (IBS). Subsequent studies have looked at esophageal dysmotility, functional dyspepsia, and functional vomiting. Although the tricyclic antidepressants have been most extensively studied, recent articles have begun to study the usefulness of the SSRIs. These findings will be summarized below.

Antidepressants for Irritable Bowel Syndrome

Antidepressants have been used for the treatment of irritable bowel syndrome for over thirty years. Numerous studies have been published but one study in particular is worthy of note. In 1987, Greenbaum and colleagues studied a group of patients with irritable bowel syndrome, both diarrhea-predominant and constipation-predominant, and treated them with either the tricyclic desipramine (Norpramin) or atropine. Atropine is an anticholinergic drug that decreases colonic motion, and is useful in treating diarrhea and intestinal spasms. Greenbaum and colleagues chose to compare desipramine to atropine to see whether it was the anticholinergic effect of desipramine that actually made it useful, or if it was something unique to the antidepressant drug. Their results were interesting.

They showed that desipramine was superior to atropine for both diarrhea-predominant and constipation-predominant irritable bowel syndromes. Interestingly, in addition to improvement in their gastrointestinal symptoms, the patients also had a better sense of their overall well being. To control for the antidepressant effect of the drug, Greenbaum did not include in his study patients with a diagnosable psychiatric disorder. (Greenbaum, 1987)

This study is important because it showed two things. First, it showed that antidepressants were

useful in themselves, and not merely because of their anticholinergic effect.

Second, the study also demonstrated that the usefulness of antidepressants in treating irritable bowel syndrome was independent of the accompanying presence of a psychiatric disorder and seemed to be a unique effect of the drug. Numerous other studies have been performed studying desipramine, as well as other tricyclic antidepressants, in the treatment of irritable bowel syndrome. By and large, these studies have been positive, although many of them have methodological flaws. Trials are underway looking at the usefulness of the SSRIs in treating irritable bowel syndrome.

Antidepressants for Non-Cardiac Chest Pain (NCCP)

In the 1970's, it was discovered that many patients who complained of chest pain did not have a cardiac origin to their pain, but rather were having pain because of esophageal dysmotility. Again, building on the knowledge that the esophagus was rich in serotonin, Cannon and colleagues studied a group of patients with non-cardiac chest pain, and carefully tested them for any evidence of cardiac pathology, psychiatric disorder, or other gastrointestinal disorders, such as peptic ulcer disease, independent of their diagnosis of esophageal dysmotility. Cannon used the tricyclic antidepressant imipramine (Tofranil) and compared it to an inert placebo, and to clonidine (an antihypertensive agent), which has no serotonergic activity but is a very strong blocker of norepinephrine in the brain.

Cannon's findings were dramatic. Patients who were treated with imipramine had significantly better improvement in their chest pain symptoms compared to patients who received clonidine or placebo. Likewise, the GI symptom improvement due to imipramine was independent of any changes induced by motility of the esophagus, or by any changes in the patients' psychiatric status, as measured by psychological testing. What the patients did report was a significant improvement in their gastrointestinal symptoms as well as improvement in their overall sense of well being. These findings are very similar to Greenbaum's findings in irritable bowel syndrome. More recently, Handa and coworkers in Korea showed the usefulness of the SSRI paroxetine (Paxil) in the treatment of non-cardiac chest pain (Handa, 1999). It is clear that this is a promising area of study.

Other Functional Gastrointestinal Disorders

In addition to irritable bowel syndrome and non-cardiac chest pain, investigators over the last five years have shown the benefit of tricyclic

antidepressants in functional vomiting (Prakash, 1998) and functional dyspepsia (Mertz, 1998).

A recent meta-analysis, looking at the quality of all the studies published in the literature using antidepressants for functional gastrointestinal disorders by and large showed these drugs to be useful and safe to use. (Jackson, 2000)

Future Direction

Where do we go from here? It is clear that the treatment for functional gastrointestinal disorders is evolving. In the past, the treatment of functional GI disorders focused on a purely medical approach emphasizing the use of *gut specific* medicines, such as fiber, antispasmodics, and other motility agents. These agents certainly play an important role in the treatment of functional gastrointestinal disorders. However, recent research has shown that use of *the biopsychosocial model*, where multiple dimensions of the patient's life, including gut function, overall well being, as well as overall quality of life and emotional status seems reasonable. (Drossman, 1998) We clearly need to focus future research on the use of multimodal treatment. The use of dietary modification, antispasmodics, antidiarrheals, antidepressants, and behavioral interventions such as biofeedback, psychotherapy, and relaxation therapy all play a synergistic and important role in improving outcomes in functional gastrointestinal disorders. The final key is the informed patient. The mere fact that you are reading this fact sheet supports the tenet that you are interested in acquiring new knowledge about irritable bowel syndrome and the other functional gastrointestinal disorders. It is clear that an informed patient who can participate more fully in their care can greatly contribute to a successful outcome for these disabling disorders.

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The International Foundation for Functional Gastrointestinal Disorders (IFFGD) is a 501(c)(3) nonprofit education and research organization. We work to promote awareness, scientific advancement, and improved care for people affected by chronic digestive conditions. Our mission is to inform, assist, and support people affected by gastrointestinal disorders. Founded in 1991, we rely on donors to carry out our mission. Visit our websites at: www.iffgd.org or www.aboutIBS.org.

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