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Antidepressants in functional dyspepsia

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> **"**A randomized clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases is currently underway to examine the effectiveness and mechanisms of the tricyclic antidepressant amitriptyline and the selective serotonin-reuptake inhibitor escitalopram in functional dyspepsia.**"**

Functional dyspepsia refers to a clinical syndrome characterized by unexplained postprandial fullness, early satiety (inability to finish a normal-size meal) and epigastric pain or burning [1]. The condition often remains very frustrating for patients and physicians, with no satisfactory or approved treatment and heterogeneous outcomes. Standard pharmacological treatment includes antisecretory agents and prokinetics, but these are often unsatisfactory leading to the use of largely unproven alternatives, including antidepressants [1]. A randomized clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is currently underway to examine the effectiveness and mechanisms of the tricyclic antidepressant amitriptyline and the selective serotonin-reuptake inhibitor (SSRI) escitalopram in functional dyspepsia.

The extent of functional dyspepsia in the USA is significant, with up to one in four people having symptoms suggestive of functional dyspepsia; many are probably mislabeled as having gastroesophageal reflux disease [1-3]. Approximately a quarter of these people seek medical assistance [2,3]; functional dyspepsia and related functional bowel diseases account for over half of all gastrointestinal consultations in the USA, and remain the most frequent gastrointestinal problems in primary care [2,3]. In addition to substantially impairing quality of life [2,3], healthcare costs for functional dyspepsia have been calculated to be enormous,

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conservatively exceeding several billion dollars annually in the USA, including billions of dollars for dyspepsia drugs [2,4,5].

Functional dyspepsia is currently considered to be a biopsychosocial disorder with disturbances of gastroduodenal motor function, heightened visceral sensitivity and possibly a CNS disturbance [6,7]. Psychosocial factors can alter motility and/or enhance sensation and influence the timing of patients' presentation to physicians [6,7].

Standard treatment includes dietary advice of no established value and peripherally active pharmacological treatment, including antisecretory agents (H_2 blockers and proton pump inhibitors) and prokinetics. In systematic reviews of the available therapies, it has been concluded that the only drugs established to be better than placebo in functional dyspepsia are antisecretory and prokinetic agents [8-10]. However, a Cochrane meta-analysis also suggested that the positive cisapride data might simply reflect publication bias, based on a funnel plot [8]. Of the prokinetics, only metoclopramide is available in the USA since the withdrawal of cisapride, and side effects limit its use; tegaserod, a serotonin type 4 receptor agonist, was of limited efficacy in a Phase II functional dyspepsia trial, and the drug has been withdrawn [11].

Many patients with dyspepsia turn to alternative therapies of totally unproven value [12]. Nonpharmacological treatments have also been tested, but only in a very limited fashion; hypnotherapy was superior to standard care in a recent single-center study, but is not widely available [13]. A systematic review concluded that psychological therapy in functional dyspepsia is not of established value because of limited data [14]. Psychological treatment also represents a labor-intensive and costly approach. The lack of effective management in functional dyspepsia is likely to promote repeated medical consultation and its associated costs, as well as substantial amounts of time lost from work [2,4,6].

Psychological factors & psychiatric disorders in functional dyspepsia

Psychosocial factors are potentially key modulators of experience, behavior and, hence, treatment outcomes, in functional dyspepsia, but data are limited. Patients with functional dyspepsia have been reported to have significantly higher levels of psychiatric illness than healthy controls [15-17] and patients with organic gastrointestinal diseases [18]. Others have confirmed higher levels of psychological distress in those with functional dyspepsia presenting in primary care [19] and in the general population [20], compared with healthy controls. Magni *et al.*, using standardized criteria, found that 67% of patients with functional dyspepsia met criteria for an anxiety disorder versus 20% for organic dyspepsia [16]. In 201 tertiary referred patients with functional dyspepsia, symptom severity was mainly determined by psychosocial factors (depression and abuse history) and somatization when gastric function was also assessed [21]. A population-based study of subjects from Northern Sweden identified anxiety but not depression as an independent risk factor for functional dyspepsia [22]. Limited data suggest that those with postprandial symptoms are more likely to suffer with psychopathology [21,22].

