**116**

Bump R[1], Yalcin I[1], Voss S [1]
1. Lilly Research Laboratories

# THE EFFECT OF DULOXETINE DOSE ESCALATION AND TAPERING ON THE INCIDENCE OF ADVERSE EVENTS (AE) IN WOMEN WITH STRESS URINARY INCONTINENCE (SUI)

Hypothesis/Aims of the Study

Nausea is both the most common treatment-emergent adverse event (TEAE) reported by women with SUI taking duloxetine and the most common AE leading to discontinuation. The incidence of nausea at 40 mg BID was significantly greater in 3 Phase 3 studies than in 1 Phase 2 study, possibly because only the latter escalated the dose. However, this across studies comparison suggesting benefit from dose escalation was contradicted by population pharmacokinetic data. Some patients experience AEs when discontinuing monoamine reuptake inhibitors (SSRI/SNRIs), leading to class label recommendations for dose tapering. No data are available to judge the value of this recommendation for duloxetine. We report a prespecified analysis of safety data from a large ethical committee approved, placebo-controlled trial conducted in Europe and the Americas having 2 aims: assess 1) the impact of dose escalation on the incidence of nausea when starting and 2) the impact of dose tapering on the incidence of discontinuation AEs when stopping duloxetine.

Study Design, Materials, and Methods

516 women with SUI 19 to 82 years old were randomly assigned to receive double-blind placebo (n = 120) or duloxetine in 1 of 3 dosing regimens: 40 mg BID for 8 weeks (n = 136), 40 mg QD for 2 weeks escalating to 40 mg BID for 6 weeks (n = 127), or 20mg BID for two weeks escalating to 40 mg BID for 6 weeks (n = 133). After the 8-week treatment period, subjects receiving duloxetine were re-randomised to 1 of 3 double-blind taper regimens: placebo only for 4 weeks (no taper, n = 107), duloxetine 40mg QD for two weeks followed by placebo for 2 weeks (n = 115) or duloxetine 20mg BID for two weeks followed by placebo for 2 weeks (n = 101); subjects taking placebo continued on placebo for 4 weeks. AEs were collected during each phase of the study and a non-inferiority analysis was performed comparing the various regimens for nausea. The pre-specified clinically important difference in nausea incidence for the non-inferiority analysis was set at 10.5%, half of the observed difference between duloxetine and placebo in the largest Phase 3 SUI trial. [1]

Results

There were significant differences in the incidence of nausea across the 4 treatment groups. Fewer women taking duloxetine 20mg BID for the first 2 weeks experienced nausea or dizziness than women using the other 2 duloxetine regimens (Table). The non-inferiority of the 40-mg BID starting dose versus either escalation regimen was rejected since the upper 95% confidence interval for the difference in nausea incidence exceeded the 10.5% non-inferiority margin (21.2% for the 20-mg BID and 13.2% for the 40-mg QD regimens). Non-inferiority was also rejected for the 40-mg QD versus the 20-mg BID starting dose (upper 95% CI for the treatment difference = 16.9%). There were also significant differences in the overall discontinuation rate due to all AEs among the groups but not for any single AE, including nausea (Table). No difference in severity of nausea or all TEAEs was seen between different regimens. The discontinuation phase data show dose tapering had no significant impact on reducing the overall incidence of discontinuation AE's but tapering to 40 mg QD for two weeks may decrease, but not eliminate, the risk of experiencing the most common discontinuation adverse event, dizziness (Table).

Effect of duloxetine dose escalation on TEAE and AE related discontinuation rates and dose de-escalation on AE rates (%)

| Treatment Phase<br>AE | | Duloxetine Groups | | | |
|---|---|---|---|---|---|
| Initial dosing regimen | Placebo | 20mg BID | 40mg QD | 80mg BID | P-value* |
| Nausea | 5.8 | 16.5 | 25.2 | 29.4 | <.001 |
| Dizziness | 0.8 | 3.0 | 7.9 | 10.3 | =.002 |
| AE discontinuations | 5.8 | 7.5 | 11.8 | 16.2 | =.033 |
| Taper regimen | Placebo | 20 mg BID | 40 mg QD | Placebo | |
| Any adverse event | 23.8 | 36.6 | 40.9 | 43.9 | =.011 |
| Dizziness | 0 | 8.9 | 3.5 | 8.4 | =.002 |

* Fishers exact test for among group differences

**Interpretation of Results:**

Starting duloxetine treatment with 20mg BID for 2 weeks before increasing the dose to the optimally effective 40 mg BID dose may 1) significantly reduce, but not eliminate, the risk of nausea and dizziness and 2) reduces the overall discontinuation rate due to AEs. The value of dose tapering is not obvious from the results of this study; however, decreasing the dose to 40 mg QD for two weeks may decrease the risk of dizziness.

**Concluding Message:**

Duloxetine dose escalation from 20 mg BID to 40 mg BID over two weeks may be an effective tactic to diminish the risk of nausea. When combined with proactive counselling about the natural history of nausea with duloxetine (mild to moderate, non-progressive, and transient), dose escalation may allow better early compliance with duloxetine treatment by women with SUI.

1. Duloxetine vs. placebo in the treatment of North American women with stress urinary incontinence. J Urol 2003; 170:1259-1263

**FUNDING: Eli Lilly and Company and Boehringer Ingelheim**