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Effect of Amitriptyline on Symptoms in Treatment Naïve Patients with Interstitial Cystitis/Painful Bladder Syndrome

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Abstract

Background—Amitriptyline is frequently used to treat patients with IC/PBS. The evidence to support this practice is derived mainly from a small single site clinical trial and case reports.

Methods—We conducted a multi-center, randomized, double blind, placebo controlled clinical trial of amitriptyline in subjects with IC/PBS who were naive to therapy. Study participants in both treatment arms received a standardized education and behavioral modification program (EBMP). The drug dose was increased over a six-week period from 10 mg up to 75 mg once daily. The primary outcome was a patient-reported global response assessment (GRA) of symptom improvement evaluated after 12 weeks of treatment.

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Results—A total of 271 subjects were randomized and 231 (85%) provided a GRA at 12 weeks of follow-up. Study participants were primarily women (83%), Caucasian (74%) with a median age of 38 years. In an intention-to-treat analysis (n=271), the rate of response of subjects reporting either moderately or markedly improved from baseline in the amitriptyline and placebo groups was 55% and 45% respectively (p=0.12). Among the subgroup of subjects (n=207) who achieved a drug dose of at least 50 mg, a significantly higher response rate was observed in the amitriptyline group (66%) compared to placebo (47%) (p=0.01).

Conclusion—When all randomized subjects were considered, amitriptyline in combination with an EBMP did not significantly improve symptoms in patients with IC/PBS who are treatment naïve. Amitriptyline, however, may be beneficial in persons who can achieve a daily dose of 50 mg or greater, although this subgroup comparison was not specified in advance.

Introduction

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a syndrome presenting with symptoms of urinary urgency, frequency, and bladder -associated pain. Despite multiple clinical trials evaluating oral and intravesical therapies, the treatment of IC/PBS remains suboptimal. Amitriptyline is one oral medication commonly used to treat patients with IC/PBS.¹ The evidence to support the use of this drug is modest, and includes a single small randomized clinical trial and a case report, both of which suggest efficacy.^{2,3}

A number of studies have documented the beneficial effects of amitriptyline in different chronic pain syndromes. Amitriptyline possesses at least three major pharmacologic actions: it has central and peripheral anticholinergic actions, blocks the active transport system in the presynaptic nerve ending that is responsible for the re-uptake of serotonin and noradrenaline, and is a sedative, an action that is presumably centrally based but perhaps also related to antihistaminic properties which may explain potential benefits in patients with IC/PBS.^{2–11} We report the results of a multi-center, randomized, placebo-controlled clinical trial of amitriptyline, in combination with an Educational and Behavioral Modification Program (EBMP) in “treatment-naïve” subjects with IC/PBS.

Methods

Study design

Men and women at least 18 years of age, who reported both bladder pain/discomfort and urinary frequency of 3 or greater on separate 0–10 Likert scales over the previous 4 weeks at each of two baseline screening visits were eligible for the study. Current symptoms had to have been present for a minimum of six weeks, and subjects were required to be “treatment-naïve,” defined as having no prior significant treatment for IC/PBS. Additional exclusion and deferral criteria are shown in Table 1.

All eligible participants received an EBMP and were randomized in a 1:1 ratio to either amitriptyline or matching placebo (Figure 1). The EBMP was aimed at increasing understanding of the bladder and voiding techniques to manage stress and pain symptoms, management of fluid intake, bladder training and urge suppression, and avoidance of food and beverages thought to exacerbate IC/PBS symptoms. It was not based on any standardized protocol recognizing the paucity of such studies in the literature.^{12–16} The dose of study drug was increased on a weekly basis from 10 mg, to 25 mg, and then to 50 mg after a call from the research coordinator confirming tolerability. At the end of three weeks, participants were evaluated and then increased to 75 mg per day, subject to maximal dose tolerability, and maintained at the highest tolerable dose until the primary outcome assessment 12 weeks after randomization (Figure 1).

Study Outcome Measures

The primary efficacy analysis was based on intention-to-treat, comparing the proportion of responders between treatment arms on a patient-reported Global Response Assessment (GRA), recorded at 12 weeks, or study withdrawal. The 7-point GRA queries “As compared to when you started the current study, how would you rate your overall symptoms now?” The seven response options are “markedly worse”, “moderately worse”, “slightly worse”, “the same”, “slightly improved”, “moderately improved”, and “markedly improved.” Participants who indicated that they were “markedly” or “moderately” improved were considered responders. Subjects who withdrew from the study for any reason, and did not provide data on the primary outcome, were considered treatment failures, and included in the denominator for calculation of response rates.

