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

Meghan Ha PharmD[1,2] | **Anna Furman PharmD**[1,3] | **Sweilem B. Al Rihani PharmD, PhD**[4] | **Veronique Michaud MSc, PhD**[4,5] | **Jacques Turgeon PhD**[4,5] | **David L. Bankes PharmD**[1]

[1]Office of Translational Research and Residency Programs (OTRRP), Tabula Rasa HealthCare, Inc., Moorestown, New Jersey, USA

[2]Wolters Kluwer, Franklin, Tennessee, USA

[3]Optum Care, Inc., Eden Prairie, Minnesota, USA

[4]Precision Pharmacotherapy Research & Development Institute, Tabula Rasa HealthCare, Inc., Orlando, Florida, USA

[5]Faculty of Pharmacy, Université de Montréal, Pavillon Jean-Coutu, 2940 Chemin de Polytechnique, QC, Canada

Correspondence
David L. Bankes, Tabula Rasa HealthCare, Inc., 228 Strawbridge Drive, Moorestown, NJ 08057, USA.
Email: dbankes@trhc.com

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Tabula Rasa Healthcare (TRHC)

Abstract

Background: Given associations with serious cognitive and physical adverse effects (e.g., dementia, falls), strong anticholinergics, like urinary antimuscarinics (UAMs), should be avoided in older adults. This feasibility study aimed to (1) evaluate the implementation rate of pharmacists' recommendations intended to de-escalate UAMs, (2) quantify the change in overall anticholinergic dosing exposure from these recommendations, and (3) investigate factors that predict recommendation implementation.

Methods: This was a retrospective, observational, before-and-after study. Pharmacists ($n = 18$) devised strategies to de-escalate UAMs in 187 participants (mean age 72.4 ± 9.4; 77.0% female; mean number of medications 12.9 ± 4.6) of 35 Programs of All-Inclusive Care for the Elderly (PACE). PACE prescribers (non-physicians and physicians) determined whether to implement recommendations. Implementation was defined as a change in the prescription records consistent with the pharmacist's recommendation at 2-, 4-, 6-, and 9-months post-recommendation. Anticholinergic dosing exposure was measured at each time point using standardized daily doses (SDD). Multivariable logistic regression was used to identify factors that predicted recommendation implementation.

Results: Across 9 months, recommendations were implemented in 118 out of 187 participants, yielding a 63.1% implementation rate. Of these, 77.1% ($n = 91/118$) implemented by month 2. Implementers' mean overall anticholinergic SDD decreased 65.4% from baseline (baseline: 2.6 [95% CI: 2.2, 3.0] to month 9: 0.9 [95% CI: 0.6,1.2], $p < 0.001$) whereas non-implementers demonstrated no significant change ($p = 0.52$). Taking <10 baseline medications (OR 2.75; 95% CI: 1.09, 7.61); baseline UAM SDD ≥2 (OR 2.20; 95% CI:

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1.11, 4.44); uncomplicated recommendations (OR 3.38; 95% CI: 1.67–7.03); and baseline calcium channel blocker use (OR 2.19; 95% CI: 1.09, 4.52) predicted implementation.

Conclusion: Our high implementation rate indicates that pharmacists' recommendations to de-escalate UAMs as a way to reduce overall anticholinergic exposure is feasible in medically complex, community-dwelling older adults. Future research should investigate whether these recommendations benefit cognitive (e.g., delirium, dementia) and/or physical functioning (e.g., falls).

