ORIGINAL RESEARCH

A Description of QT-Interval Prolonging Drug Interactions with Fluoroquinolones in Older Women with Uncomplicated Urinary Tract Infections

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ABSTRACT

Background

Fluoroquinolone (FQ) antibiotics are associated with QT-interval prolongation and Torsades de Pointes (TdP). Female sex, older age, and other QT-interval prolonging medications further increase risk for TdP. Our aim was to describe QT-interval prolonging drug interactions when FQs were dispensed to women who resided in long-term care (LTC) for uncomplicated urinary tract infections (UTIs).

Methods

This retrospective cohort study used administrative health data from the Nova Scotia Seniors' Pharmacare program from January 2005 through March 2020. The cohort included women residing in LTC dispensed a FQ antibiotic within five days of a diagnostic code for an uncomplicated UTI in physician billing data. Additional drug dispensations were collected 30 and 90 days after the FQ to identify drug interactions that resulted in potentially increased QT-interval prolongation risk. Drug interactions were described. A Mann-Kendall trend test assessed the change in the frequency of FQ-drug interactions over the study period.

Results

Annual dispensation of FQs ranged from 12–28% of antibiotic dispensations for presumed uncomplicated UTI. The proportion of FQ dispensations associated with a QT-interval prolonging drug interaction increased over time (p=.00007). Within 30 days of the FQ dispensation, the most common drug interactions identified were: furosemide (n=702, 20.3% of FQ-drug interactions), citalopram (n=566, 16.4% of FQ-drug interactions), and trazodone (n=461, 13.3% of FQ-drug interactions).

Conclusions

An increasing proportion of women dispensed a FQ for uncomplicated UTI experienced a potential QT-interval prolonging drug interaction over the study period. When prescribing FQs to older women, addressing potentially modifiable risk factors for TdP, and monitoring closely, is warranted.

Key words: fluroquinolone, drug interaction, long-term care, Torsades de pointes

INTRODUCTION

Urinary tract infections (UTIs) are increasingly common in women as they age[(1)] and are the most common infection diagnosed in long-term care (LTC) settings.[(2,3)] Guidelines for uncomplicated UTI management[(3,4)] do not include fluoroquinolone (FQ) antibiotics among the firstline choices for empiric antimicrobial selection due to increasing antimicrobial resistance,[(5–7)] an increased propensity to cause harm including development of Clostridioides difficile infection, and the possibility of rare but serious adverse effects including ruptured aorta,[(8–10)] tendinopathy or tendon rupture, psychosis, hypoglycemia, peripheral neuropathy, retinal detachment, and QT-interval prolongation.[(8,11)]

The known potential for FQ antibiotics to prolong the QT-interval[(12)] is associated with an increased risk of serious arrhythmias, including Torsades de Pointes (TdP). TdP is a serious and potentially fatal arrhythmia.[(13,14)] FQ antibiotics decrease repolarizing ionized potassium currents by inhibiting the outward rapid delayed rectifier potassium current and increasing the duration of the action potential, which can prolong the QT-interval. Some fluoroquinolones (FQs), including gatifloxacin, levofloxacin, and sparfloxacin, bind to a protein called the human Ether-a-go-go-Related Gene (hERG). When FQs bind to hERG channels, they act as antagonists and block the Kv11.1 voltage-gated potassium channel, which contributes to the rapid delayed rectifier current of the cardiac action potential. Blocking the Kv11.1 channel prolongs the duration of individual ventricular action potentials, which in

turn leads to QT-interval prolongation.[14,15] Systematic review and meta-analysis has demonstrated that the pooled relative risk for serious arrhythmias across all FQs was 2.29 (95% CI: 1.2-4.36) and 1.6 (95% CI: 1.17-2.20) for cardiovascular death. Different FQs show different relative risks for serious arrhythmia, with the greatest relative risk of 6.37 associated with gatifloxacin use, followed by moxifloxacin at 4.20, ciprofloxacin at 1.73, and levofloxacin at 1.41.[11,14]

FQs have well documented effects on cardiac polarization, but many other medications and risk factors exist that can prolong the QT-interval through both similar and different mechanisms. Combining drugs and disease states that can prolong the QT-interval can further increase risk of serious arrhythmia. Other risk factors for QT-interval prolongation and serious arrhythmia include female sex, older age, genetic predisposition, electrolyte abnormalities, and other underlying cardiac conditions.[16] Older women living in LTC are already known to be at increased risk of QT-interval prolongation or serious arrhythmia due to the presence of risk factors including advanced age and sex. It is not known how frequently potentially QT-interval prolonging medications are used by older women who reside in LTC who are prescribed FQs.