A number of secondary outcomes were also assessed including pain, urgency, and frequency on 0–10 point Likert scales, a 24-hour voiding diary, the O’Leary-Sant IC Symptom and Problem Indices,¹⁷ the University of Wisconsin IC Symptom Inventory,¹⁸ the Health Status Questionnaire for Quality of Life (SF-36¹⁹), the Hospital Anxiety and Depression Scale (HADS²⁰), and the Female Sexual Function Index (FSFI²¹) or International Index of Erectile Function (IIEF²²). Adverse events, regardless of their presumed relationship to study treatment, were summarized by body system, as derived from the Common Toxicity Criteria (CTC) and classified/graded on a scale from one (“mild”) to three (“severe”), according to MedDRA v6.0 criteria.²³

Adherence to EBMP at six weeks was assessed in four categories: i) symptom management, ii) fluid management, iii) diet modification, and iv) bladder training. For each of these four EBMP categories, adherence was defined as the overall percentage of participants who reported adhering to each component of the EBMP at each phone contact or clinic visit. Adherence to study drug was calculated by taking the average of the percentage of pills reported taken at both six weeks and 12 weeks. To ensure balance across treatment arms, a stratified randomization was used within each of the ten (10) clinical sites. The target sample size was chosen to detect a difference in response rates between 40% and 60% for the primary analysis comparing GRA response rates. Assuming 80% power to detect the specified difference (20%) between groups at a two-sided $\alpha = 0.05$ level of significance using Fisher’s exact test, a total of 270 participants (135 per arm) was targeted. This sample size included adjustments for participant withdrawals, clustering within clinical sites, and interim monitoring.

Statistical analysis

Baseline demographic characteristics, and primary and secondary symptom measures, were summarized and compared between treatment groups to assess balance of randomization using appropriate exact non-parametric tests. Time to study withdrawal was compared between treatments using the log-rank test. Frequencies of each grade of adverse event in each body system were calculated. Comparisons of adverse event rates, classifying each patient according to worst grade reported both across and within body systems, were performed using an exact Kruskal-Wallis test.

The primary analysis compared GRA response rates using the exact conditional test (ECT) version of the Mantel-Haenszel test to control for clustering by clinical center.²⁴ The pooled rate difference and 95% confidence interval across clinical centers were calculated using the “metan” routine within Stata v 10 (College Station, TX, 2008).²⁵ GRA response rates were also examined within subgroups defined by the dose achieved while on study. For secondary efficacy outcomes, changes from baseline to 12 weeks were calculated for those subjects with data at both time points, not representing intention to treat analyses.

Results

Subjects were recruited into the study from February 2005 to October 2007. Among the 319 subjects who agreed to participate in the study, 271 were randomized, and 231 (85%) completed 12 weeks of follow-up (Figure 2). Twenty-three subjects (17%) withdrew from the amitriptyline group and 17 (13%) from the placebo group ($p=0.26$).

Study participants were predominantly female (83%) and white (74%), with a median age of 38 years (Table 2). Overall, baseline symptoms were moderate to severe. Treatment groups were comparable across all baseline measures evaluated.

For the primary outcome, there was no statistically significant difference between treatment groups: 55% (74/135) of the subjects assigned to amitriptyline plus EBMP reported they were markedly or moderately improved compared to 45% (61/136) of subjects assigned to placebo plus EBMP ($p=0.12$, Table 3). Consistent with intention-to-treat analytic strategies, participants who did not provide data at 12 weeks, including 24 (18%) subjects on amitriptyline and 17 (13%) subjects on placebo, were considered treatment non-responders.

Table 3 also summarizes changes in selected symptom outcomes from baseline to 12 weeks by treatment arm for those with available data at those time points, and provides confidence intervals for these differences. Results for these secondary efficacy endpoints were qualitatively similar, with all outcomes demonstrating greater improvement for amitriptyline than placebo. Additional secondary outcomes related to quality of life and sexual function demonstrated no differences between the two arms (data not shown).

