Opening the door to new therapeutic options with open label studies for children with detrusor overactivity

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The current *CUAJ* study by Nadeau and colleagues[1] discusses the efficacy of double anticholinergic therapy in children with detrusor overactivity and refractory urinary incontinence and adds to the previous experience by the same authors. It reiterates the safety and efficacy of this treatment option over a longer follow-up duration of 36 months in a marginally larger cohort. The study used a rigorous pre-inclusion and post-inclusion follow-up protocol and it is reassuring that the beneficial effects dominated the side effects over this follow-up duration without a significant dropout rate or change in compliance.

It would have been valuable to know the percent of patients who responded to anticholinergic monotherapy and the possible predictors of requirement of double therapy at onset as this can guide future counselling and therapy. Can the absence of side effects on an optimized dose of a single drug indicate the possibility of dose escalation to achieve response or suggest poor compliance? The study results would have been significantly more convincing if the inclusion criteria only included patients who did not respond to monotherapy, while showing side effects.

Continence is a binary variable and there is increasing recognition of the need for a universal strict definition of urinary continence to ensure adequate reporting in pediatric studies.[2] In this study, the overall "complete dryness" rate was 41% with similar results in the neurogenic detrusor overactivity (NDO) and non-neurogenic (DO) detrusor overactivity groups. On the other hand, the significant decrease in the Patient Perception of Bladder Condition (PPBC) scores suggests a better patient-reported outcome than the objective assessment of continence. Does that indicate that perhaps, as urologists, we are being too harsh on our reporting or is this a reflection of patient expectations and a result of excellent patient follow-up and counselling?

In the NDO bladder group, anticholinergic therapy plays a dual role beyond incontinence, improving bladder compliance and reduces filling pressures. The absence of urodynamic data in the form of end-fill or detrusor leak point pressures and compliance, combined with a 40% complete continence rate, makes this option less appealing in this subset of patients.

The authors deserve credit for persisting with the off-label use of solifenacin in the pediatric population and this study strengthens the quantity of evidence in the pediatric population. Since the authors already followed these patients fairly systematically prior to enrollment, a crossover trial design would have been feasible and would have subsequently marginally enhanced the level of evidence presented.

A persistent question related to anticholinergics in pediatric patients has been the effect of these drugs on cognition, especially in the neurogenic population where baseline cognition may be impaired. The SENIOR trial, given its limitations and the elderly age group, did not show cognitive impairment for solifenacin, but oxybutynin impaired power and continuity of attention.[3] Therefore, the effect of long-term use of these agents in pediatric patients is still unanswered.

The carrot and stick policy of the FDA with the Pediatric Exclusivity provision (allows 6 additional months of market exclusivity) and the Pediatric Research Equity Act (allows the FDA to demand pediatric studies if the drug is likely to be used in pediatric patients) has spurred pharmaceutical companies to conduct more pediatric studies. This is a vital and long-felt need expressed by pediatric practitioners who have found it hard to extrapolate results of adult studies to pediatric patients. Mybetriq's (Astellas Canada Inc.) FDA approval notice requires several deferred pediatric studies to be conducted as part of the approval requirements.

However, the lag time before possible pediatric approval is likely to be more than 10 years. Until then, similar off-label pediatric studies are required and justified to bring forth newer therapeutic options for our children.

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