The objective of this investigation was to assess the proportion of women 65 years of age and older residing in LTC in Nova Scotia (NS), Canada diagnosed with an uncomplicated UTI prescribed a FQ who experienced a potential QT-interval prolonging drug interaction with the prescribed FQ antibiotic. Additionally, the study included an assessment of the annual change in the rate of QT-interval prolonging drug interactions and a description of the most common QT-interval prolonging drug combinations over a nearly 16-year follow-up period.

METHODS

Design and Data Sources

This was a retrospective cohort study using de-identified health administrative data from Nova Scotia (NS), Canada. The definition of UTI and how to identify associated antibiotics was adapted from work by the Canadian Network of Observational Drug Effect Studies (CNODES).[17] Data accessed included patient level data from NS physician billing data and the Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD; https://www.cihi.ca/en/discharge-abstract-database-metadata-dad) to identify those with a UTI, and data from the NS Seniors' Pharmacare Program (NSSPP) was used to identify dispensed medications. Diagnosis and dispensing data were linked by a provincial data custodian (Health Data Nova Scotia).

Population

The target population included women aged 65 years and older who were beneficiaries of the NSSPP and resided in LTC in NS, Canada. Those women who had a diagnosis of uncomplicated UTI as identified by ICD 9 codes 95.X, 599.X or ICD 10 codes J40-J44, N39.X in the NS Physician billing data or the Canadian Discharge Abstract Database between January 2004 and March 2020 were selected. Antibiotics (ATC code J01) dispensed within five days of the identified UTI diagnosis were captured. To limit the analysis to those with an uncomplicated UTI, those with pregnancy less than 270 days prior to the event date, hospital discharge less than 30 days prior to the event date, or those with factors suggestive of a more complicated UTI recorded within 365 days of the UTI date were excluded. Complicated UTI was considered when a UTI had been diagnosed in the 90 days preceding the current UTI code identified, or a diagnosis of kidney or bladder stones, ureteral abnormality, vesicoureteral reflux, neurogenic bladder, neurologic condition, or diabetes was also present. Those with f wer than 365 days of NSSPP coverage, fewer than 365 days of health data in the database prior to the UTI event date, or fewer than 35 days of data after the UTI event date were also excluded. Only those dispensed a FQ antibiotic at the time of the UTI event diagnosis were selected for further assessment.

For the selected cohort, all other medications dispensed from the NSSPP records were captured to identify any additional QT-interval prolonging medications prescribed and dispensed concurrently with the FQ antibiotic. Medications that increased the risk of QT-prolongation were identified using the resource crediblemeds.org.[14] Any drugs with known, possible, or conditional risk of TdP that were dispensed within 30 and 90 days of the UTI diagnosis date were included as drug interactions. The three risk categories were defined as: a) known risk of TdP: Cause QT-interval prolongation and are clearly associated with risk of TdP even if taken as directed; b) possible risk of TdP: Cause QT-interval prolongation but lack evidence for risk of TdP when taken as directed; and c) conditional risk of TdP: Associated with TdP under certain conditions such as hypokalemia, interacting drugs, or electrolyte disturbances.[16] Drug interactions between FQ antibiotics and other medications implicated in potential QT-interval prolongation were reported annually (calendar year). In each year, only the 10 most frequently dispensed QT-interval prolonging drugs were identified. Collated results included only those drugs which were among the top 10 interactions in each of the individual years. This prevented any potential errors related to those years where a drug was not reported in the data collected.

Statistical Analysis

Drug interactions between FQ antibiotics and other medications that can prolong the QT-interval were described and reported as the proportions of FQ dispensations. Descriptive statistics included details of the proportion of patients concomitantly receiving a drug with "conditional", "possible", or "known" risk of QT-interval prolongation within 30 days of FQ dispensation. Descriptive statistics were repeated for the proportion of patients concomitantly receiving a drug with "conditional", "possible", or "known" risk of QT-interval prolongation within 90 days of FQ dispensation. A Mann-Kendall trend test assessed for increasing or decreasing FQ-drug interactions over the 15-year period of follow-up. Analysis was completed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and some

figures were prepared with R version 4.2.2 (R Foundation for Statistical Computing, https://www.r-project.org/foundation/) or Excel version 16.69.1 (Microsoft, Redmond, WA).