Adherence to protocol treatment, both to study drug and EBMP, which all subjects received, was also evaluated. Among the 241 subjects evaluable for EBMP adherence, adherence at six weeks was 75% (181/241) for symptom management, 83% (201/241) for fluid management, 82% (196/240) for diet modification, and 71% (172/241) for bladder training. For the drug therapies, 64 (47%) attained and remained on the highest dose on the amitriptyline arm, as compared to 105 (77%) on the placebo arm ($p<0.001$). Subjects were classified into three groups based on the maximum dose obtained at six weeks and 12 weeks (Table 4). Only 46% of subjects on amitriptyline achieved a dose of at least 50 mg per day and maintained it throughout the 12 weeks of follow-up, whereas 72% of subjects on placebo maintained this equivalent dose. Furthermore, a number of subjects in both treatment arms (20% for amitriptyline, 15% for placebo) who achieved a dose of at least 50 mg per day by six weeks decreased their dose during the second six weeks of follow-up.

We also evaluated GRA response with respect to achieved dose of drug, although we recognize that there may be numerous biases in such an analysis. The overall GRA response rate was approximately 57% for adherers in any of the four EBMP categories, whereas it was lower among non-adherers. This neared statistical significance for diet modification, which demonstrated only a 41% response rate among non-adherers ($p=0.051$). In the subgroup of subjects ($n=160$) who were able to achieve and maintain a daily dose of study drug of at least 50 mg per day, the responder rate was significantly greater in the amitriptyline group (77%) compared to (53%) placebo ($p<0.001$).

Overall, 80% (217/271) of participants reported at least one adverse event (AE), classified primarily as mild (32%, 87/271) or moderate (42%, 114/271). The overall AE rate was 88% on the amitriptyline arm and 72% on the placebo arm ($p=0.0013$). (Table 5) Within systems, constitutional symptoms such as fatigue ($p=0.018$), gastrointestinal problems ($p=0.0012$), neurological symptoms including dizziness ($p=0.030$), and renal/genitourinary problems ($p=0.025$) were significantly more common on the amitriptyline arm. Five serious adverse events (SAEs) were reported; none were classified as related to the study drug.

Discussion

This is the first large scale multi-center randomized clinical trial of amitriptyline in IC/PBS. The primary intention-to-treat analysis of overall response rates demonstrated no statistically significant difference between amitriptyline (55%) and placebo (45%) for overall response rates in relatively treatment naïve patients managed with an aggressive EBMP. Although several secondary outcomes suggested a beneficial effect of amitriptyline, these findings are possibly subject to bias due to study withdrawals. Participants who were able to maintain a dose of at least 50 mg per day of amitriptyline reported a significantly higher response rate (77%) compared to an equivalent dose of placebo (53%). However, adherence to a higher dose on either treatment was also associated with higher response rates; as was adherence to the EBMP, and these do not represent randomized comparisons. Although a higher rate of adverse events was experienced by subjects assigned to amitriptyline, most were mild or moderate.

Ours is the first large-scale clinical trial focused on treatment naïve subjects. Most prior trials in IC/PBS have evaluated treatment refractory subjects. It is possible that treatment refractory patients have a more severe form of the disease. The widespread use of amitriptyline as a first-line therapy in IC/PBS, underlines the importance of its assessment in a group of subjects who are treatment naïve.

Another unique aspect of this study was the EBMP received by both treatment groups early in follow-up. While the design of the study did not permit assessment of the effect of this program as compared to a control, it was implemented because investigators strongly believed that at least minimum care should be provided to participants of a trial involving a placebo, especially for newly diagnosed subjects. It is important to note that the observed overall response rate of 45% for subjects randomized to placebo is higher than the majority of previously published studies on IC/PBS. This may represent not only a possible placebo effect in the “treatment naïve” patient population, but also possible benefits of the EBMP.

Although amitriptyline is commonly used to treat patients with IC/PBS, the evidence upon which this practice is based is limited. It has been two decades since the first report of treating IC patients with this drug was reported.³ Among 25 patients with IC who had failed hydrodistention and intravesical dimethylsulfoxide (DMSO), a daily dose of amitriptyline beginning with 25 mg and increased to 75 mg over a 3-week period, 8 of the 20 patients who tolerated this dose reported a complete resolution of symptoms. Improvements in pain, daytime frequency, urgency, and dyspareunia were also noted.

