A prospective, randomized placebo-controlled double-blind study of fluoxetine in patients with somatization disorder in two general medical clinics.

Emmy Ludwig

A. Study Rationale and Purpose

Somatoform disorders are characterized by physical complaints that occur in the absence of identifiable physical pathology. Although we now recognize several such illnesses [*], their long and colorful history dates back to the ancient Greek concept of hysteria, a malady of "a wandering uterus." The term hysteria became so charged and full of diverse meaning that the eponym Briquet's syndrome was adopted as a more neutral moniker after Paul Briquet, a French physician who in 1859 first conceived of hysteria as polysymptomatic disorder. His conception was used to develop a checklist of symptoms, which has evolved into the DSM criteria by which we diagnose somatization disorder today.[i]

Somatization disorder is a condition beginning early in life, and is thought to be more common in women. It is characterized by recurrent and diverse somatic symptoms, which, although often dramatically described, remain unexplained after thorough, often extensive testing. To fulfill the criteria for a DSM-IV diagnosis of somatization disorder, a patient must have at least eight unexplained symptoms, including four pain, two gastrointestinal, one sexual and one pseudoneurological.[ii] The condition is thought to have a prevalence of between 0.13 and 0.4% in the general population. (1-4 per 1000) However, these patients tend to congregate in the primary care and general hospital setting because of their intense perception of themselves as very ill. In this setting, the prevalence has been estimated as 5% or—even more strikingly—one patient per busy clinic day for the average primary care provider.

Specialty practices, especially GI and gynecology, may see patients with somatization disorder with prevalence upwards of 15-20%.[iii]

These patients have historically been difficult and frustrating to treat. The disorder has been associated with significant impairment in physical and occupational functioning as well as with increased utilization of health care resources.[iv] Patients are often dissatisfied by the results of their work-up and are prone to "doctor shop." In turn, physicians are often angered and fatigued by the myriad of complaints and the lack of objective data with which to provide solutions to these problems.[v,vi] Patients are frequently resistant to seeking psychiatric help for what they perceive as somatic complaints. For this reason, the primary care forum is the most likely place a patient will go for help.[vii] Thus, seeking treatment options conducive to this arena is an important goal to help both patient and doctor.[viii]

Trials of pharmacotherapy for somatoform disorders have been scarce. There is some data that suggest that antidepressants could be helpful. Tricyclic antidepressants have been shown to be efficacious in chronic pain syndromes.[ix] More recently, functional somatic disorders, such as irritable bowel disorder and chronic fatigue syndrome[x] have shown modest improvement with SSRI therapy.[xi] Fallon et al[xii] showed improvement in hypochondriasis through the use of SSRIs.

Most relevant is a study by Noyes, et al from 1998 that examined the SSRI fluvoxamine as a treatment for somatoform disorders. 29 patients with somatoform disorders were identified at a general medicine clinic; they received fluvoxamine 300 mg daily for eight weeks. At the end of the period 61% of patients who had received medication for at least two weeks were at least moderately improved. The primary endpoint used was a score on the Clinician-Rated Global Improvement Scale. Additional measurements of symptomatology were made through patient questionnaires, including the Brief Symptom Inventory. Four of the seven patients identified as having somatization disorder had at least a

[*] somatization disorder, hypochondriasis, conversion disorder and pain disorder

moderate improvement from baseline scores, an improvement that was statistically significant ($p<0.05$.) [xiii]

We plan to undertake a placebo controlled double blind study of fluoxetine in patients with diagnosed somatization disorder identified from a general medicine clinic. The purpose is to determine the efficacy of an SSRI in improving global measures of functioning and in reducing distressing symptomatology in patients with somatization disorder. Fluoxetine is selected because it is the only SSRI which is generically available, and if found to be effective in this population, could be most easily used in a larger clinic population.

B. Study Design, Study Procedures, and Statistical Analysis

Study subjects will be identified as having somatization disorder and then randomized to placebo or fluoxetine 20 mg once daily. After randomization, each study subject will complete the Hopkins Symptom Checklist 90 (HSCL-90) questionnaire twice, once at the beginning of the study and again two weeks later. In addition, that patient's primary care physician (PCP) will complete the Social and Occupational Functioning Assessment Scale (SOFAS) for the patient at the beginning of the study.

Following completion of the study at six months, patients will again fill out the HSCL-90 twice at two-week intervals. The original PCP will again assess the patient and score them using the SOFAS.

