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# Re: Safety, Tolerability, and Efficacy of LiRIS 400 mg in Women with Interstitial Cystitis/Bladder Pain Syndrome with or without Hunner Lesions

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Voiding Function and Dysfunction, Bladder Physiology and Pharmacology, and Female Urology

# Re: Safety, Tolerability, and Efficacy of LiRIS 400 mg in Women with Interstitial Cystitis/Bladder Pain Syndrome with or without Hunner Lesions

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**Editorial Comment:** The lidocaine-releasing intravesical system (LiRIS®) is a passive, non-resorbable intravesical system inserted cystoscopically and designed to provide continuous, controlled release of lidocaine into the bladder over a 2-week period, after which it is removed. There was a positive anticipation that this treatment system might provide symptomatic relief for at least a segment of patients with interstitial cystitis/bladder pain syndrome (IC/BPS), based on the logic of the rationale and from results in 2 small studies, 1 of which was presented at the American Urological Association annual meeting in 2016,[1] showing positive results in patients with Hunner lesions (HL). This article reports the results from 2 phase 2 studies conducted to assess efficacy and safety of this device in patients with IC with and without HL. Daily average pain score change from baseline using the numeric rating scale (NRS) was the primary end point. The secondary end point for patients with HL was a change in the number of lesions assessed by cystoscopy. Other study end points included average daily worst pain, micturition episode frequency and urgency episode frequency. Interestingly, exclusions consisted of a pain catastrophizing scale score of over 38 at screening, as well as other factors.

The study design was interesting. In study 1, there were 2 consecutive 14-day treatments: LiRIS-LiRIS, placebo (filled device)-LiRIS and placebo-placebo. In study 2, the patient received either LiRIS or placebo for a continuous 14-day period. In study 1, 59 patients were randomized and received treatment. A total of 11 patients discontinued the study. In study 2, 131 patients were randomized and received treatment. A total of 21 patients discontinued in both studies. The primary time point was week 4 for after removal of treatment, day 28 in study 1 and day 14 in study 2. For study 1, there were numerical but not statistically significant trends in favor of the lidocaine group, with a drop in the NRS pain score from 5.5–2.6 and 6.0–2.8, and 5.6–4.1 in the placebo group. In study 2, there was no significant difference in the reduction of HL between the 2 groups; the same was true of the patients who had HL in study 1. In both studies, lidocaine was measurable "in the majority of patients" in urine and plasma for at least 14 days following insertion of the device. Urinary concentrations were 1,600 to 3,000 times plasma concentrations.

Patient-reported outcomes in study 1 were inconclusive with large variability in a small sample size. In study 2, there was an improvement for both groups but no statistical difference in study 1, with 19.4% of patients reporting dysuria, 16.1% urinary tract infection, hematuria and bladder discomfort 12.9% each, and bladder pain 9.7%. The authors' conclusion was, "The results of the studies did not demonstrate a significant treatment effect for LiRIS 400 mg compared with placebo for treatment of IC/BPS with or without HL." Looking at mean baseline scores vs least squares mean change for various parameters, and calculating percent change for the drug-drug vs placebo-placebo group in study 1, there certainly are numerical differences for all but 1 important parameter: daily average pain score, at 49% decrease vs 27%, daily worst pain score 40% vs 22%, micturition frequency 23% vs 15%, but urgency episodes per day 49% vs 53%. The placebo response is not as high as I would have expected compared to drug effect for anything except urgency episodes. None of the patient-reported outcomes was specifically reported except to say that there was no change. It could be that the dose of drug was

not high enough (it is unclear what would constitute a dangerous plasma concentration) or the intravesical contact was not long enough. The intellectual property surrounding continuous delivery intravesically certainly seems worthy of exploration for other problems such as overactive bladder in women, and I suspect that somewhere this is already in the works. So could this well-reported study be considered a "successful failure" from some standpoints?

### Reference

1. Peters K, Seifu Y, Cutie C et al: MP72-16 Safety, tolerability, and preliminary efficacy of LiRIS® 400 mg in women with ulcerative interstitial cystitis. J Urol, suppl., 2016; **195:** e958.

## Re: Overactive Bladder Phenotypes: Development and Preliminary Data

J. G. Blaivas, E. S. W. Li, L. Dayan, M. E. Edeson, J. Mathew, A. L. O'Boyle, B. L. Amare, D. C. Chaikin, J. P. Weiss and K. J. Kreder

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**Editorial Comment:** The editorial comment to the primary article, provided by Patrick Shenot, wisely states, "a validated phenotype classification of [overactive bladder (OAB)] based on objective clinical and physiologic measures that guides treatment would clearly enhance our care of our patients with OAB." The authors of the primary article would doubtless agree with this. Jerry Blaivas, widely known for his innovative thinking, has come up with a methodology for phenotyping patients with OAB that was subjected to a small trial at his institution and others. Subjects included those with an OAB symptom score of greater than 8. The phenotype algorithm first divided all patients into 3 groups based on a 24-hour voided volume from a bladder diary, greater than 2.5 L, 1–2.5 L or less than 1 L. Each of these 3 phenotypes was further divided into a second tier based on maximal voided volume (350 ml or above, 150–350 ml or less than 150 ml). The third tier divided the 9 resulting subgroups into 18 minor phenotype groups based on normal or abnormal peak flow rates and post-void residual urine volume. Normal peak flow rate was considered greater than 12 ml per second and normal post-void residual equal to or less than 100 ml. A total of 18 final phenotypes resulted. The resultant number of patients in each of the 18 subgroups varied from 0 to 42. There is no question that this represents innovative thinking and a potential new approach to therapy for OAB. The simple questions that anyone would raise are, is it applicable to both men and women (the original study group was composed of 261 men and 138 women), and is it reproducible in a larger group of patients? The real question, however, as posed by the editorial comment (see above) is: Does this clearly enhance our care of patients with OAB, over and above the use of something quite simple, like the American Urological Association algorithm? Regardless of the phenotype, would anyone not use behavioral modification, drug therapy and then go on to consideration of the very few other modalities that we have for management, ie various forms of neuromodulation and intradetrusor botulinum toxin, taking into consideration the individual factors and most bothersome symptomatology for each patient, along with other parameters that define each specific patient (eg detrusor underactivity, a large residual urine volume, for example greater than 250 ml, refusal to entertain the possibility of self-catheterization, mixed incontinence and doubtless others). Would successful treatment change any of these phenotypic variables? The idea deserves further development and testing.

### Suggested Reading

Lightner DJ, Gomelsky A, Souter L et al: Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019. J Urol 2019; **202:** 558.