

## SEASONAL DIFFERENCES IN PATTERNS OF IMPROVEMENT IN URINARY SYMPTOMS FOR JAPANESE OAB PATIENTS TREATED BY THE OXYBUTYNYN.

### Hypothesis / Aims of Study

Overactive bladder syndrome (OAB) is a symptom complex with urgency and frequency, with or without urge incontinence. It is often said that the urinary symptoms of OAB are influenced by seasons. In other words, the symptoms worsen in colder seasons and improve in warmer seasons. Therefore, efficacy of an OAB treatment may vary according to seasons but such clinical research has not been reported yet. We explored seasonal differences in the efficacy of the oxybutynin for Japanese OAB patients based on the clinical data from the long term dosing study of the oxybutynin transdermal patch. Oxybutynin is a widely used dual blocker of muscarinic acetylcholine receptors and calcium channels for the treatment of OAB.

### Study design, materials and methods

The study was a multi-center, open-label and single dose level study to examine safety, tolerability and efficacy of 52 weeks repeated dosing with the oxybutynin transdermal patch for Japanese OAB patients with pure urge or mixed urinary incontinence. Eligibility criteria included: 1) one or more episodes of urge incontinence per day, 2) dominance (>50%) of urge incontinence, and 3) 8 or more episodes of urination per day. After 2 weeks baseline washout period, during which the patient received placebo patches, the patient applied a 39 cm<sup>2</sup> oxybutynin patch every 3 to 4 days (2 patches/week) for 52 weeks. Efficacy variables were incontinence frequency per week and urination frequency per day. The planned number of patients was 330.

In order to see seasonal differences in the efficacy of the drug, these variables and their changes from baseline were summarized over the baseline and treatment periods in 3 patient subgroups divided by their month of enrolment, 1) February or March, 2) April or May, 3) June, July or August. Repeated-measures analysis of variance was applied to test the seasonal differences in the pattern of improvement in each urinary symptom with following covariates, baseline value of each symptom, subgroup of months of enrolment, sex, age, measurement time, and confounding terms of 'subgroup of enrolled months' and 'measurement time'. All statistical analyses were conducted using the FAS (full-analysis-set) population.

### Results

A total of 366 patients (40 male and 326 female) with an average age of 59.2 years were enrolled in the study from February 2004 to August 2004. Average incontinence frequencies in the 3 subgroups were 23.5 for Feb.-Mar. (n=124), 23.3 for Apr.-May (n=73) and 19.7 for Jun.-Aug. (n=117). Average urinary frequencies were 11.4 for Feb.-Mar., 10.7 for Apr.-May and 10.9 for Jun.-Aug. Both baseline frequencies were largest in the subgroup enrolled in winter months. On the other hand, the patterns of improvement in urinary symptoms were different among the groups. The changes from baseline values of the urinary symptoms from 12th to 28th weeks were larger in the subgroups enrolled in winter or spring months than those in the subgroup enrolled in summer months, but they were very similar after one year of the treatment. These results were suited to the change of seasons because the seasons from 12th to 28th weeks were autumn and winter for the subgroup enrolled in summer months, spring and summer for the subgroup enrolled in winter months, and summer and autumn for the subgroup enrolled in spring months. The differences of the pattern of improvement by the months of enrolment were statistically significant with adjustment for other covariates, baseline values, sex and age. (Fig.1:P<0.001, Fig.2:P<0.001)

Figure 1: Changes of Incontinence frequency for the 3 patient subgroups divided by enrolment months

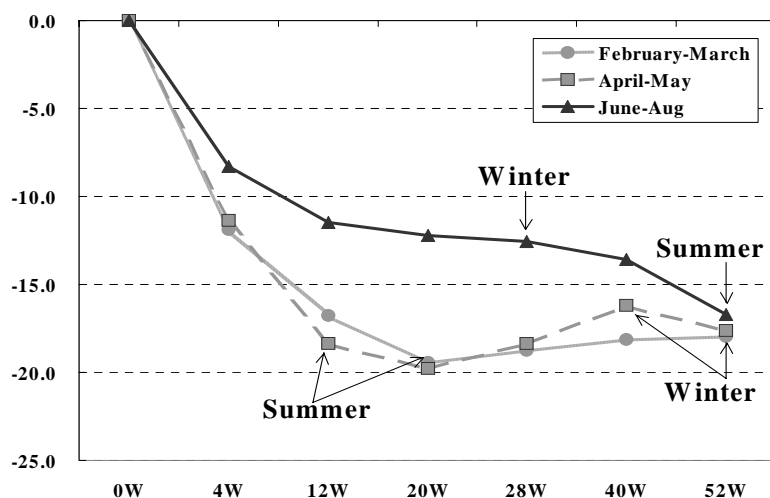
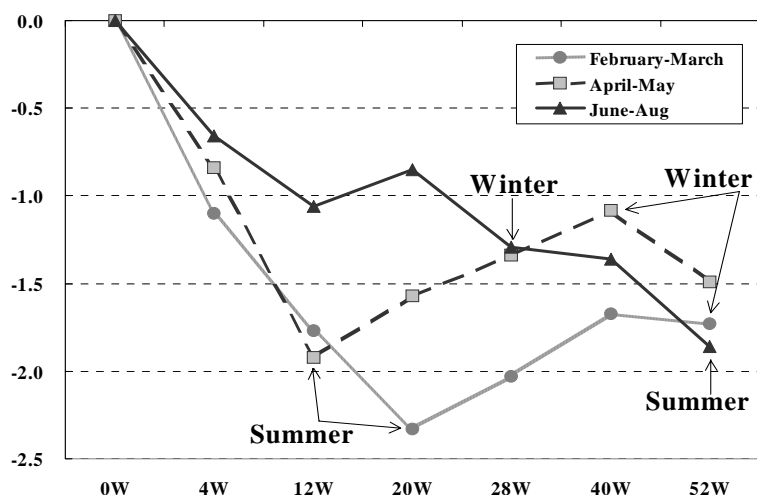


Figure 2: Change of Urination frequency for the 3 patient subgroups divided by enrolment months



Interpretation of results

While prominent improvement of OAB symptoms was observed in the patients who had received the oxybutynin transdermal patches for a year, patterns of improvement were different among the patient groups according to the seasons when the treatment started. The results indicate the seasonal influence on the efficacy outcome of OAB treatment because the seasonal differences in the patterns of improvement were statistically significant with adjustment of baseline severity and other covariates. It is not only through physiological effects of ambient temperature such as amount of sweating and other activity of the autonomic nerve system, but also through non-physiological effects since heater/air-conditioners are usually used in most houses and buildings throughout all seasons in Japan.

Concluding message

Critical consideration of season is necessary for study design and efficacy analysis for the investigation of OAB treatment.

**FUNDING:** Sankyo Company, LTD.

**DISCLOSURES:** NONE

**CLINICAL TRIAL REGISTRATION:** This clinical trial has not yet been registered in a public clinical trials registry.

**HUMAN SUBJECTS:** This study was approved by the Institute review board of Sankyo Company, LTD. and followed the Declaration of Helsinki Informed consent was obtained from the patients.