A Randomized Controlled Trial of Fluvoxamine in Prostatodynia, a Male Somatoform Pain Disorder

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Background: Prostatodynia is a common and often disabling condition that affects males and has the characteristics of a somatoform pain disorder. It presents with urogenital pain and urinary symptoms. Failure of conventional treatment and a successful uncontrolled pilot study with fluvoxamine in this condition prompted this study.

Method: In a randomized double-blind trial, 42 patients with prostatodynia were assigned to receive either fluvoxamine (N = 21) or placebo (N = 21) for up to 8 weeks. Doses were adjusted according to therapeutic need. The median dose of fluvoxamine was 150 mg (range, 50–300 mg). Self-rated pain scores, urinary flow rates, and depression and anxiety scores were measured at baseline and several times throughout the study period.

Results: The groups were similar at baseline, and the results were examined by intent-to-treat analysis either using the last observation carried forward or, in the case of dichotomous measures, counting treatment dropouts as treatment failures. Fluvoxamine was significantly more likely to reduce pain intensity (p = .01) and normalize urinary flow rates (p = .03) with a clinically significant number needed to treat value of 1.5 (confidence interval = 1.12 to 5.50). This therapeutic effect could not be attributed to change in mood, as the 2 groups did not differ with respect to affective ratings at the end of the study. The fluvoxamine-treated group had significantly lower (p = .02) final scores on the General Health Questionnaire, indicating an overall benefit from pain relief.

Conclusion: Fluvoxamine is a viable treatment for prostatodynia. Dose-ranging studies and longer trials are needed to evaluate this agent further.

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Prostatodynia is a common and often disabling condition affecting men. This disorder meets ICD-10[1] criteria for somatoform pain disorder and DSM-IV[2] criteria for pain disorder. It presents with suprapubic or perineal pain along with irritative or obstructive urinary tract symptoms of more than 6 months' duration.[3] The diagnosis is one of exclusion based on negative findings on physical and rectal examination along with negative findings on examination of fractional urine samples and expressed prostatic secretion.[4] Sufferers often see multiple physicians and undergo extensive testing, all adding to their frustrations with the problem.[3]

Turkington et al.[5] reported a high incidence (52%) of psychiatric problems associated with this condition, although this syndrome has been largely ignored by psychiatric practitioners. The exact incidence of prostatodynia is not known. It is thought to be low in general urology outpatient clinics, but it may account for as many as 25% of office visits for genitourinary tract problems[6] in the United States in specialist prostatitis clinics. Similarly, 31% of patients in a German prostatitis clinic had prostatodynia.[7]

The disorder has a chronic course that responds poorly to conventional treatment with anti-inflammatory agents and antibiotics.[8] Medical treatment of this disorder is unsatisfactory, and failed treatment with sequential courses of antibiotics and analgesics leads patients to request orchidectomy or prostatectomy, which usually exacerbates the chronic pain syndrome. Antidepressants have their use in the management of pain.[9] The tricyclic antidepressants, however, have the limitation of anticholinergic side

Table 1. Baseline Characteristics: Age, Visual Analogue Pain Scores, GHQ, HAM-A, HADS, MADRS, Diagnosis, and Urinary Flow Rate[a]

Characteristic	Placebo (N = 21) Median (range)	Fluvoxamine (N = 21) Median (range)	Statistic	Significance[b]
Age, y	42 (49)	41 (54)	206.5 (437.5)[c]	.93
Rating scale				
Visual analogue pain scale	5.5 (9)	5.0 (7)	265 (496)[c]	.27
GHQ	8 (20)	5 (21)	245 (454.5)[c]	.13
HADS anxiety	5 (15)	5 (16)	207.5 (417.5)[c]	.63
HADS depression	2 (11)	5 (12)	155 (365)[c]	.33
MADRS	6 (22)	5 (35)	237 (444.5)[c]	.69
HAM-A	6 (21)	4 (33)	213.5 (468)[c]	.87
	N	N		
Diagnosis of depression or anxiety	3	6	4.5[d]	.45
Abnormal urinary flow rate (50% less than expected for age with abnormal pattern)	6	8	0.11[e]	.74

[a]Abbreviations: GHQ = General Health Questionnaire, HADS = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]All p values are 2-sided; none were significant.
[c]Mann-Whitney U (rank sum).
[d]Fisher exact test, expectation of A.
[e]Yates-corrected χ^2; df = 1.