KEYWORDS

anticholinergic burden, deprescribing, pharmacists, Programs of All-Inclusive Care for the Elderly, urinary antimuscarinics

INTRODUCTION

Among older adults, a growing body of epidemiological data suggests that cumulative exposure to anticholinergic medications is associated with serious cognitive and physical adverse effects, such as delirium, dementia, and falls.[1–6] Given these risks, the American Geriatrics Society Beers Criteria® recommends avoiding medications with strong anticholinergic properties and minimizing the use of multiple anticholinergics.[7] As others show, adhering to this recommendation can be facilitated through pharmacist-driven interventions aimed at de-escalating anticholinergics.[8]

Urinary antimuscarinics (UAMs) represent a particularly relevant class for pharmacists to de-escalate. First, UAMs can significantly contribute to cumulative anticholinergic exposure: they are taken chronically and are recommended first-line for urge or mixed urinary incontinence (UI) by clinical practice guidelines.[9,10] Second, UI becomes increasingly prevalent with age and medical complexity; therefore, UAMs are often taken by individuals who are most at risk of serious anticholinergic adverse effects.[11] Third, their real-world effectiveness is dubious. Compared to placebo, patients taking UAMs only report about 0.5–0.7 fewer UI episodes per day and are only 10% more likely to be continent.[12] Nevertheless, UI is associated with poor quality of life, loneliness, isolation, depression, and anxiety.[11] Thus, patients may actually resist UAM de-escalation attempts.[11]

To our knowledge, no study has examined pharmacist-led interventions directed specifically at UAM de-escalation. We aimed to determine whether such interventions are feasible in medically complex, community-dwelling older adults. Specifically, we (1) examined the proportion of interventions that were implemented by prescribers; (2) quantified the change in overall anticholinergic exposure; and (3) investigated factors associated with intervention implementation.

Key points

- Following a pharmacist's recommendation, PACE prescribers were able to successfully de-escalate urinary antimuscarinic therapy in 63.1% (n = 118/187) of medically complex older adults over a 9-month period.
- Overall anticholinergic exposure (as measured by standardized daily doses) decreased by 65.4% ($p < 0.001$) among PACE participants in whom de-escalation occurred.
- Successful urinary antimuscarinic de-escalation was most likely to occur when pharmacists issued uncomplicated recommendations and when participants took <10 medications, calcium channel blockers, and higher urinary antimuscarinic doses.

Why does this paper matter?

Our results suggest that it is feasible for clinicians to target urinary antimuscarinics for de-escalation (i.e., deprescribing) as a way to mitigate risks associated with anticholinergic drug exposure in vulnerable older adults.

METHODS

Design and approvals

This retrospective, observational, before-and-after evaluation of pharmacy data was granted a waiver of informed consent (Biomedical Research Alliance of New York, protocol 19-12-072-420).

Context

A de-centralized pharmacy (CareKinesis) for about 100 Programs of All-Inclusive Care for the Elderly (PACE) conducted this study. PACE is a U.S. government funded program that provides comprehensive care to older adults ≥55 years who qualify for a "nursing facility level of care," yet can maintain independent, community living with assistance.[13] An average PACE "participant" is aged 77 years, has 6 chronic comorbidities, and needs assistance with activities of daily living.[14] Currently, >250 PACE centers operate in 30 states.[15]

During routine practice, pharmacists use a clinical decision support software (MedWise) that can identify participants taking potentially inappropriate anticholinergics. Using clinical judgment, pharmacists may recommend anticholinergic de-escalation when appropriate (e.g., long duration of use, side effects present, not obtaining reasonable benefit, etc.). Recommendations are communicated to PACE "prescribers" (i.e., physicians, nurse practitioners, physician assistants) via telephonic or electronic (e.g., e-mail, fax) methods. Prescribers choose whether to implement recommendations.

Procedures and definitions

UAM de-escalation recommendations

At the time of this study, pharmacists recorded their clinical recommendations in a spreadsheet. We queried the spreadsheet for recommendations to "de-escalate" darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium. "De-escalate" was defined as a recommendation to:

1. Stop the UAM (*type 1 recommendation*).
2. Reduce UAM plasma concentrations *(type 2 recommendation)* by:
   a. Reducing the UAM's dose or
   b. Resolving a pharmacokinetic drug interaction (PK DI) that reduces the UAM's expected clearance.
3. Change the UAM to another medication (*type 3 recommendation*) to:
   a. Another medication without anticholinergic properties (e.g., mirabegron) or
   b. Another UAM that, in the pharmacist's professional judgment, would be less likely to cause CNS adverse effects (e.g., oxybutynin to trospium).

