due to nocturnal polyuria. Various parameters are reported, extracting data from 2 randomized, placebo controlled trials in patients with 2 or more nocturnal voids per night. A greater reduction in the mean number of nocturnal voids was seen in men (1.26 voids, baseline 3.0 vs 0.89 voids with placebo, baseline 3.0) than in women (1.46, baseline 2.9). The rate of patients who achieved a 50% decrease was 41% vs 28% in men receiving desmopression vs placebo and 58% vs 40% in women; 33% responder rates were 70% vs 47% in men and 76% vs 63% in women. The authors believe, and I agree, that the findings substantiate clinically meaningful benefit of these dosages in men and women. However, the high placebo effect is noteworthy and has frequently been an issue in the more recently conducted studies on nocturia. Missing from the report, which I think and hope will appear in subsequent publications, are other parameters that are important to evaluate in such a study, including first uninterrupted sleep period, quality of life, instances of hyponatremia, urine volumes and rapidity of onset.

Alan J. Wein, MD, PhD (hon)

Re: Novel Immediate/Sustained-Release Formulation of Acetaminophen-Ibuprofen Combination (Paxerol®) for Severe Nocturia Associated with Overactive Bladder: A Multi-Center, Randomized, Double Blinded, Placebo-Controlled, 4-Arm Trial

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Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/30592553

Editorial Comment: Using a clever rationale, these authors report the results of treatment for nocturia associated with overactive bladder with a combination of 150 mg ibuprofen and 325 mg acetaminophen formulated into an immediate/sustained release tablet (50% immediate and 50% sustained release). This was a phase 2, double-blind, randomized, placebo controlled trial evaluating the efficacy and safety of 3 different doses of the compound in patients with nocturia (2.5 voids or more per night) for more than 3 months. All had a poor response or were unwilling to make lifestyle modifications, or undergo behavioral or conservative therapy. Both compounds inhibit the prostaglandin pathway but at different points. Cyclooxygenase-2 inhibitors and prostaglandin inhibitors have been shown to decrease urine production, inflammation and detrusor tone, perhaps by blocking the “sensitization” effects of prostaglandins on the bladder during filling/storage. The authors cite prior evidence that ibuprofen and acetaminophen have “synergy” on analgesic effect (did they mean synergistic or additive effect?). Half of each tablet is reported as being released during the first hour of sleep via the immediate release preparation and the other half is released in a sustained manner for up to 6 hours.

The authors measured several parameters in this exploratory study, including nocturnal volume, although they specifically said they excluded the first void after concluding sleeping. The first void should be included in the nocturnal volume. They screened 133 patients and ultimately included 86. A total of 80 patients completed 14 treatment days. Low, mid and high dose groups consisted of 1, 2 or 3 tablets containing the active ingredient. All participants received 3 tablets. Respective results for the decrease in average nocturnal voids for the low, medium and high dose groups with baselines were 3.3 minus 1.1, 3.9 minus 1.4 and 3.6 minus 1.3. Corresponding placebo number was 3.6 minus 0.3. Average increases with baselines for durations of first uninterrupted sleep in hours were 2.2 plus 0.6, 2.0 plus 0.7 and 2.1 plus 1.2, with placebo being 1.8 plus 0.4. The authors report a decrease in nocturnal volume in all groups and a significantly greater decrease in the drug groups vs placebo, although no numbers were given. It is unclear how many of these patients had nocturnal polyuria, although based on other studies one could assume that approximately 80% had nocturnal polyuria.

Compared to the study by Weiss et al.,1 this series certainly had different inclusion characteristics. This was a group of patients with overactive bladder, of whom approximately 35% had benign prostatic hyperplasia. The difference in placebo results between this and the study by Weiss et al are quite significant without a clear reason. If one does a rough calculation of the rate of decrease in

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nocturnal voids for placebo, it is approximately 8% in this study and either 28% (in men) or 41% (in
women) in the series by Weiss et al. Nevertheless, this is a clever rationale and we all look forward to
phase 3 trials with a longer treatment duration using this intriguing combination of well-known
compounds.

Reference

1. Weiss JP, van der Meulen EA and Juul KV: Low-dose desmopressin orally disintegrating tablet: suggested clinically meaningful benefit in patients
with nocturia due to nocturnal polyuria. Eur Urol Focus 2018; doi: 10.1016/j.euf.2018.11.001.

Re: Vibegron, a Novel Potent and Selective β3-Adrenoreceptor Agonist, for
the Treatment of Patients with Overactive Bladder: A Randomized,
Double-Blind, Placebo-Controlled Phase 3 Study

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Eur Urol 2018; 73: 783–790. doi: 10.1016/j.eururo.2017.12.022

Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/29366513

Re: Overactive Bladder: Advancement or More of the Same

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Eur Urol 2018; 73: 791–792. doi: 10.1016/j.eururo.2018.01.028

No Abstract

Editorial Comment: Yoshida et al begin by stating that vibegron is a novel, potent, selective
β3-adrenoreceptor agonist that demonstrates pharmacological activity in vitro and in vivo. A phase
2b, randomized, double-blind, placebo and tolterodine controlled clinical study (NCT01314872)
previously revealed that vibegron was effective and well tolerated in 1,395 patients with overactive
bladder. Yoshida et al evaluated this drug vs placebo in a Japanese population, predominantly
women with a mean age of less than 60 years. They also included a smaller number of subjects
(approximately a third compared to the other arms) treated with imidafenacin, an anticholinergic
medication approved in Japan for overactive bladder, whose mechanism of action is said to be M1
and M3 muscarinic receptor antagonism. Interestingly they did not comment on this arm of the
study at all, but listed the results in the tabularizations and figures. The study had a 2-week
placebo run-in but it is unclear whether placebo responders were eliminated.

In patients with a mean number of urgency episodes per day of 3.5 to 3.8 and urgency incontinence
episodes of 1.9 to 2.2 the drug was more effective than placebo in producing favorable results. In the
accompanying editorial comment Badlani notes that the only noticeable difference based on the active
comparison in this study was an increase in the incidence of dry mouth with imidafenacin. The
question everyone will ask is, what's the difference between this drug and mirabegron? Mirabegron is
known to inhibit CYP2D6, a CYP450 enzyme, and therefore drug-drug interaction should be
considered. However, vibegron did not show any induction or inhibitory effect on CYP enzymes,
suggesting no risk of drug-drug interaction. In addition, there were no reported increases in heart
rate, blood pressure or QTc interval, but it is unclear how detailed an analysis was done for these
parameters. In practice there seem to be few reports of such issues with mirabegron. There are other
β3 agonists that are in earlier stages of development. It will be interesting to see how this agent
matches against mirabegron in a head-to-head trial, if one is ever done, and what will happen to the
second agent, third agent, etc to become available when mirabegron goes generic.