# Clinical Efficacy and Tolerability of the Nicotinic Channel Modulator Dexmecamylamine in Subjects with Overactive Bladder

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**Purpose:** We evaluated the efficacy and tolerability of the nicotinic channel modulator dexmecamylamine for overactive bladder.

**Materials and Methods:** This was a randomized, double-blind, placebo controlled trial in 768 randomized subjects. Those with at least a 6-month history of overactive bladder were randomized to 0.5, 1 or 2 mg dexmecamylamine or placebo in a ratio of 1:1:1:2, respectively. Subjects completed a 3-day diary before each visit associated with the 12-week treatment period. They were required to have 8 or more micturitions per day and 3 or more urinary urge incontinent episodes per day if overactive bladder wet at the end of a placebo run-in period. Co-primary end points for the study included a change from baseline 1) in micturition frequency per 24 hours at week 12 and 2) in urge urinary incontinence episodes per 24 hours at week 12. Secondary end points were voided volume, nocturia episodes, OABq (Overactive Bladder Questionnaire) and urgency questionnaire.

**Results:** Dexmecamylamine (2 mg) produced a statistically significant decrease in micturition frequency ($p = 0.03$) but did not produce a statistically significant decrease in urge incontinence (wet) episodes ($p = 0.38$). Secondary end points, including volume voided in the 1 mg group only, CGI-I (Clinical Global Impression of Improvement), visual analog scale urgency impact, intensity and severity, were statistically significant at week 12 for the 2 mg dose. Dexmecamylamine was well tolerated in this subject population with a low incidence of discontinuations due to adverse effects. Constipation, dry mouth and urinary tract infection showed a dose dependent increase in frequency.

**Conclusions:** Dexmecamylamine does not appear to offer an enhanced therapeutic profile for the treatment of overactive bladder relative to current therapies.

**Key Words:** urinary bladder, overactive; urinary incontinence, urge; receptors, nicotinic; drug tolerance; treatment outcome

**Abbreviations and Acronyms**

AE = adverse event

DEX = dexmecamylamine

OAB = overactive bladder

OAB-V8 = OAB 8-Question Awareness Tool

PK = pharmacokinetic

PPBC = Patient Perception of Bladder Condition

UUI = urinary urge incontinence

VAS = visual analog scale

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Overactive bladder is a syndrome characterized by symptoms of "urgency with or without urge incontinence, usually with frequency and nocturia" with urgency defined as "the complaint of a sudden compelling desire to pass urine which is difficult to defer."[1] The prevalence of OAB increases with age and is difficult to determine due to the attached stigma, which may prevent patients from seeking medical care. OAB is estimated to affect 17% of the adult population in the United States and it is ranked among the 10 most common medical conditions.[2–4]

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DEX is a selective nicotinic acetylcholine receptor channel modulator.[5,6] DEX is a use dependent potent inhibitor of the α3 nicotinic receptor subtype (eg α3β2 and α3β4).[5,6] Such receptors are expressed in urothelium and regulate bladder smooth muscle contraction and urinary urge in the rat.[7] In an anesthetized rat model intravesical instillation of DEX at concentrations of 1 and 10 μM produced meaningful decrements in bladder contractility and micturition frequency according to manufacturer data. Such concentrations also increased bladder capacity while not affecting the amplitude of bladder contractions. DEX is almost completely absorbed from the gastrointestinal tract and greater than 90% is excreted unchanged in urine.[8] The exposure differential results in the ability of DEX to target local nicotinic receptors in urothelium that affect bladder contraction frequency while limiting systemic side effects. Consequently the potential for DEX to treat OAB through its action on nicotinic acetylcholine receptors in the bladder urothelium warranted further investigation.

DEX is the S-(+)-enantiomer of mecamylamine, an agent previously marketed as Inversine® to treat hypertension. More recently DEX was evaluated as adjunctive therapy for major depressive disorder in a large international phase 3 depression program.[9] In the depression studies DEX had no apparent effect on mood or behavior and scores on C-SSRS (Columbia Suicide Severity Rating Scale) did not differ between active treatment and placebo. Although DEX failed to demonstrate efficacy for treating depression, the compound proved to be well tolerated at doses up to and including the top dose evaluated (4 mg twice daily).[9] Prior experience with Inversine and DEX suggested that doses greater than 2 mg twice daily are associated with unacceptably high rates of constipation in an OAB population.

