Hosp Pharm 2014;49(9):809–810

www.hospital-pharmacy.com
doi: 10.1310/hpj4909-809

Off-Label Drug Uses

Amitriptyline: Interstitial Cystitis (Painful Bladder Syndrome)

Joyce A. Generali, RPh, MS, FASHP (Editor),[*] and Dennis J. Cada, PharmD, FASHP, FASCP[†]

This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts,* a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Interstitial cystitis/bladder pain syndrome is a chronic condition characterized by an unpleasant suprapubic sensation of the urinary bladder (pain, pressure, discomfort) accompanied by lower urinary tract symptoms of more than 6 weeks' duration that are not due to infection or other causes.[1] Interstitial cystitis/bladder pain syndrome is more prevalent in women but can affect men as well. Etiology is poorly defined and therefore hampers classification and treatment; current treatments are not uniformly effective.[1-3] Mast cell degranulation within the bladder wall, possibly related to histamine release, has been proposed as a contributing factor in the inflammatory process.[3] Amitriptyline acts via the blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and norepinephrine, and blockade of histamine H_1 receptors.[4]

PATIENT POPULATION

Adults with signs and symptoms of interstitial cystitis/bladder pain syndrome.

DOSAGE AND DURATION

Ten to 25 mg daily titrated weekly over several weeks, to a target dose of 75 to 100 mg as tolerated for up to 23 months.

RESULTS

Amitriptyline in the management of interstitial cystitis/bladder pain syndrome has been studied in a limited number of controlled and noncontrolled trials (enrolling more than 200 patients) demonstrating efficacy rates of 50% to 66%, with greater efficacy rates (up to 77%) at sustained higher doses (at least 50 mg daily).[5-7] Tolerance at higher doses is unlikely. National guidelines recommend oral amitriptyline as a second-line treatment option that may provide benefit in a subset of patients; however, adverse events potentially affecting quality of life (eg, drowsiness, nausea) are common.

Guidelines

American Urological Association

American Urological Association (AUA) guidelines on the diagnosis and management of interstitial cystitis/bladder pain syndrome present a tiered approach to treatment based on expert opinion and an evidence-based review of published data. First-line treatment, which includes education regarding normal bladder function and self-care practices/behavioral modifications that can improve symptoms, is recommended for all patients. Second-line therapy includes multimodal pain management, physical therapy, and oral (amitriptyline, cimetidine, hydroxyzine, or pentosan hydrochloride) or intravesical (dimethylsulfoxide, heparin, or lidocaine) agents that have demonstrated limited efficacy in a subset of patients and an uncertain risk-benefit ratio. Evidence for amitriptyline includes a single randomized controlled trial and 2 observational studies demonstrating benefit superior to placebo but also the potential for adverse effects that compromise quality of life (eg, sedation, drowsiness, nausea). Based on its potential for

[*]Editor-in-Chief, *Hospital Pharmacy*, and Clinical Professor, Emeritus, Department of Pharmacy Practice, University of Kansas, School of Pharmacy, Kansas City/Lawrence, Kansas, e-mail: jgeneral@ku.edu; [†]Founder and Contributing Editor, *The Formulary*, and Editor, *Off-Label Drug Facts*, e-mail: Dennis.Cada@wolterskluwer.com.

benefit in a small subset of patients, amitriptyline was assigned an option strength recommendation. Third-line treatment includes bladder distention or Hunner lesion treatment. Sacral/pudendal nerve stimulation is recommended as fourth-line management. Oral cyclosporine or botulinum toxin injections administered by an experienced clinician are recommended as fifth-line management. Surgical intervention (eg, substitution cystoplasty, urinary diversion) is suggested as sixth-line therapy.[1]

Controlled trial

In a double-blind, placebo-controlled, multicenter trial published after the AUA guidelines were issued, 271 therapy-naive adult patients with interstitial cystitis/bladder pain syndrome were randomized to receive placebo or amitriptyline for 12 weeks. Amitriptyline was increased at weekly intervals from 10 mg to 25 mg, then to 50 mg daily. At the end of 3 weeks, patients were evaluated and, based on tolerability, the dose was increased to a maximum of 75 mg daily; this dose was maintained as tolerated until the 12-week assessment. All patients participated in an Educational and Behavioral Modification Program (EBMP). The primary outcome was the proportion of responders between treatment arms based on a 7-item global response assessment (GRA) scale that ranks symptoms from markedly worse to markedly improved. Responders were defined as patients indicating moderately or markedly improved symptoms; noncompleters were considered treatment failures. Secondary outcomes included urinary pain, urgency, and frequency measured via an 11-point Likert scale, a 24-hour voiding diary, and a variety of symptom scales. A total of 235 subjects completed the 12-week trial, with 23 (17%) and 17 (13%) withdrawing from the amitriptyline and placebo groups, respectively. Mean ages were 38 years and 39.9 years, respectively. Response rates at 12 weeks were not significantly different between the amitriptyline and placebo groups (55% vs 45%, respectively; $P = .12$); however, in the subset of patients achieving a dose of at least 50 mg daily, a significantly higher response rate was observed in the amitriptyline group (66% vs 47% with placebo; $P = .01$). It should be noted that of the patients who achieved a dose of at least 50 mg daily by 6 weeks, approximately 20% in the amitriptyline group and 15% in the placebo group decreased their dose in the second 6-week period. In the subset of patients who achieved and maintained the higher dose for the remainder of the study, response rates were higher for both groups and were significantly higher in the amitriptyline group compared with placebo (77% vs 53%; $P < .001$). In addition, overall GRA response rates were higher in patients who adhered to the EBMP compared with nonadherers.[5]

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

In reviewed data, adverse events were very common (affecting up to 80% of patients) and included sedation, drowsiness, dizziness, and nausea.[1,5-7]

THERAPY CONSIDERATIONS

Amitriptyline in the management of interstitial cystitis/bladder pain syndrome has been studied in a limited number of controlled and noncontrolled trials demonstrating efficacy rates of 50% to 66%, with higher efficacy rates (up to 77%) at sustained higher doses (at least 50 mg daily). Tolerance at higher doses is unlikely. AUA guidelines recommend oral amitriptyline as a second-line treatment option that may provide benefit in a subset of patients; however, adverse events potentially affecting quality of life (eg, drowsiness, nausea) are common.

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