"*Mixed type composite*" *(MTC)* recommendations combine types 1, 2, or 3 to provide the prescriber multiple options. Supplementary Figure S1 summarizes intervention workflow.

Implementation, relapse, and anticholinergic exposure

At 2, 4, 6, and 9 months after the recommendation, we evaluated dispensing records for implementation and anticholinergic exposure. We allowed a 31-day grace period around each follow-up. For participants missing data in this window, we input the last observed value if that value represented ≥50% of the days from the previous time point; otherwise, the value was left missing.

Implementation was defined as an alteration in dispensing records consistent with a type 1, 2, or 3 recommendation. Participants for whom recommendations were implemented were considered "implementers." Implementers "relapsed" if the UAM therapy returned to the baseline status (or higher exposure).

We quantified anticholinergic exposure similar to Gray et al.,[5] calculating standardized daily doses (SDDs) as follows: $\sum_{n=1}^{k} \frac{TDD_n}{MEDD_n}$; where n is the number of medications with anticholinergic properties, 1 is the first anticholinergic found in the participant's list, k is the last anticholinergic found in the participant's list, TDD is defined as the total daily dose of the anticholinergic, and MEDD is defined as the minimum effective daily dose of the anticholinergic medication. For participants with PK DIs, we adjusted TDDs to reflect the impact on expected drug concentrations (calculated from MedWise). Supplementary Tables S1 and S2 report the anticholinergics, their MEDDs, and example SDD calculations.

Subjects

Any participant with a de-escalation recommendation between 1 March 2018 to 31 July 2019 was considered for analysis ($n = 202$). UAMs must have been "taken" (i.e., dispensed or enrolled with UAM) prior to the recommendation ($n = 201$). Participants must have dispensing data through the 2-month follow-up ($n = 187$). (Notably, we considered the most recent recommendation as baseline for 10 participants with 2 recommendations.)

Analysis

We quantified intervention feasibility in two ways. First, we calculated an overall "implementation rate," which was derived with the following equation piloted for this study:

$$\frac{\text{Number who implemented across available claims}}{\text{Number at baseline}} \times 100\%.$$

Additionally, we reported the number of participants that relapsed at each time point.

Second, anticholinergic exposure (overall and UAM-specific SDDs) obtained at baseline and follow-up were analyzed using a linear mixed model with two fixed factors to compare implementers and non-implementers. Comparisons were measured at each time point with an interaction term between the two factors. The dependent variable was log-transformed to fulfill the normality (Shapiro–Wilk test) and variance (Brown and Forsythe's variation of Levene's test statistic) assumptions.

Lastly, we evaluated whether the following variables predicted recommendation implementation:

1. Age (>75 vs ≤75 years).
2. Sex.
3. New PACE enrollment (≤90 days).
4. Polypharmacy (≥10 chronic medications).
5. Baseline prescribed UAM SDD ≥2 (vs <2).
6. UAM taken (oxybutynin vs any other).
7. Formulation (extended vs immediate release).
8. Recommendation communication method (telephonic vs electronic).
9. Recommendation type.
10. Concomitant chronic medication that increases incontinence risk[16] (included sodium-glucose cotransporter 2 inhibitors).

First, the chi-square test compared each factor between implementers and non-implementers. Next, variables with $p < 0.20$ were checked for multicollinearity (Phi coefficients ≤0.30 for all variables) then placed in a final multivariable logistic regression model.[17]

p-Values ≤0.05 were considered significant. Analyses were conducted in MS Excel (Microsoft 2019), SAS v9.4 (SAS Institute Inc., Cary, NC), and R (version 4.0.5).

RESULTS

Of the 187 participants ($n = 35$ PACE organizations), the majority took oxybutynin (63.6%, $n = 119$) and extended-release UAM formulations (52.9%, $n = 99$). To de-escalate, pharmacists ($n = 18$) most frequently recommended UAM discontinuation (type 1, 36.4%, $n = 68$). Table 1 reports full demographic and intervention details.