## MATERIALS AND METHODS

### Study Design

This was a randomized, double-blind, placebo controlled, parallel group, fixed dose study (ClinicalTrials.gov No. NCT01868516). A sufficient number of subjects were screened and completed a 2-week run-in period so that approximately 750 were randomized into the double-blind treatment period of the study. There were 3 DEX arms (0.5, 1 and 2 mg, respectively) with 150 subjects planned per arm and 1 placebo arm with 300. The protocol, informed consent form and investigator brochure were provided to the investigators and received institutional review board approval before the first subject was enrolled at an investigational site.

The 4 study phases comprised a screening period including a 2-week washout for subjects on OAB medications, a single blind, 2-week placebo run-in period, a 12-week double-blind treatment period and a 2-week followup period (fig. 1). The study consisted of 7 visits.

Enrollment was designed to ensure that at least 75% of study subjects exhibited UUI during the run-in period. This represented the OAB wet subpopulation. However, randomization was not stratified according to OAB type. The proportion of screened OAB dry subjects was limited early in the study to ensure the required wet-to-dry ratio. The primary study objective was to assess the efficacy of DEX vs placebo in subjects with OAB as defined by the co-primary end points, including a change from baseline in 1) micturition frequency per 24 hours to week 12 and 2) UUI episodes per 24 hours to week 12. This analysis was based on the subset of subjects who were classified as OAB wet at baseline. The number of subjects needed was based on the ability to detect a difference of 1.0 point for both co-primary end points with 91% power using a 2-sided test with a significance level of 5% ($p < 0.05$) and assuming a SD of 2.5 at both end points with normally distributed errors and a dropout rate of approximately 15%.

### Patient Eligibility

Subjects were required to have a prior documented medical history of OAB for 6 months or more, a score of greater than 15 on the OAB-V8 screening questionnaire[10] to indicate sufficient OAB symptom bother, and an average of 8 or more micturitions per 24 hours and no UUI episodes in the 3-day run-in diary (dry subjects), or 3 or greater UUI episodes and an average of 8 or more micturitions per 24 hours in the 3-day run-in diary (wet subjects). Additional inclusion criteria were age 18 years or greater, body mass index 38 kg/m$^2$ or less, ability to ambulate and accurately complete a daily diary, and willingness to discontinue any current OAB medications. Subjects were excluded from randomization if they had a diagnosis of a neurological disease affecting bladder function, predominantly nonurge incontinence, insensate or overflow incontinence, post-void residual volume greater than 150 ml, males with benign prostatic hyperplasia, or prostate specific antigen 4 ng/ml or greater, history or presence of significant urinary pathology such as a history of malignancy, cystitis or recurrent urinary tract infections, polyuria (greater than 3,000 ml per day), renal insufficiency, heart failure, intravesical

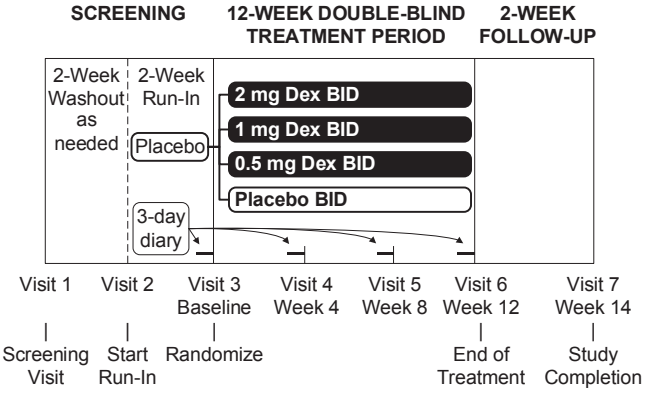


**Figure 1.** Study design. *BID,* twice daily.