Effects of Amitriptyline and Escitalopram on Sleep and Mood in Patients With Functional Dyspepsia

Linda M. Herrick,* Michael Camilleri,* Cathy D. Schleck,‡ Alan R. Zinsmeister,‡ Yuri A. Saito,* and Nicholas J. Talley*§

*Gastroenterology and Hepatology, ‡Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; §Faculty of Health and Medicine, University of Newcastle, Callaghan, New South Wales, Australia

BACKGROUND & AIMS: Tricyclic antidepressants are effective in reducing symptoms of functional dyspepsia (FD). We performed a post hoc analysis of data from a previous randomized clinical trial to determine whether the benefits of an antidepressant on gastrointestinal symptoms in patients with FD were mediated by improving sleep or reducing anxiety. We explored the relationships between psychological measures, quality of sleep, and relief of symptoms.

METHODS: We analyzed data from a multicenter, double-blind trial that evaluated the efficacy of antidepressants on symptoms of FD, from October 2006 through October 2012. Patients (n = 292) were randomly assigned to groups given 50 mg amitriptyline, 10 mg escitalopram, or placebo for 12 weeks. During the study, participants completed the following validated psychological questionnaires: Symptom Check List 90, Symptom Somatic Checklist, Hospital Anxiety Depression Scale, Profile of Mood States, State Trait Anxiety Inventory, and Pittsburgh Sleep Quality Index at baseline and 12 weeks following treatment.

RESULTS: Baseline scores for the psychological and sleep measures were similar among groups; after 12 weeks there were no significant differences in scores among groups. Baseline mean global Pittsburgh Sleep Quality Index scores indicated poor sleep quality in all groups at baseline and after 12 weeks. Overall, antidepressants affected sleep duration scores: patients given amitriptyline had lower (better) scores than patients given placebo or escitalopram (P = .019). In all groups, responders had decreased anxiety and improvements in some sleep components.

CONCLUSIONS: In a post hoc analysis of data from a clinical trial that evaluated the effects of antidepressants in patients with FD, amitriptyline was found to reduce symptoms of FD, but its mechanism is unlikely to involve reductions in psychological distress. The drug may modestly improve sleep.

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Keywords: SCL-90; SSC; HADS; POMS; STAI; PSQI; Antidepressants; Functional Dyspepsia; Mood; Sleep.

Abstract: Patients who present with chronic or recurrent postprandial fullness, early satiety, upper abdominal bloating, or epigastric pain or burning and who have no obvious structural explanation (eg, a peptic ulcer identified at esophagogastroduodenoscopy), are labeled as having functional (or nonulcer) dyspepsia (FD). The symptoms are considered to arise from the gastroduodenal region and affect up to 20% of people in the United States.1,2 Disturbances of gastroduodenal motor function including delayed gastric emptying, heightened visceral sensitivity, and duodenal inflammation characterized by increased eosinophils have been reported in subsets of patients with FD.3 Although functional dyspepsia is not life-threatening, it substantially affects quality of life and medical costs.4–6 Psychosocial factors and somatization likely play a role in FD, with greater FD symptom severity correlated with depression and somatization.7–10 Higher levels of psychological distress have been observed in patients with FD, in patients who consult and in the community, suggesting an etiologic link.11–14 Other symptoms linked to FD include fatigue and sleep disturbances.15–18 The explanation for poor sleep in FD is not clear, but may be primary or secondary to nighttime gastrointestinal symptoms.

Abbreviations used in this paper: AMI, amitriptyline; FD, functional dyspepsia; FDTS, Functional Dyspepsia Treatment Trial; 5-HT, 5-hydroxytryptamine; HADS, Hospital Anxiety Depression Scale; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; SCL-90, Symptom Check List 90; SSC, Symptom Somatic Checklist; SSRI, selective serotonin reuptake inhibitor; STAI, State Trait Anxiety Inventory.