Implementation

As Figure 1 depicts, 118 participants de-escalated their UAM, yielding an implementation rate of 63.1% (118/187).

TABLE 1 Full study baseline characteristics ($n = 187$)

Variable	Value
PACE participants, *n*	187
PACE organizations, *n*	35
Enrolled within 90 days of recommendation, *n* (%)	32 (17.1)
Age, mean ± SD	72.4 ± 9.4
Female, *n* (%)	144 (77.0)
Chronic medications, mean ± SD	12.9 ± 4.6
UAM therapy at baseline, *n* (%)	
Oxybutynin	119 (63.6)
Solifenacin	32 (17.1)
Tolterodine	24 (12.8)
Tropsium	6 (3.2)
Fesoterodine	5 (2.7)
Oxybutynin and solifenacin	1 (0.5)
UAM dosage formulation at baseline, *n* (%)	
Extended-release (ER)	99 (52.9)
Immediate-release (IR)	85 (45.5)
Transdermal	2 (1.1)
ER and IR	1 (0.5)
Number of concomitant medications[a] that may cause incontinence, mean ± SD	2.9 ± 1.4
Medication classes[a] that may cause incontinence, *n* (%)	
Selective serotonin reuptake inhibitors	91 (48.7)
Calcium channel blockers	68 (36.4)
Diuretics	68 (36.4)
Gabapentin/pregabalin	67 (35.8)
ACE-inhibitors	51 (27.3)
Antipsychotics	42 (22.5)
Alpha-antagonists	26 (13.9)
Cholinesterase inhibitors	25 (13.4)
Miscellaneous anticholinergics[b]	25 (13.4)
Opioids	22 (11.8)
Nonsteroidal anti-inflammatory drugs	17 (9.1)
Others[c]	23 (12.3)
Pharmacist intervention information	
Clinical pharmacists, *n*	18
Communication method with prescriber	
Telephonic, *n* (%)	137 (73.3)
Electronic, *n* (%)	50 (26.7)
Specific recommendations rendered	
Type 1, *n* (%)	68 (36.4)
Type 2, *n* (%)	42 (22.5)

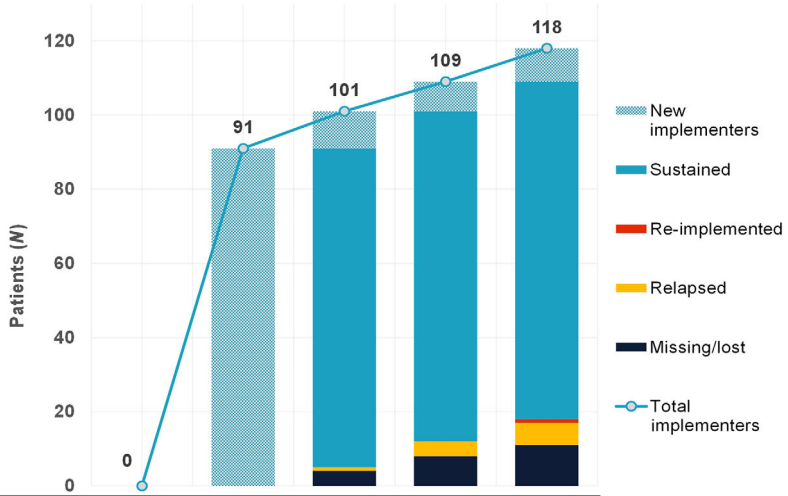
(Continues)

TABLE 1 (Continued)

Variable	Value
Type 3, *n* (%)	23 (12.3)
MTC, *n* (%)	54 (28.9)

Abbreviations: ACE, angiotensin-converting enzyme; MTC, mixed-type composite; PACE, Programs of All-Inclusive Care for the Elderly.
[a]Assessed at baseline.
[b]This includes amitriptyline, benztropine, chlorpheniramine, cyclobenzaprine, dicyclomine, diphenhydramine, doxepin, hydroxyzine, meclizine, hyoscyamine, and nortriptyline.
[c]Includes alpha-agonists, sedative hypnotics, lithium, thiazolidinedione, and sodium-glucose cotransporter 2 inhibitors. All had frequencies <5%.