This research received ethics approval (REB # 2016-3954) and subsequent annual approvals from the Health Sciences Research Ethics Board, Dalhousie University, Halifax, NS.

RESULTS

We identified in total 15,276 unique uncomplicated UTI events in 7,078 women over 15 years of follow-up. FQs were dispensed in 22.2% (n=3,454) of the uncomplicated UTI events. Details of the UTI events and their treatment were previously published.[18] FQ dispensation for UTI events varied over follow-up, but was highest in 2012 with 300 (27.4% of UTI events) events and the lowest in 2018 with 64 (12.3% of UTI events) events. The most often dispensed FQ was ciprofloxacin (n=2,923, 84.6% of FQ dispensations) followed by norfloxacin (n~345, ~10% of FQ dispensations). Even though the number of UTI events treated with a FQ declined over the period of follow-up, the proportion of those FQ-treated UTI events with a potential QT-interval prolonging drug interaction increased (Figure 1). There was a statistically significant increase in the proportion of FQ dispensations associated with a potential QT-interval prolonging drug interaction over time (p=.00007).

The most common drug interactions identified during the study period are shown in Figure 2. Our data request was for the top 10 interacting drugs in each year of follow-up. Over the study period, the most dispensed interacting medications varied such that, in some years, drugs were not reported in favour of others. There were eight drugs reported in each year of follow-up. Of these only two were known to have a risk of QT-interval prolongation (citalopram and domperidone), and six had a conditional risk of QT-interval prolongation which means that, when combined with other drugs or other risk factors, they can cause QT-interval prolongation (furosemide, trazodone, omeprazole, risperidone, quetiapine, and hydrochlorothiazide[14]). The three most common medications identified to cause a potential QT-interval prolonging drug interaction were furosemide (n=702, 20.3% of FQ-drug interactions), citalopram (n=566, 16.4% of FQ-drug interactions), and trazodone (n=461, 13.3% of FQ-drug interactions) (Figure 2).

DISCUSSION

We identified that between 12% and 28% of the uncomplicated UTI events in older women residing in LTC were treated with a FQ between 2005 and 2020. Over the period of study, the number of women dispensed a FQ decreased, but an increasing proportion had FQ-drug interaction that could cause a prolonged QT-interval and increased risk of TdP. Most (6