The primary endpoint will be an improvement in score on the SOFAS of the fluoxetine treated group over the placebo group. The SOFAS is a scale from 1-100 with 100 representing superior functioning, 60 representing moderate difficulty in social or occupational functioning, and 40 representing major impairment (please see attached.) The SOFAS is a derivative of the Global Assessment of Functioning (GAF) Scale; the SOFAS focuses exclusively on a patient's level of social and occupational functioning and is not directly influenced by the overall severity of psychological symptoms alone [xiv,xv] In addition, changes in functioning due to "medical" problems are included in the assessment of impairment. A baseline score of 60 +/- 10 will be assumed for both groups; the physician will repeat the evaluation six months into the study. An improvement in score to 70 +/- 10 will be anticipated in the fluoxetine group, with no change in the placebo.

In addition, patients will be asked to complete the HSCL–90, which consists of 90 items rated on five point linear scale (see attached.[xvi]) The HSCL-90 is an expansion of an earlier instrument (HSCL-58), which has been validated in multiple studies. Patients have shown high test-retest coefficients (above .80) when tested at weekly intervals.[xxii] These five point distress scales range from 1 "not at all" through " a little, moderately, and quite a bit" to "extremely" for rating a number of items on "how much that problem has bothered you." This additional marker of disease state and improvement will allow us to assess changes in symptomatology of somatization and depression. Improvement or lack thereof can therefore be assessed independently from the primary outcome of improved quality of social and occupational functioning. A mean score of 2.5 will be assumed as a baseline mean with projected improvement to 1.7 +/- 0.8 in the treated group and no change in the placebo group.

Statistical analysis will include measurement of the change in global assessment score over six months for each individual in the placebo group and in the treatment group. To achieve 80% power and a p value of $<.05$, at least 34 patients must be randomized to two groups of 17 each in the placebo and fluoxetine arm. 44 patients will be randomized to ensure sufficient power in the event of patient dropout. The mean change from baseline scores will be compared using an unpaired t-test. Data will be analyzed on an intent-to-treat basis.

C. Study Drugs

Both placebo and study drug—fluoxetine 20 mg tablets—will be stored and dispensed by the Columbia Presbyterian Medical Center Research Pharmacy.

D. Medical Devices

None.

E. Study Questionnaires

The SOFAS and the HSCL-90 will be used (please see above and attached.)

F. Study Subjects

a. Inclusion criteria

- Diagnosis of somatization disorder as defined by DSM IV (procedure for diagnosis as outlined below)
- Men and women with age greater than 30
- Native English or Spanish speaker (with ability to read in that language to fifth grade level)
- Able to commit to one year of treatment at AIM or ACNC

b. Exclusion criteria

- Allergy or hypersensitivity to selective serotonin reuptake inhibitors in the past
- Concurrent Axis I or II disorder as defined by DSM IV (e.g. major depression, generalized anxiety disorder, active psychosis, dementia, substance abuse)
- Past documented episode of psychosis or delusional disorder
- Current use of antidepressant or anti-anxiety therapy, including pharmacotherapy (SSRIs, TCAs, MAOIs, benzodiazapines,) or individual or group psychotherapy

G. Recruitment of Subjects:

Subjects will be recruited via physician referrals from two general medical clinics at NYPH-CPMC: AIM and ACNC. Once a somatoform disorder is suspected, a trained study nurse will administer the somatoform module of the Structured Clinical Interview for DSM-IV [xxiii] to further identify a patient with somatization disorder. Once a patient has been identified, and met inclusion and exclusion criteria for the study they will sign informed consent. Randomization will occur after patient has been assigned a unique alphanumeric identifier.

H. Confidentiality of Study Data

All participants in the trial will be assigned a unique 6 digit alphanumeric identifier with which all data will be coded.

All data will be kept in the study office and only persons associated with the study will have access to it.

I. Potential Conflict of Interest

None.

J. Location of Study

All research and study drug distribution will occur at the Associates in Internal Medicine (AIM) offices of NYPH-CPMC (Vanderbilt Clinic 2nd floor) or at ACNC.

K. Potential Risks

A time commitment will be required to fill out the questionnaires, and to attend at least five additional clinic visits over the course of a year.

If patients receive the study drug, common side effects of the SSRIs include nausea, dry mouth, sleepiness, insomnia, and sexual dysfunction.

Few allergic reactions have been reported.

L. Potential Benefits

Multiple trials both prospective and retrospective have shown an improvement in both quality of life and symptomatology in patients who receive treatment with antidepressants.

M. Alternative Therapies

If patients choose not to participate in this study they may receive best supportive care including referral to psychotherapy, or a trial of anti-depressants off-study as their PMD sees fit.

N. Compensation to Subjects

Patients will receive $25 for the initial completion of the questionnaire, and an additional $75 at the conclusion of the study.

O. Costs to Subjects

None.

P. Minors as Research Subjects

Minors will not be participating in this study.

Q. Radiation or Radioactive Substances

No radioactive substances will be used in this study.

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