Rationale for antidepressant medications in the treatment of functional dyspepsia

Antidepressants are used in the treatment of functional dyspepsia based on three propositions. First, antidepressants could reduce the severity of psychological symptoms, particularly anxiety and depression, which are thought to exacerbate the symptoms of functional dyspepsia, and may in some cases be etiologically linked to the syndrome, although this is controversial [7,18,23]. Second, antidepressants have central analgesic actions [24], and there is limited evidence of CNS dysfunction (e.g., based on changes in cerebral blood flow) [25]. Antidepressants reduce affective arousal and have sleep restorative actions [26,27]. Third, these drugs may have local pharmacological actions on the upper gut, although any changes have been modest and agent-specific [28,29].

The choice of antidepressant medication should depend upon the target symptoms, the overall clinical picture (including comorbid disorders) and the side-effect profile. The therapeutic response and side effects of antidepressant medication tend to vary between individuals [26,30], suggesting that constitutional factors influence the response and pharmacogenomics may be relevant.

There is accumulating evidence that low doses of a tricyclic are efficacious in the irritable bowel syndrome and other functional gastrointestinal disorders [26,27,31,32], but the mechanisms remain obscure.are also The selective serotonin-receptor antagonists are also established to have a benefit in irritable bowel syndrome [32]. Few trials have focused on functional dyspepsia, and here any evidence of efficacy is weak to nonexistent. Mertz *et al.* randomized just seven patients to 4 weeks of amitriptyline 50 mg taken at bedtime versus placebo in a crossover design [33]. All patients reported significantly less severe gastrointestinal symptoms after 4 weeks on amitriptyline. However, the subjective symptom improvement on amitriptyline was not associated with a normalization of the perceptual responses to gastric distension in this small but important pilot study. In the Mertz trial, 71% (five out of seven) reported global symptom improvement versus 29% (two out of seven) on placebo; this translates into a number-needed-to-treat of two [33]. There has only been one published randomized controlled trial with an SSRI in functional dyspepsia, despite their reasonably widespread use in clinical practice for patients with the syndrome. In an 8-week trial of venlafaxine extended-release (2 weeks 75 mg once daily, 4 weeks 150 mg once daily and 2 weeks 75 mg once daily) or placebo in 160 patients, the proportion of symptom-free patients after 8 weeks of treatment was 37% on the SSRI and 39% on placebo, a nonsignificant difference [34].

It is our clinical experience that both tricyclics in low dose and SSRIs at standard doses can be effective in providing symptomatic relief in functional dyspepsia when treatment is prescribed for at least 1 month in women and men. Moreover, the symptom benefit appears to persist on stopping therapy for a prolonged period in some cases. However, very little trial data are available to support use of these agents, and the risk–benefit ratio is unclear in functional dyspepsia or its subgroups. Furthermore, there have not been any systematic trials comparing these two classes of compounds head-to-head in functional dyspepsia, and no

long-term follow-up studies at all. Moreover, mechanisms for any benefit have not been established.

The current trial

The aims of the current NIDDK study are to:

- Determine whether antidepressant therapy is more efficacious than placebo in the relief of the symptoms of functional dyspepsia, adjusting for psychological and psychiatric comorbidity. We will also determine if antidepressant therapy reduces disability, improves quality of life and influences clinical response over 6 months after ceasing medication;
- Determine if gastric emptying (motor dysfunction) and the nutrient drink test (a test that assesses global gastric function including gastric hypersensitivity and/or gastric accommodation) is altered by antidepressant therapy with a tricyclic or SSRI, and whether subgroups with altered physiology are associated with treatment outcome. In a substudy, we will directly determine if impaired gastric accommodation (by a validated noninvasive imaging method using ^{99m}Tc-single-photon emission computed tomography) and the symptom response to a nutrient drink test is altered by an SSRI or tricyclic antidepressant;
- Determine if polymorphisms of *GNβ3* and the serotonin-reuptake transporter predict outcome in functional dyspepsia patients receiving a tricyclic antidepressant or SSRI therapy.

This double-blinded randomized clinical trial compares the tricyclic antidepressant amitriptyline in low dose (50 mg) and the SSRI escitalopram in standard dose (10 mg) to placebo. We will be enrolling 400 patients through seven sites in the USA: Mayo Clinic sites in Rochester, MN, Jacksonville, FL and Scottsdale, AZ; Saint Louis University, MO; Northwestern Medical Center in Chicago, IL; Dartmouth-Hitchcock Medical Center in Lebanon, NH; and Baylor College of Medicine in Houston, TX. Information regarding the study can be obtained at ClinicalTrials.gov [101] or by contacting dyspepsia@mayo.edu.

We feel that this important study will contribute significant knowledge to the effectiveness and potential mechanisms of functional dyspepsia. In light of few proven options, continued clinical trials are needed to guide care for this frustrating condition.

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Biographies

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