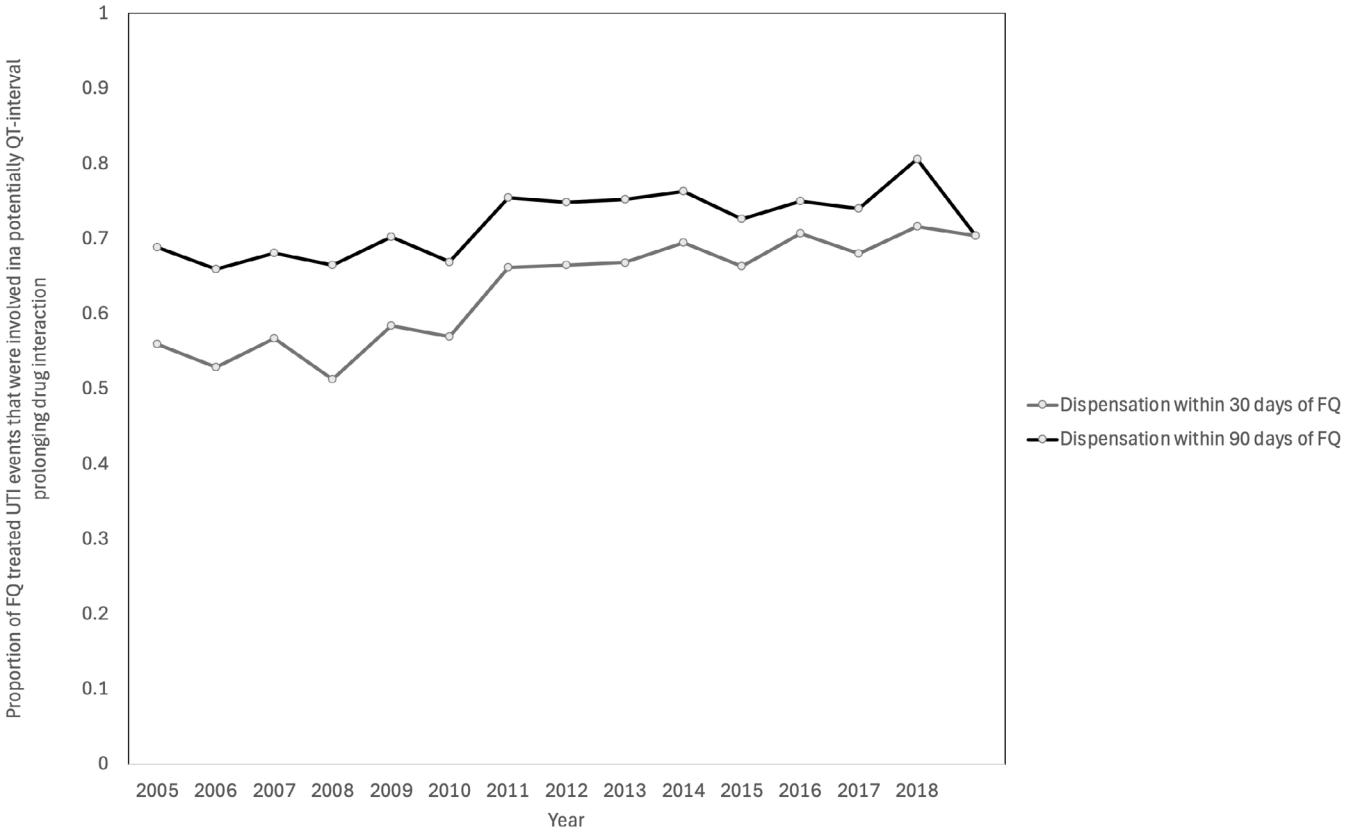

FIGURE 1. Proportion of UTI events treated with a fluoroquinolone that were involved in a potentially QT-interval prolonging drug interaction within 30 and 90 days of an uncomplicated urinary tract infection diagnosis in women 65 years of age and older who reside in long-term care