Table 2. Pain Scores in the Fluvoxamine Group Versus the Placebo Group by Week Analyzed Using Mann-Whitney U Test[a]

Mann-Whitney U Test Result	Week 0	Week 2	Week 4	Week 6	Week 8
Score					
RS	437.5	488.5	528.5	534	553
U	206.5	257.5	297.5	303	322
2-Sided p value	.27[b]	.36[b]	.05	.04	.01

[a]Abbreviation: RS = rank sum.
[b]Not significant.

effects, particularly urinary retention. Therefore, selective serotonin reuptake inhibitors (SSRIs) may be a more rational choice as an antidepressant treatment for prostatodynia. The analgesic properties of SSRIs have support from preclinical literature.[10] In an open pilot study of treatment with the SSRI fluvoxamine, over 70% of patients with prostatodynia found relief.[5] Fluvoxamine being the most successful treatment of this relatively refractory pain syndrome, we decided to carry out a randomized, double-blind, placebo-controlled trial to evaluate this therapeutic option.

METHOD

Patients were recruited from referrals for genital pain to a urology outpatient clinic of a general hospital. The inclusion criteria were male sex, age of 18 years or over, and perigenital pain of at least 1 year's duration with absence of local or systemic infection and absence of local inflammation. Fractional urine samples and expressed prostatic secretion were tested for routine microbiology and chlamydia isolation. All patients had undergone systematic evaluation including plain abdominal radiology to exclude kidney or bladder stones, cystoscopy to exclude stricture and bladder pathology, and ultrasound of kidneys and bladder. Peak flow was recorded, as was pattern of flow, and readings were analyzed only if more than 150 mL of urine was passed. Neuropsychiatric illness, suicide risk, history of treatment with fluvoxamine, and current treatment with any antidepressants were the exclusion criteria.

Forty-two consecutive patients with prostatodynia were assessed by a liaison psychiatrist in the clinic and enrolled in a double-blind, placebo-controlled study of the potent SSRI fluvoxamine in the treatment of their chronic perigenital pain and related urinary and sexual symptoms. The total duration of the study was 8 weeks. Enrolled patients were assessed initially and every 2 weeks on a 0-to-10 visual analogue pain scale. The Montgomery-Asberg Depression Rating Scale (MADRS)[11] and Hamilton Rating Scale for Anxiety (HAM-A)[12] were administered at baseline and at weeks 4 and 8; the Hospital Anxiety and Depression Scale (HADS)[13] and the General Health Questionnaire (GHQ)[14] were administered at the start and end of the study. Urinary flow was measured at baseline and at the end of the study period using a flowmeter with a full bladder and analyzed by a genitourinary clinician blind to the diagnosis as improved or unimproved on the basis of a greater than 50% improvement in peak urinary flow rate with improvement in pattern of flow.

After initial assessment, patients were randomly assigned to treatment using a computer program and allocated in a double-blind design to receive fluvoxamine, 50 mg, or 1 matched placebo tablet. If there was no improvement in pain, the dose of fluvoxamine was increased by 50 mg or by 1 placebo tablet every 2 weeks. At review, mean analogue pain score over the previous 2 weeks was recorded, as were affective symptoms. Compliance was assessed by counting the remaining pills at follow-up, and patients' reports were used to clarify concurrent medication use.

The protocol for the study was approved by the appropriate local ethical committee. All patients gave full written informed consent after the study had been explained.

Data were analyzed using the StatsDirect[15] statistical package. Both ordinal data and continuous data were analyzed using the Mann-Whitney U test. Nonparametric

Table 3. Outcome Scores at the End of the Study[a]

Scale	Placebo (N = 21) Median (range)	Fluvoxamine (N = 21) Median (range)	Statistic[b] RS	U	Significance[c]
Visual analogue pain scale	5.75 (9)	1.25 (5)	553	322	.01
GHQ	5.1 (19)	1.0 (19)	553	272	.02
HADS anxiety	5.4 (11)	4.0 (11)	445	196	.21[d]
HADS depression	4 (12)	2 (11)	406	196	.87[d]
MADRS	5 (26)	2 (18)	480	249	.48[d]
HAM-A	11 (17)	4.5 (13)	489	258	.35[d]

[a]Abbreviations: GHQ = General Health Questionnaire, HADS = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, NS = not significant, RS = rank sum.
[b]Mann-Whitney U test.
[c]2-Sided p values.
[d]Not significant.

statistics were justified, as the continuous variables showed nonnormal distribution when tested using the Shapiro Wilk test. The Fisher exact test and chi-square tests were used, where appropriate, for categorical variables.

RESULTS

Of 42 predominantly middle-aged men with prostatodynia (median age = 41 years; range, 18–72 years), 29 patients completed the study. There were 8 dropouts in the fluvoxamine group, chiefly due to side effects (nausea, sedation, and diarrhea), and 5 in the placebo group due to perceived side effects (diarrhea, dizziness, and headache). This difference was not significant (Yates-corrected $\chi^2 = 0.45$, p =. 50); therefore, an intent-to-treat analysis was performed with the last observations carried forward.

