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Reply to: Commentary on: Pharmacist-driven interventions to de-escalate urinary antimuscarinics in the Programs of All-Inclusive Care for the Elderly

We would like to thank Drs. Snyder and Mujais for their interest in our work and we sincerely appreciate their commentary regarding vibegron’s negligible effect on blood pressure. In addition to this attribute, we want to highlight another aspect of vibegron’s pharmacology that is especially pertinent for Programs of All-Inclusive Care for the Elderly (PACE) participants. Due to these attributes, we might have observed fewer outright overactive bladder (OAB) treatment cessations if vibegron was available at the time of our study.

Given the prevalence of polypharmacy in PACE, avoiding drug interactions is a critical aspect of adverse drug event (ADE) risk mitigation. Unlike mirabegron, vibegron has a lower propensity to cause interactions because it does not inhibit the cytochrome P450 (CYP) 2D6 isoenzyme. CYP2D6 interactions are relevant because (1) several common medications are CYP2D6 substrates (e.g., antidepressants, antipsychotics, opioids, urinary antimuscarinics), and (2) they are costly and potentially fatal. In fact, CYP2D6 interactions account for 35% of all CYP450-mediated drug interactions identified by PACE pharmacists.

At the study’s practice site, the MedWise Risk Score (MRS) helps pharmacists quantify the risk of such interactions. The MRS is an ADE risk stratification tool that is computed from five modifiable risk factors, two of which include anticholinergic burden and CYP450 interaction burden. In several populations—including PACE—elevated scores have been associated with negative outcomes, such as ADEs, hospitalizations, emergency visits, mortality, and increased cost of care. At our study’s practice site, PACE participants with an elevated MRS are prioritized for medication reviews, where pharmacists collaborate with providers to devise lower risk (i.e., lower MRS) regimens.

To be clear, pharmacists assess the potential impact on the MRS before making recommendations to PACE providers. At the time of our study, pharmacists may have found mirabegron to be riskier (i.e., would result in a higher MRS) than the baseline antimuscarinic for patients taking concomitant CYP2D6 substrates. In such cases, the de-escalation strategy would have been limited to decreasing the antimuscarinic’s dose or discontinuing the

This letter comments on the letter by Daniel Snyder and Salim Mujais. [Correction added after first online publication on 23 January 2023. The spelling of Dr. Snyder’s name has been corrected, along with an additional spelling correction.]
antimuscarinic. If it was available, switching to vibegron may have been another option since it does not inhibit CYP2D6.4

Nevertheless, this does not mean pharmacists should have recommended vibegron to everyone. First, vibegron—though it may not significantly raise blood pressure—is not entirely risk-free in cardiovascular patients. Like mirabegron, vibegron can increase digoxin concentrations.9 Looking back at our data, this interaction could have been relevant for one patient if a β3-adrenergic agonist was started.

Second, recommending “no drug treatment” may have been reasonable for some PACE participants and within the guidance provided by the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogential Reconstruction (SUFU). Statement 4 of the AUA/SUFU 2019 non-neurogenic OAB clinical practice guidelines states: “OAB is not a disease; it is a symptom complex that generally is not a life-threatening condition. After assessment has been performed to exclude conditions requiring treatment and counseling, no treatment is an acceptable choice made by some patients and caregivers.”10

In the discussion of this statement, the guidelines mention that pharmacologic treatment can be inappropriate for patients who cannot perceive improvements in quality of life, such as incontinent older adults with significant cognitive and/or mobility impairments.10 This is an important consideration in PACE. According to the National PACE Association, 46% of PACE participants have dementia, and 83% require assistance with at least one activity of daily living (e.g., toileting, walking, transfer).3 For participants with significant cognitive or functional limitations, pharmacotherapy may be less beneficial than non-pharmacological supports (e.g., diapering, and toileting assistance).

In summary, we hope our original paper and the subsequent commentary it has generated underscore the broader theme: OAB pharmacotherapy must be individualized to help improve symptoms and quality of life and mitigate the risk of ADEs in complex, poly-medicated, older adults.

**CONFLICT OF INTEREST**
David Bankes and Jacques Turgeon are employees of Tabula Rasa Healthcare, which is the developer of the MedWise Risk Score.

**SPONSOR’S ROLE**
None.

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