Despite these encouraging results, it was 15 years later that the first randomized, placebo-controlled clinical trial was reported.² A total of 50 patients (88% women) who met the NIDDK symptom criteria for IC were randomized to either amitriptyline (up to 100 mg nightly) or placebo and followed for four months. Reduction in the O’Leary-Sant Symptom and Problem Index score was significantly greater in the amitriptyline group, with mouth dryness the most frequent side effect. In our study, although side effects were primarily mild to moderate, less than 50% of subjects randomized to amitriptyline were able to achieve and maintain a dose of at least 50mg per day through the treatment period. Despite our inability to show a beneficial effect of the drug in our primary intention-to-treat analysis, we did observe significant improvement in the GRA response rate in subjects who maintained higher doses. Whether this observation accurately reflects the true efficacy of this drug or is a result of bias cannot be determined.

Conclusions

Amitriptyline as compared to placebo, both provided in combination with a program of EBMP did not overall demonstrate statistically significantly improved symptoms as determined by

the GRA, in a group of predominantly female and relatively treatment-naïve patients with IC/PBS. The side-effect profile of amitriptyline was acceptable although adherence to higher doses was fairly low. Nevertheless, in a subgroup of subjects who achieved a dose of at least 50 mg per day, there was a suggestion that the drug was more effective than placebo.

Key of Definitions for Abbreviations

AE	adverse event
EBMP	Education and Behavioral Modification Program
GRA	global response assessment
IC	Interstitial Cystitis
PBS	Painful Bladder Syndrome
SAEs	serious adverse events

References

1. Rovner E, Probert KJ, Brensing C, et al. Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. *Urology* 2000;56:940. [PubMed: 11113737]
2. van Ophoven A, Pokupic S, Heinecke A, et al. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol* 2004;172:533. [PubMed: 15247722]
3. Hanno PM, Buehler J, Wein AJ. Use of amitriptyline in the treatment of interstitial cystitis. *J Urol* 1989;141:846. [PubMed: 2926877]
4. Baldessarini RJ. Drug and the treatment of Psychiatric disorders. Goodman and Gilman's the pharmacological basis of therapeutics 1985:387.
5. Barrett, DM.; Wein, AJ. Adult and Pediatric Urology 2. Vol. 1. Anonymous Year Book Medical Publishers Inc; 1987. Voiding dysfunction: Diagnosis, classification, and management; p. 863
6. Hanno PM. Amitriptyline in the treatment of interstitial cystitis. *Urol Clin North Am* 1994;21:89. [PubMed: 8284851]
7. Hanno PM, Wein AJ. Medical treatment of interstitial cystitis (other than Rimso-50/Elmiron). *Urology* 1987;29:22. [PubMed: 2436377]
8. Kirkemo AK, Miles BJ, Peters JM. Use of amitriptyline in interstitial cystitis (abstract). *J Urol* 1990;143:279A.
9. Pranikoff K, Constantino G. The use of amitriptyline in patients with urinary frequency and pain. *Urology* 1998;51:179. [PubMed: 9610578]
10. Renshaw DC. Desipramine for interstitial cystitis. *JAMA* 1988;260:341. [PubMed: 3379739]
11. van Ophoven A, Hertle L. Long-term results of amitriptyline treatment for interstitial cystitis. *J Urol* 2005;174:1837. [PubMed: 16217303]
12. Fantl, JA.; Newman, DK.; Colling, J., et al. Clinical Practice Guideline No. 2, 1996 Update. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 96-0682; Mar. 1996 Urinary Incontinence in Adults: Acute and Chronic Management.
13. Fantl JA, Wyman JF, McClish DK, et al. Efficacy of bladder training in older women with urinary incontinence. *JAMA* 1991;265:609. [PubMed: 1987410]
14. Jeffcoate TN, Francis WJ. Urgency incontinence in the female. *Am J Obstet Gynecol* 1966;94:604. [PubMed: 5906586]
15. Parsons CL, Koprowski PF. Interstitial cystitis: successful management by increasing urinary voiding intervals. *Urology* 1991;37:207. [PubMed: 2000675]
16. Jarvis GJ. The management of urinary incontinence due to primary vesical sensory urgency by bladder drill. *Br J Urol* 1982;54:374. [PubMed: 7116103]