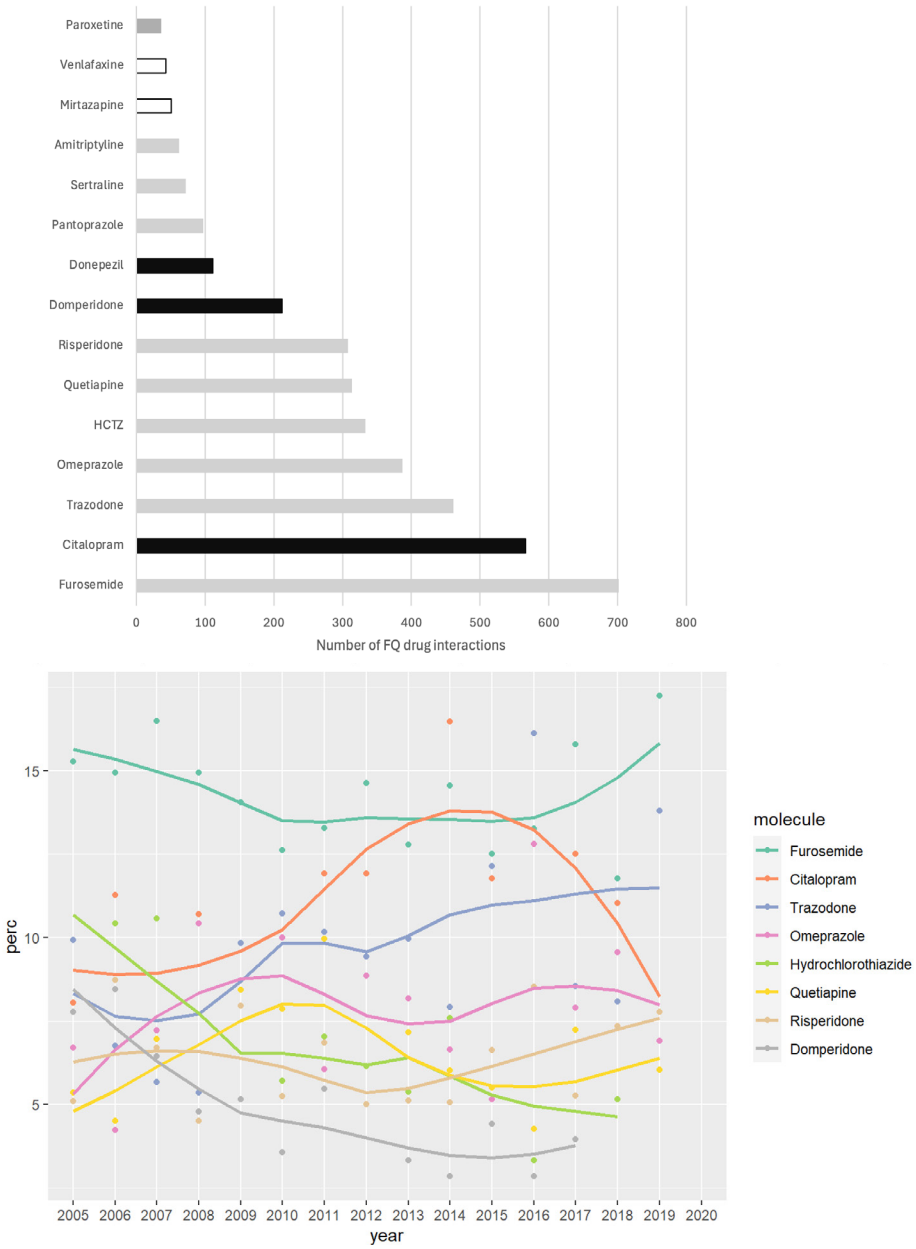

FIGURE 2. Top eight specific medications with known or conditional risk of QT-interval prolonging drug interactions with fluoroquinolone antibiotics between 2005 and 2019 in women 65 years of age and older who reside in long-term care

of 8) of the identified drug interactions, including the most frequently identified (furosemide), were categorized as posing a "conditional" risk of QT-interval prolongation and serious arrhythmia (i.e., Torsade's de Pointe). However, the second most-common drug interaction identified occurred between a FQ and citalopram. Both FQs and citalopram are categorized as "known risk of TdP".[13]

All the subjects in the present study were older women which further adds to their baseline risk profile and makes them more likely to be at risk of TdP. In addition to age and sex, the patient population of older women residing in LTC may have a higher prevalence of diabetes[19] and other underlying health conditions compared to the general population of older women, which further increases baseline risk of serious arrhythmia.[20] In addition, this population generally is at an increased risk of polypharmacy,[21] resulting in multiple interacting drugs that may cause additive QT prolongation.[22] This further underscores the importance of careful consideration when prescribing FQs in this population.

QT-interval prolonging medications have been increasingly dispensed and used in recent years.[21] This may account for the increase in the proportion of QT-interval prolonging drug interactions, including those observed with citalopram in this study. Since the beginning of the COVID-19 pandemic, there has been growth in the prescribing of antidepressants such as citalopram. In one example, among women living in

LTC, antidepressant use increased 2.7% from 2019 to 2021.[23] Also consistent with our findings, in Sweden, those living with dementia were commonly prescribed medications that can prolong the QT-interval, with 41.6% prescribed at least one medication from the CredibleMeds online database.[24] In older adults who have underlying mental health conditions, the risk of drug–drug interactions with FQ exposure may be particularly high. In a population of Iranian adults receiving care in a geriatric psychiatry setting, 70.7% were prescribed drugs that interacted to increase risk of TdP.[25]

For most older women with an uncomplicated UTI, FQs likely should be avoided, but when they are required, the decision to use the FQ should be made consciously with assessment of potential QT-interval prolonging drug interactions and with plans for monitoring for risk factors that can increase risk of TdP. It may be possible to use clinical decision support tools at the point of prescribing that can target QT-interval prolonging medications with an aim to reduce QT-interval prolonging drug interactions.[26] Drug interaction tools can be used but require knowledgeable clinicians to interpret the findings. Programs in Australia for pharmacists in aged care settings to assist in the evaluation of QT-interval prolonging drug interactions found that there was incomplete understanding of implicated medications and the level of risk.[22] Increased education is likely important for clinicians in aged care settings, such as long-term care. If the risk is considered high (i.e., multiple interacting medications, or other risk factors like electrolyte abnormalities), it may be worthwhile to hold interacting medications for the duration of the prescribed FQ or until a monitoring plan can be safely implemented. Monitoring should also include regular clinical assessment, as well as assessment of baseline QT-interval and serum electrolytes and correction of electrolyte abnormalities when needed.

