AUTHOR REPLY: The nuances of GRADE

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We would like to thank the members of the British Society for Sexual Medicine (BSSM) for their feedback and well-intentioned comments regarding the recently published Canadian Urological Association (CUA) erectile dysfunction (ED) guideline.[1] We appreciate having this platform to respond to their concerns and clarify our position.

We sincerely believe that the primary divergence between us is a matter of understanding the nuances of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[2] and the evidence-to-decision (EtD) framework[3] by which the recommendations were formulated. The results of our analyses are available transparently in the guideline Appendix. This well-established framework considers multiple factors (importance of the question, desirable effects, undesirable effects, certainty in the evidence of effects, patient values and preferences, the balance of desirable and undesirable effects, resources required, certainty about resources required, cost effectiveness, equity, acceptability to stakeholders, and feasibility of implementing the recommendation) to formulate patient-centric and less biased recommendations based on the analysis of high-quality evidence. The CUA is making a concerted effort to develop guidelines using a strong methodological framework, such as GRADE. Guidelines not using such frameworks risk the loss of transparency in their reasoning behind recommendations and are prone to overstating the strength of recommendations. It is misleading to state a position strongly because one ***feels*** strongly. A strong recommendation must be supported in consideration of the quality of available evidence and other important factors for clinical decision-making, which are encompassed in the EtD framework.

In the EtD framework, a conditional recommendation does not imply that "everyone should do" the course of action recommended. Importantly, this approach and a conditional recommendation stress that the clinician is not making the decision for the patient but that the clinician's role is to help the patient regarding the best course of action for them through a shared decision-making process. The best course of action is the one that most aligns with patient's values and preferences when considering the relevant tradeoffs. This approach is, in our opinion, the ultimate way to practice patient-centered and evidence-informed medicine.

In their letter, BSSM members note that we do not recommend daily tadalafil as a treatment option for patients with ED. This statement is a misinterpretation of the recommendation and is not accurate. We made a conditional recommendation against the general ***preferential*** use of daily tadalafil rather than on-demand tadalafil (or any other on-demand phosphodiesterase type 5 inhibitor [PDE5i]); however, both treatment options are acceptable, and the patient-specific choice will be based on multiple factors.

Many of the comments made by members of the BSSM in favor of daily tadalafil are, in fact, accounted for in the guideline when it states that certain patient-centered factors may influence what dosing regimen the patient ultimately decides to pursue. To illustrate, if a patient with ED has a high desire for sexual spontaneity, then daily tadalafil may be a better option for them. Additionally, if a patient with ED has comorbid symptomatic benign prostatic hyperplasia, then of course daily tadalafil may be a good option for them. Conversely, factors such as cost, desire not to take a daily medication, and frequency of intercourse, may lead a patient to consider on-demand dosing based on their values and preferences. Preference for daily vs. on-demand dosing lies with the patient based on their values and preferences instead of clinicians preferentially prescribing daily-dose regimens for their patient with ED.

We absolutely agree with and support the involvement of the patient's partner in discussions regarding sexual health and ED assessment and management. We applaud investigators that include this important perspective in their work and hope more researchers capture the partner's perspective in future studies. The study by Conaglen and colleagues

demonstrated that female partners preferred daily or on-demand tadalafil over sildenafil.[4] A followup study of the same cohort of patients in the "real-world" setting with two years of followup interestingly found that long-term adherence to PDE5is was only 71%, and despite this, the vast majority of couples continued to be sexually active and satisfied without treatment.[5] As well, many couples required less medication than on trial, citing less need for them and the high cost as the two main factors for decreased use. This data speaks to the natural history of couples presenting with sexual concerns over time and that numerous factors play a role in medication preference, dosing frequency, and continued use.