17. O'Leary MP, Sant GR, Fowler FJ Jr, et al. The interstitial cystitis symptom index and problem index. *Urology* 1997;49:58. [PubMed: 9146003]
18. Goin JE, Olaleye D, Peters KM, et al. Psychometric analysis of the University of Wisconsin Interstitial Cystitis Scale: implications for use in randomized clinical trials. *J Urol* 1998;159:1085. [PubMed: 9474236]
19. Ware, JE.; Kosinski, M.; Dewey, JE. How to Score Version Two of the SF-36 Health Survey. 2000.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361. [PubMed: 6880820]
21. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;26:191. [PubMed: 10782451]
22. Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822. [PubMed: 9187685]
23. National Cancer Institute. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. DCTD, NCI, NIH, DHHS; Mar 31. 2003 (<http://ctep.cancer.gov/protocolDevelopment/electronicapplications/docs/ctcae3.pdf>), Publish Date: August 9, 2006
24. Mehta, C.; Patel, N. Proc-StatXact For SAS(r) Users: Statistical software for Exact Nonparametric Inference. 1997.
25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557. [PubMed: 12958120]

Appendix

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Figure 1.
Study Design: Interventions and Study Drug Dose Escalation Schedule

Figure 2.

Consort Diagram for Flow of Subjects through Study Phases, by Treatment Arm

Table 1

Exclusion and Deferral Criteria

Medical History:	cardiac arrhythmia, other cardiac conduction disturbance, and/or significant cardiovascular disease; liver disease; narrow angle glaucoma; neurologic disease affecting bladder function, bladder or urethral cancer;
Current Medical Conditions:	severe debilitating or urgent concurrent medical condition; bladder, urethral, or ureteral calculi; evidence of urethritis; presence of urethral diverticulum; residual urine >100cc; uninvestigated hematuria ≥ 5 cells/hpf or pyuria; presence of significant pelvic pathology or abnormalities on exam or imaging, including prolapse beyond the hymenal ring or pelvic mass; positive urine culture or a clinical UTI during past 6 weeks; active genital herpes within the prior 12 weeks; (Men Only): evidence of chronic bacterial prostatitis; unevaluated suspicious prostate exam or history of prostate cancer; (Women Only): pregnant or breastfeeding; IC/PBS symptoms present only during menses; active vaginitis; recent vaginal delivery or C-section
Treatment History:	amitriptyline or other tricyclic antidepressant, hydroxyzine or other antihistamine, pentosanpolysulfate (>4 weeks), DMSO or any other intravesical therapy (>1 treatment), biofeedback, or pelvic floor physical therapy for IC/PBS symptoms; cyclophosphamide;
Current Treatment at Baseline Visit:	tricyclic, selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), or monoamine oxidase (MAO) inhibitor antidepressant; anticoagulant agents;
Procedure History:	pelvic radiation; augmentation cystoplasty, cystectomy, or cystolysis, neurectomy (hypogastric nerve ablation), or implanted nerve stimulator; (Men Only): History of TURP or any other similar prostate surgery.

Table 2

Baseline Characteristics by Treatment Group*

	Amitriptyline	Placebo
Number of Subjects Randomized [†]	135	136
# (%) Female	115 (85%)	111 (82%)
Mean ± s.d. Age	38.0 ± 13.8	39.9 ± 14.0
Race		
# (%) White/Caucasian	96 (71%)	104 (77%)
# (%) Black/African-American	18 (13%)	15 (11%)
# (%) Multi-race, Asian, Other	21 (16%)	17 (13%)
# (%) Ever Diagnosed with IC/PBS	62 (46%)	75 (55%)
Mean ± s.d. Years Since Diagnosis (if applicable)	1.4 ± 4.0	1.2 ± 3.0
Mean ± s.d. Years Since Onset of Initial Symptoms	6.3 ± 9.0	6.5 ± 9.9
Mean ± s.d. Pain Score (0–10)	5.8 ± 1.5	6.0 ± 1.8
Mean ± s.d. Urgency Score (0–10)	6.4 ± 1.8	6.4 ± 1.8
Mean ± s.d. Frequency Score (0–10)	6.8 ± 1.7	6.8 ± 1.8
Mean ± s.d. 24 -hour Voiding Frequency	13.9 ± 5.2	13.7 ± 5.7
Mean ± s.d. Nighttime Voiding Frequency	2.4 ± 1.8	3.0 ± 2.8
Mean ± s.d. IC Symptom Index	12.2 ± 3.1	12.0 ± 3.6
Mean ± s.d. IC Problem Index	11.1 ± 2.8	11.2 ± 3.0
Mean ± s.d. Wisconsin Symptom Survey	25.9 ± 8.6	26.7 ± 8.3

* For the symptom scores shown, the measurements at the two baseline visits were averaged to give the overall baseline score.