Managing risk factors for QT-interval prolongation and potential drug interactions that increase risk of QT-interval prolongation in older adults is challenging. FQ antibiotics for patients with bacteriuria generally should be avoided; but when necessary, we suggest implementing a patient-specific monitoring and management strategy.[27–30] This may include monitoring of modifiable risk factors for TdP such as K^+ and Mg^{2+}, heart rate, nutritional status (particularly for anorexia, vomiting and diarrhea), and renal dysfunction. There are also known non-modifiable risk factors of TdP including a genetic predisposition to a long QT-interval, family history of sudden cardiac death, a previous history of TdP, older age, female sex, low left ventricular ejection fraction, left ventricular hypertrophy, or ischemia, structural heart disease, impaired elimination due to renal or hepatic dysfunction, and thyroid disease.[16,28,30] When the risk of TdP is increased due to presence of these factors, it is reasonable to assess QT-interval with an ECG. In populations of older women living with comorbidity in LTC, the risk of TdP is elevated even before a drug interaction. The need to manage UTI events, extra monitoring, and potential additional testing needs to be carefully considered and balanced with the patient's other goals of care.

While our findings provide insight into potential pathways to pharmacovigilance in older women with bacteriuria, several limitations should be considered. The analysis is limited by a lack of clinical data on our patient population to further quantify risk of serious arrhythmia (e.g., underlying medical conditions, laboratory values, baseline QTc interval) and for having no assessment of patient outcomes related to the co-prescribing of medications with the potential for QT-interval prolongation. The eight most dispensed medications that can cause prolonged QT-interval were summarized annually, and presented only as aggregate results, which limits conclusions that can be made. Use of dispensation data allows only knowledge of medication dispensation and does not permit confirmation that patients were still receiving the potentially interacting drugs dispensed within 30 or 90 days of the FQ dispensation.

The decline in FQ dispensation was encouraging and likely related to wide-spread knowledge translation efforts to improve antimicrobial stewardship. In Canada, Choosing Wisely[31–33] and institutional programs have focused on reductions in FQ dispensation.[34] Improved management of bacteriuria—including more appropriate antibiotic use, a decrease in *Escherichia coli* non-susceptibility to FQs, and a decrease in FQ use through implementation of various antimicrobial stewardship initiatives—has also been reported in the literature.[35] Most interventions were multifaceted and included education in combination with guideline development, audit, and feedback, and/or implementation of computer decision support. Although improvement in use of FQs has been observed in patients with bacteriuria, the proportion of FQ-drug interactions has increased, suggesting ongoing challenges with polypharmacy among older adults.[21] In addition to continued implementation of antimicrobial stewardship initiatives and judicious use of FQs, medication review and deprescribing of other unnecessary medications in this population may further improve the proportion of drug interactions that present.

CONCLUSION

Many older women residing in LTC with an uncomplicated UTI have underlying comorbidities resulting in concomitant use of drugs that may prolong the QT-interval and increase risk of TdP. These findings underscore the importance of judiciously prescribing FQs in this patient population and further support recommendations to limit use of fluoroquinolones for women with uncomplicated UTIs to avoid serious arrhythmia. When using FQs, practitioners should ensure patients are closely monitored for QT-interval prolongation to mitigate risk of harm.

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CONFLICT OF INTEREST DISCLOSURES

Emily Black has received funding to support research projects unrelated to this work from Pfizer Canada and Shoppers Drug Mart. Ingrid Sketris has received research grant support from the Drug Evaluation Alliance of Nova Scotia and salary support from the Canadian Network for Observational Drug Effect Studies (CNODES). Shanna Trenaman has received research grant support from the Drug Evaluation Alliance of Nova Scotia for an unrelated research project. The remaining authors have no financial or personal relationships with commercial entities to disclose.

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