Baseline characteristics of the 2 groups are displayed in Table 1. There were no significant differences between the groups in terms of the baseline characteristics. At assessment, 62% (N = 26) of the patients complained primarily of testicular pain, with 26% (N = 11) reporting perineal pain and 5% (N = 2), penile pain. Other sites for pain included groin (40% [N = 17]) and loin (14% [N = 6]). The mean duration of the pain was 6.9 years, with no significant differences between the groups (p = .95). Troublesome urinary symptoms (frequency/urgency, 50% [N = 21]; hesitancy, 12% [N = 5]; and dysuria, 5% [N = 2]) and sexual dysfunction (post-ejaculation pain, 52% [N = 22]; erectile impotence, 12% [N = 5]; premature ejaculation, 10% [N = 4]; and lowered libido, 10% [N = 4]) were often present.

The median dose of fluvoxamine taken at the end of the study was 150 mg (range, 50–300 mg). Although it is customary to conceptualize improvement in terms of percentage change from baseline values, we felt that this would be untenable for pain scores since the scale used was a visual analogue type yielding ordinal rather than interval data. The fluvoxamine-treated group showed significant improvement in pain self-ratings compared with the placebo group (Table 2). This significance was apparent by week 4—the midpoint of the study. Table 2 also depicts the statistical difference between the pain scores of the 2 groups with increasing significance levels over time.

The 2 groups did not differ on measures of affective symptoms using the HADS, HAM-A, or MADRS (Table 3), indicating that improvement in pain scores was not a result of mere change in mood. Endpoint GHQ scores of the fluvoxamine-treated patients were significantly lower than those of the placebo group (see Table 3). This was objective evidence that fluvoxamine treatment had changed the patients' health status for the better, as would be expected with reduction in pain.

Only 1 of 6 patients in the placebo group showed improvement in urinary flow rate compared with 7 of 8 in the fluvoxamine group. This highly significant finding (2-sided p = .03, Fisher exact test expectation of A = 2.57) translates to a clinically significant number needed to treat (NNT) figure of 1.5 (confidence interval [CI] = 1.12 to 5.50). We also did an intent-to-treat analysis of urinary flow rates, treating dropouts as treatment failures. The urinary flow rates showed significant improvement, yielding a respectable NNT value of 3 (CI = 1.83 to 11.90)—still a clinically significant finding despite the wide CI.

A similar intent-to-treat analysis using patients' subjective rating of their improvement as "improved" or "not improved" showed a positive trend in the fluvoxamine-treated group, but this trend did not achieve statistical significance (p = .21), probably because of the dropouts in both groups.

DISCUSSION

A recent review[9] concluded that antidepressants are effective in reducing pain intensity in psychogenic or somatoform pain disorder. However, none of the 11 studies reviewed used fluvoxamine or studied prostatodynia, confirming that SSRIs as a group have not been evaluated for pain relief. Our study clearly demonstrated the therapeutic action of fluvoxamine in improving the pain component of prostatodynia. The high dropout rates in both limbs of the study may indicate a general characteristic of the patients in this study. However, if we can encourage patients to tolerate the early side effects of fluvoxamine, then it is highly likely that they will achieve significant pain relief within 4 weeks with added improvements in urinary symptoms.

The change in urinary flow rate was a particularly significant finding in this study. Even when dropouts were taken into account, fluvoxamine had clear-cut effectiveness, with improvement in this objective outcome measure. There has been much debate about the underlying mechanisms in prostatodynia.[16] The impressive responsiveness of

this syndrome to fluvoxamine would fit with deficiencies in spinal serotonin (5-HT) systems perhaps triggered by infection, trauma, or certain surgical procedures.[5] Increasing spinal 5-HT turnover would have the effect of raising the pain threshold and exerting a tonic effect on bladder function. All patients with prostatodynia should have a trial of fluvoxamine instead of persevering with endless courses of antibiotics and analgesics. Interestingly, at least 1 recent study[17] found specific action of fluvoxamine on pain rather than just depressive symptoms, when compared with fluoxetine.

Further studies in this area are now indicated with larger sample sizes and specific attention to all of the symptoms of this syndrome. A study addressing the change in quality of life after treatment with fluvoxamine is also warranted. Perhaps a dose-ranging study to assess benefits and adverse effects at different doses could identify the optimal dose of fluvoxamine for the treatment of prostatodynia. This study could be followed by a longer treatment trial of fluvoxamine in this condition.

Drug names: fluoxetine (Prozac and others), fluvoxamine (Luvox and others).

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