[†] Approximately nine subjects on each arm were missing data on voiding frequency, and eight subjects on each arm were missing data on years since symptoms began. At most one subject was missing data for all other measures.

Table 3**Primary and Selected Secondary Symptom Outcomes**

	Amitriptyline	Placebo	Difference (95% Confidence Interval)
Number of Subjects Randomized	135	136	271
Primary Endpoint: Response Rate at 12 weeks*	74 (55%)	61 (45%)	10% (−2%, 22%)
Secondary Endpoints: Change from Baseline to 12 weeks			
Number of Subjects Analyzed [†]	111	119	230
Pain Score	−2.6 ± 2.5	−2.3 ± 2.4	−0.4 (−1.0, 0.3)
Urgency	−3.0 ± 2.5	−2.5 ± 2.6	−0.5 (−1.2, 0.1)
Frequency	−3.5 ± 2.3	−2.6 ± 2.5	−0.9 (−1.5, −0.3)
24-hour Voiding Frequency	−4.4 ± 5.4	−2.0 ± 3.9	−2.4 (−3.7, −1.0)
Night-time Voiding Frequency	−0.9 ± 2.4	−0.9 ± 2.4	−0.01 (−0.7, 0.7)
IC Symptom Index	−4.8 ± 3.7	−3.3 ± 3.9	−1.5 (−2.5, −0.5)
IC Problem Index	−5.2 ± 3.9	−3.9 ± 4.0	−1.2 (−2.3, −0.2)
University of Wisconsin Symptom Survey	−13.1 ± 10.2	−9.3 ± 9.3	−3.8 (−6.3, −1.3)

* For the primary response endpoint, responders are defined as those reporting “Markedly Improved” or “Moderately Improved” on the GRA. Patients for whom the GRA value is missing are considered non-responders and included in the denominator for the assessment of response rates using an intention -to-treat analysis.

[†] The analysis of secondary endpoints was not per intention -to-treat due to withdrawals and missing data. The sample sizes for the voiding frequency measures were approximately 92 for amitriptyline and 95 for placebo. At most two subjects were missing data for all other measures.

Table 4**Response Rates at 12 Weeks by Measures of Adherence to Therapy**

	Amitriptyline	Placebo
Number of Subjects Randomized	135	136
Subjects Evaluable for Adherence at 12 weeks	112 (83%)	119 (88%)
Highest Dosage Achieved at Six and 12 Weeks:		
≥ 50 mg Achieved and Maintained at 12 Weeks	62 (46%)	98 (72%)
≥ 50 mg Achieved But Reduced to < 50 mg by 12 Weeks	27 (20%)	20 (15%)
≥ 50 mg Not Achieved	46 (34%)	18 (13%)
Response Rates at 12 Weeks:		
≥ 50 mg Achieved and Maintained at 12 Weeks	48/62 (77%)	52/98 (53%)
≥ 50 mg Achieved But Reduced to < 50 mg by 12 Weeks	11/27 (41%)	3/20 (15%)
≥ 50 mg Not Achieved	15/46 (33%)	6/18 (33%)

Table 5

Significant, Cumulative Adverse Events by Body System and Treatment Group

Body System	Amitriptyline	Placebo
Number of Subjects Randomized	135	136
Highest grade of adverse event	119 (88%)	98 (72%)
Constitutional Symptoms (primarily fatigue, malaise)	61 (45%)	42 (31%)
Dermatology/Skin	9 (7%)	10 (7%)
Gastrointestinal (primarily dry mouth, constipation)	57 (42%)	32 (24%)
Infection, Fever	9 (7%)	14 (10%)
Musculoskeletal	7 (5%)	3 (2%)
Neurologic (primarily dizziness, somnolence)	45 (33%)	29 (21%)
Ocular, Visual	3 (2%)	7 (5%)
Pain (primarily headache)	43 (32%)	48 (35%)
Pulmonary	15 (11%)	13 (10%)
Renal/Genitourinary	22 (16%)	10 (7%)