Most (77.1%, $n = 91/118$) implemented by the 2-month follow-up. By study conclusion, six participants (5.1%, $n = 6/118$) relapsed. Table 2 shows that implementation was accomplished most frequently by discontinuation (42.4%, $n = 50/118$), switching to mirabegron (27.1%, $n = 32/118$), or dose reduction (15.3%, $n = 18/118$). Overall, 45.5% (85/187) participants finished the study without a UAM (includes those switching to mirabegron). Most recommendations (78.8%, $n = 93/118$) were implemented exactly as proposed by the pharmacist (Supplementary Table S3 reports the 25 [21.1%] recommendations where implementation differed from



	Baseline	2 months	4 months	6 months	9 months
Total implementers	0	91	101	109	118
New implementers	0	91	10	8	9
Sustained	0	0	86	89	91
Relapsed	0	0	1	4	6
Re-implemented	0	0	0	0	1
Missing/lost	0	0	4	8	11

FIGURE 1 Implementation and persistence of recommendations

TABLE 2 Description and timing of the first implemented intervention

	2 months	4 months	6 months	9 months	Overall
Implemented intervention(s)	91	10	8	9	118
Completely stopped UAM (type 1)	35	5	4	6	50 (42.4)
Switched UAM to mirabegron (type 3)	23	4	2	3	32 (27.1)
Decrease UAM SDD (type 2)	16	1	1		18 (15.3)
Resolved DDI[a] (type 2)	10		1		11 (9.3)
Stopped UAM and resolved DDI[a] (MTC)	2				2 (1.7)
Decrease UAM SDD and resolved DDI[a] (type 2)	2				2 (1.7)
Switch UAM to CNS UAM (type 3)	1				1 (0.8)
Switched UAM to mirabegron and resolve DDI[a] (MTC)	1				1 (0.8)
Switch UAM to CNS UAM at lower SDD (MTC)	1				1 (0.8)

Abbreviations: CNS UAM, a urinary antimuscarinic with fewer central nervous system side effects (pharmacist judgment); DDI, drug interaction; MTC, mixed-type composite recommendation; SDD, standardized daily dose; UAM, urinary antimuscarinic.
[a]A drug interaction was considered resolved if the perpetrator drug was changed or if the timing of administration was altered to mitigate competitive inhibition between perpetrator and UAM.

proposed recommendations). Supplementary Table S4 reports implementation by site.

Anticholinergic exposure

As Supplementary Figure S2 illustrates, implementers experienced a 65.4% decrease ($p < 0.001$) in total anticholinergic SDD (2.6 [95% CI: 2.2–3.0] to 0.9 [95% CI: 0.6–1.2]) and a 75.0% ($p < 0.001$) decrease in UAM-specific SDD (2.0 [95% CI: 1.8–2.2] to 0.5 [95% CI: 0.3–0.6]), over 9-months. No significant change from baseline was observed for either total ($p = 0.52$) or UAM-specific ($p = 0.054$) SDD in non-implementers. There were no differences between groups at baseline for total ($p = 0.45$) or UAM-specific SDD ($p = 0.36$); however, mean SDDs (total and UAM-specific) were different at each follow-up time point ($p < 0.001$ for all). Supplementary Table S5 reports each medication's relative contribution to the SDD at each time period.

Predictors of implementation

Our multivariable logistic regression found that taking <10 chronic medications (OR 2.75; 95% CI: 1.08, 7.61); baseline UAM SDD ≥2 (OR 2.19; 95% CI: 1.11, 4.44); non-MTC recommendations (OR 3.38; 95% CI: 1.67–7.03); and baseline calcium channel blocker (CCB) use (OR 2.18; 95% CI: 1.09, 4.52) were significant predictors of implementation (Supplementary Table S6 reports univariate analysis; Supplementary Table S7 summarizes the regression).

