



Invited Commentary | Urology

# Combination Therapies for Erectile Dysfunction—A Synergy of Modalities Holds the Key

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The systematic review and meta-analysis by Mykoniatis et al<sup>1</sup> compared the literature on combination therapy vs monotherapy for the treatment of erectile dysfunction (ED). The authors found that combination therapy with phosphodiesterase type 5 (PDE5) inhibitors in conjunction with other accepted treatment modalities, including tadalafil, low-intensity extracorporeal shockwave therapy (Li-ESWT), vacuum erectile device, or antioxidants, was associated with statistically significant improvements in symptoms as measured by the International Index of Erectile function (IIEF) score, with no increase in adverse effects. However, certain limitations exist in this review and should be considered when interpreting the its conclusions.

Since the first PDE5 inhibitor, sildenafil citrate, was approved by the US Food and Drug Administration in 1998,<sup>2</sup> this class of medications has revolutionized the management of ED. To date, 4 individual PDE5 inhibitors have been approved by the US Food and Drug Administration; they have unique properties but a similar overall efficacy. These PDE5 inhibitors, in addition to intracavernosal injection therapies, are associated with the most successful non-device-based current strategies for mild to moderate cases of ED.

Mykoniatis et al<sup>1</sup> found a modest but statistically significant improvement in objective IIEFs scores (1.76 points; 95% CI, 1.27-2.24) with the use of combination therapy compared with standard PDE5 inhibitor monotherapy. It must be noted that statistical significance does not equate to clinical significance, and an overall improvement in the IIEF score of less than 2 points is a rather nominal change. Indeed, the authors discussed the minimal clinically important difference, which was the smallest difference in IIEF score that patients perceive as beneficial after treatment. Mykoniatis et al<sup>1</sup> emphasized that to reach this MCID, improvements in the IIEF score of 2, 5, and 7 points from baseline scores must be reported in patients with mild, moderate, and severe ED, respectively; however, the authors noted that these “phenomenally modest additional mean improvement” in IIEF score after combination therapy were not achieved in the studies included in their review.

A limitation of this systematic review and meta-analysis, which the authors mentioned, was the significant heterogeneity of both the populations and the combination therapies analyzed. Therefore, caution must be exercised when considering the clinical efficacy of any combination treatment modality for ED. Because of their clear superiority as first-line treatment options, prospective studies with head-to-head comparisons of PDE5 inhibitors vs other strategies are lacking. Mykoniatis et al<sup>1</sup> highlight this gap in the scientific literature along with the dearth of randomized clinical trials that compare various combinations of treatments.

We believe that combination therapy with dual short- and long-acting PDE5 inhibitors may have an additive effect and should be considered, even as a first-line initial strategy in cases of more advanced ED. Tadalafil with its longer half-life, ability to be absorbed with a high-fat meal, and unique twin success in the treatment of benign prostatic enlargement, may be an ideal agent to prescribe daily along with an on-demand PDE5 inhibitor. To date, only 1 randomized clinical trial has investigated this combination.<sup>3</sup>

Because it appears that PDE5 inhibitors will remain the mainstay of ED management for the foreseeable future, an ideal complimentary therapeutic strategy is one that will act in synergy with these drugs. New modalities, including Li-ESWT and plasma-rich platelet and stem cell therapies, are

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all worthy of evaluation but are still considered to be experimental because further large and well-designed prospective studies are required. With only a handful of small randomized clinical trials performed to date, Li-ESWT does appear to be associated with greater subjective improvements than other combinations, but the data are preliminary at best.<sup>4</sup> Intuitively, the proposed mechanism of microtrauma that results in neoangiogenesis of vascular endothelial cells coupled with possible nerve regeneration and remodeling as well as the increase in local neuronal nitric oxide concentration may very well directly potentiate the activity of PDE5 inhibitors.

As the worldwide prevalence of ED continues to increase, it behooves those clinicians who treat men with ED to continue to try new complementary and synergistic treatment options. These new options should also be assessed in the appropriate prospective clinical settings.

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#### ARTICLE INFORMATION

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