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Antidepressants have been used in the treatment of FD to reduce anxiety and depression, to induce centrally mediated analgesia, to reduce affective arousal, and for restorative effects on sleep, although the mechanism is unknown. The antidepressant effects of tricyclic antidepressants are thought to be owing to an overall increase in serotonergic neurotransmission. Tricyclic antidepressants also block histamine-H1 receptors, α1-adrenergic receptors, and muscarinic receptors, which accounts for their sedative, hypnotic, and anticholinergic effects (eg, blurred vision, dry mouth, constipation, urinary retention). Histamine-H1 antagonism may be associated with induction of sleep. Moreover, selective serotonin reuptake inhibitors (SSRIs) target the SLC6A4 serotonin reuptake channel, and therefore may affect multiple serotonin receptors at different locations. Activation of 5-hydroxytryptamine (5-HT)1A receptors in the dorsal raphe nucleus by serotonin may play a role in the regulation of rapid eye movement (REM) sleep. In a multicenter, randomized, placebo-controlled clinical trial, the efficacy of amitriptyline (AMI) and escitalopram were assessed over a 12-week period, showing the efficacy of AMI in reducing symptoms, particularly in patients with normal baseline gastric emptying.

We hypothesized that any benefit of an antidepressant on gastrointestinal symptoms in FD would be mediated through improvements in sleep and reduction of anxiety. We therefore aimed to explore the relationships between psychological measures, quality of sleep, and relief of FD symptoms using data collected in a randomized clinical trial assessing the effects of AMI, escitalopram, or placebo on symptom relief, physiological testing, and genetics.

Materials and Methods

Trial Design

This was a post hoc cross-sectional analysis of baseline and 12-week data from all patients enrolled in the Functional Dyspepsia Treatment Trial (FDTT). The FDTT was a 12-week, multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy of antidepressants on FD symptoms (Clinicaltrials.gov_NCT00248651). Details of the FDTT study have been published previously. Subjects were required to meet Rome II criteria for FD and were randomized to placebo, 50 mg AMI, or 10 mg escitalopram in a 1:1:1 ratio. Subjects were excluded if they were receiving current antidepressant therapy, undergoing psychiatric treatment, had a current history of drug or alcohol abuse, currently were taking psychotropic medication for depression or psychosis, or scored 11 or higher on the depression scale of the Hospital Anxiety Depression Scale (HADS). They were excluded if they had other significant illnesses or had undergone major abdominal surgery.

The protocol was approved by ethics or institutional review boards at each site before study site initiation. All authors had access to data related to variables in this article.

Measurement

Subjects completed a number of validated psychological questionnaires including the Symptom Check List 90 (SCL-90), Symptom Somatic Checklist (SSC), HADS, Profile of Mood States, State Trait Anxiety Inventory (STAI), and the Pittsburgh Sleep Quality Index (PSQI) at baseline and after 12 weeks of treatment. The SCL-90 is a measure of psychological state consisting of 90 questions on a 5-point Likert scale. The SCL-90 has 9 scales: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The SSC measures the frequency and bothersomeness of 12 non-gastrointestinal symptoms on a 5-point Likert scale. The overall mean score was computed for each subject. The HADS is a self-report 14-item scale recommended for detecting mild mood disorders in nonpsychiatric outpatients and has been used with patients with irritable bowel syndrome. The Profile of Mood States is a 65-item survey with 6 subscales. The STAI is a self-report inventory of baseline and situational anxiety measuring both positive and negative emotional states. There are twenty 4-point Likert questions for each component of the survey: baseline and situational. The PSQI contains 19 self-rated questions with 7 component scores. The PSQI assesses sleep quality and disturbances over a 1-month time period. The 7 component scores (range, 0–3) are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global PSQI score (range, 0–21) can be calculated with a score greater than 5 yielding a diagnostic sensitivity of 90% and a specificity of 87% (κ = 0.75) in distinguishing good and poor sleepers; a higher score indicates worse sleep quality.

Adequate relief of FD, the primary end point for the clinical trial, was defined as adequate relief for at least 5 of 10 follow-up telephone calls or visits while on treatment (excluding the first 2 weeks for AMI dose escalation). Subjects were called weekly and asked the following yes/no question: “In the past 7 days, have you had adequate relief of your stomach symptoms?” This self-report global measure is widely accepted and has been tested for responsiveness in FD.

Demographic Data

Demographic data were collected at the beginning of the study including age, sex, body mass index, and race. Before randomization, subjects were categorized by subtype of dyspepsia (ulcer-like vs dysmotility-like, Rome II criteria), gastric emptying status (delayed or
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