DISCUSSION

This retrospective analysis of 187 medically complex, community-dwelling older adults found that nearly two-thirds ($n = 118$) de-escalated their UAM, where the overwhelming majority (1) did so within 2 months of a pharmacist's intervention and (2) sustained the de-escalation over 9 months. For these participants, prescribers implemented 80% of pharmacists' recommendations exactly as proposed. Implementers reduced their overall anticholinergic exposure by 65% (measured by SDD), which was predominantly driven by UAM discontinuation (85/118). Collectively, we believe our results underscore the feasibility of these interventions.

In juxtaposition, other anticholinergic deprescribing studies report implementation rates between 17% and 44%.[8,18,19] The PACE model likely facilitated our higher rate. First, interprofessional collaboration is the cornerstone of PACE care.[13] At this pharmacy, significant collaboration with pharmacists occurs, which is demonstrated by prescriber acceptance rates exceeding 70% for other interventions.[20–23] Second, PACE may eliminate some financial barriers to implementation. This may be especially important for the 25% who switched to mirabegron, a brand-name drug that is significantly more expensive than older, generic UAMs (e.g., oxybutynin). PACE participants do not pay out-of-pocket for medications; thus, for those outside of PACE, switching to mirabegron is only feasible for those who can afford it. Additionally, capitation permits PACE to provide incontinence-wear at no cost to the participant. Future research should examine the role of these supplies since we could not analyze utilization.

PACE aside, UAM de-escalation significantly reduced anticholinergic exposure, which may carry implications for cognitive and physical functioning. For instance, implementers reduced their mean SDD from about 2.5 to 1. Gray et al. found that patients taking SDDs of 2.5 would need about 1.2 years of cumulative exposure to significantly increase risk of dementia, whereas those taking SDDs of 1 would need 3 years.[5] A similar relationship exists between falls and cumulative anticholinergic exposure.[3] Therefore, future UAM deprescribing research must evaluate these outcomes.

Until then, we identified four factors that predicted UAM de-escalation, which may help pharmacists wishing to deploy this service. First, pharmacists could avoid overwhelming prescribers with several recommendation options (i.e., MTC recommendations). Indeed, high implementation (e.g., 85%) despite a small number of recommendations per patient (e.g., ≤1) has been reported elsewhere.[24,25] Second, pharmacists could prioritize those with UAM SDDs ≥2 (e.g., oral oxybutynin 10 mg/day), who may be particularly amenable to de-escalation because intolerable adverse effects are more likely with higher doses.[26] Third, concomitant CCBs can cause urinary retention and overflow incontinence, which may be beneficial for those with urge UI.[27,28] Though this requires further research, UAM de-escalation may be more successful because CCBs attenuate urge UI symptoms. Fourth, polypharmacy can make deprescribing more challenging for prescribers.[29] Indeed, those taking >10 medications de-escalated UAMs less frequently than their less complex counterparts, who, arguably, may be less likely to benefit from de-escalation.

Limitations

- We were unable to assess any participant-specific outcome, so conclusions cannot be drawn about this intervention's benefit.

- UAM adherence is generally poor,[12] yet we could not (1) validate UAM ingestion or (2) estimate adherence because all chronic medications are automatically dispensed on cycle. Nevertheless, adherence packaging and PACE homecare nursing support may have improved adherence here.
- We could not consider non-drug or clinical factors (e.g., ethnicity, pad use, symptom severity, UI subtype) in our regression.
- We could not assess participant input when making therapy changes. It is difficult to speculate how direct-to-prescriber recommendations influenced acceptance.
- We defined anticholinergic exposure using a list that closely aligned with the AGS Beers Criteria[7]; thus, the decrease in exposure could be attenuated had we included weaker anticholinergics (e.g., Anticholinergic Cognitive Burden[30]).
- Generalizability outside of PACE must be confirmed by other research.