The guideline committee used the International Index of Erectile Function (IIEF)-EF score to measure improvement in erectile function when comparing studies, which is the most robust validated measure used in trials assessing ED outcomes.[6] When analyzing the randomized controlled trials (RCTs) that compared daily vs. on-demand tadalafil, the followup period of 8–12 weeks was chosen because the vast majority of studies reported data with this followup period. A systematic review that investigated longer followup periods, from 24–36 weeks, demonstrated very similar results as our meta-analysis (pooled mean difference in IIEF-EF of 1.24 [95% confidence interval 0.03–2.44);[7] however, one of the four included studies actually only had 12 weeks of followup given its crossover design.[8] We included three of the four studies from the Zhou systematic review in our meta-analysis, using 12-week followup data for direct comparison between RCTs to decrease heterogeneity between studies. In our literature search, we were unable to find RCTs or studies to support the claim made by members of the BSSM that longer followup demonstrates increasing superiority for daily tadalafil vs. on-demand regimens.

In the guideline, we reiterate that for treatment-refractory patients, clinicians should review dosing, technique, side effects, and consider re-treatment, which could include changing from an on-demand to a daily dose PDE5i regimen. In the letter from members of the BSSM, daily tadalafil is quoted to effectively salvage 50% of men failing on-demand PDE5is. In our literature search, very little high-quality evidence to support this claim was found, especially with a 50% salvage rate. The only study that quoted a salvage rate close to 50% is an open-label study of 101 men determined to have failed on-demand tadalafil and 37% more men taking tadalafil 10 mg daily compared to tadalafil 20 mg on-demand responded positively to the SEP3 question (Did your erection last long enough for you to have successful intercourse?).[9] This study also reports that 41% of patients taking tadalafil 10 mg daily had an IIEF-EF score equal to or better than 26 compared to zero patients taking tadalafil on-demand. Apart from its small size, there are numerous methodological flaws and biases in this study that limit its applicability to the general ED population (method used to determine tadalafil failure, very narrow inclusion criteria, no measure of frequency of on-demand use, no mention of why failure occurred, no mention of education provided to on-demand treatment failures, failure to report raw IIEF scores in each treatment group, and the sole author has a disclosed conflict of interest to the company that manufactures tadalafil), and practically, tadalafil 10 mg is not approved for daily use.

In contrast, a study by Hatzimouratidis and colleagues determined that proper patient education regarding on-demand PDE5i use was more effective in salvaging non-responding patients than daily dosing regimens.[10] Discussing a daily dose regimen for a patient that is non-responsive to on-demand PDE5-inhibitors after ensuring proper use through patient education is reasonable (as is discussing a change for a patient not responding to daily dose to on-demand); however, given the similar clinical efficacy of the dosing regimens in patients with ED, we don't feel giving the patient the choice threatens their potential treatment success or future relationship with their partner.

As an argument in favor of daily dosing, members of the BSSM highlighted potential benefits of long-term daily tadalafil beyond its effect on sexual function. These additional effects, apart from improvements in voiding function, are seen in longitudinal studies that are hypothesis-generating and don't form the bedrock of evidence in guideline creation, especially when RCT data in multiple trials directly addressing the clinical question exist. We look forward to future studies evaluating the protective role of PDE5-inhibitors to help bring further clarity to these fascinating associations.

We concede that this guideline has limitations and unanswered questions, as our colleagues from the BSSM allude to. We distinctly address these at the end of the guideline document and specifically state that the guideline is focused on patients with ED as a single presenting symptom, albeit we acknowledge many patients will have other urological conditions that may impact their ED management. We also state that "the recommendations in this guideline need to be contextualized based on the patient's history and presenting symptoms and conditions that may be influencing sexual function in its entirety." This statement is not an excuse for not digging deeper into the literature; it is a function of high-quality evidence not existing to adequately address these clinical circumstances and others in the field of ED. We hope more evidence emerges to address these gaps so guideline recommendations can reflect unbiased, balanced, and evidence-informed decisions to guide clinicians treating ED in the future.

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