CONCLUSION

It is feasible for pharmacists to target urinary antimuscarinics for de-escalation as a way to reduce overall anticholinergic exposure in medically complex, community-dwelling older adults.

AUTHOR CONTRIBUTIONS

Conceptualization: David L. Bankes; *Methodology*: David L. Bankes, Veronique Michaud, Jacques Turgeon, Sweilem B. Al Rihani; *Formal analysis*: David L. Bankes, Meghan Ha; *Investigation*: David L. Bankes, Meghan Ha, Anna Furman; *Resources*: Jacques Turgeon; *Writing—original draft preparation*: Meghan Ha; *Writing—review and editing*: all authors; *Visualization*: Meghan Ha, David L. Bankes; *Supervision*: Jacques Turgeon; *Project administration*: David L. Bankes; *Funding acquisition*: Jacques Turgeon. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

Sweilem B. Al Rihani, Veronique Michaud, Jacques Turgeon, and David L. Bankes report current employment and stock ownership with Tabula Rasa HealthCare (TRHC) d/b/a CareKinesis pharmacy. Drs. Meghan Ha and Anna Furman were previously employed by TRHC as post-graduate year 1 pharmacy residents.

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ORCID

Sweilem B. Al Rihani https://orcid.org/0000-0003-2415-4664
Veronique Michaud https://orcid.org/0000-0002-1399-6447
Jacques Turgeon https://orcid.org/0000-0002-7978-9280
David L. Bankes https://orcid.org/0000-0001-6358-2288

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Supplementary Appendix S1. Supporting methods, results, and figures.
Supplementary Figure S1. Workflow summary.
Supplementary Table S1. Anticholinergics overlapping Gray et al.'s list.
Supplementary Table S2. Example SDD calculation for a hypothetical participant taking two anticholinergic drugs.
Supplementary Table S3. "Altered" implementation encountered in data.
Supplementary Table S4. Site-level implementation.
Supplementary Figure S2. Changes in mean standardized daily dose across study.
Supplementary Table S5. Relative contributions of anticholinergic medications to standard daily dose.
Supplementary Table S6. Univariate analysis.
Supplementary Table S7. Predictors of recommendation implementation from multivariable logistic regression.

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Editor's Note

This is a very nicely done and reported study of "de-escalating" or deprescribing urinary antimuscarinics among 187 participants at 35 PACE sites. The intervention was very effective, but there are some caveats that should be mentioned. The most commonly targeted drug was oxybutynin, which in pill form can have several bothersome side effects, especially intolerable dry mouth. Many people stop taking it before its effectiveness can be determined because of this side effect. Some patients' urge incontinence or overactive bladder is much better on it, enabling them to go out to shows, shopping or meals, or take airplane trips. Some people take it intermittently for these situations. Long-term use has been associated with incident cognitive impairment, so this possibility has to be included in the risk-benefit calculation.

Another caveat is that this study was done just as beta-3 agonists were coming on the market, including mirabegron and vibegron. These drugs have about the same efficacy as antimuscarinic agents, but do not have the bothersome anticholinergic effects. They can raise the systolic blood pressure by 4–8 mm Hg, but this is generally not a problem unless blood pressure is poorly controlled. Another potential problem with these drugs, as is true for most new agents, is their expense due to high copayments.

Finally, this study is framed with the assumption that antimuscarinic drugs should be de-escalated or deprescribed in all older adult. Some actually benefit markedly in terms of function and quality of life, and even more importantly safety. Overactive bladder and urge incontinence pose major risks for falling as anywhere from a quarter to half of falls are associated with attempts to toilet. Behavioral therapies such as pelvic muscle exercises among cognitively intact and prompted voiding for those who need toileting assistance can be highly effective in selected older adults. But for those who fail to respond to these interventions and who are bothered or at risk from their symptoms, a 1–2 month trial of drug therapy in addition to behavioral therapy should be considered.

-Joseph G. Ouslander, MD