

Original Research Article

The Influence of Patient Characteristics on Anticholinergic Events in Older People

Mohammed Saji Salahudeen Prasad S. Nishtala Stephen B. Duffull

School of Pharmacy, University of Otago, Dunedin, New Zealand

Key Words

Anticholinergic events · Risk factors · Adverse events · Elderly · Older people · Antimuscarinic response · Anticholinergic burden

Abstract

Aims: To examine patient characteristics that predict adverse anticholinergic-type events in older people. **Methods:** This retrospective population-level study included 2,248 hospitalised patients. Individual data on medicines that are commonly associated with anticholinergic events (delirium, constipation and urinary retention) were identified. Patient characteristics examined were medicines with anticholinergic effects (ACh burden), age, sex, non-anticholinergic medicines (non-ACM), Charlson comorbidity index scores and ethnicity. The Akaike information criterion was used for model selection. The data were analysed using logistic regression models for anticholinergic events using the software NONMEM. **Results:** ACh burden was found to be a significant independent predictor for developing an anticholinergic event [adjusted odds ratio (aOR): 3.21, 95% CI: 1.23–5.81] for those taking an average of 5 anticholinergic medicines compared to those taking 1. Both non-ACM and age were also independent risk factors (aOR: 1.41, 95% CI: 1.31–1.51 and aOR: 1.08, 95% CI: 1.05–1.10, respectively). **Conclusion:** To our knowledge, this is the first study that has examined population-level data in a nonlinear model framework to predict anticholinergic-type adverse events. This study evaluated the relationship between important patient characteristics and the occurrence of anticholinergic-type events. These findings reinforce the clinical significance of reviewing anticholinergic medicines in older people.

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Introduction

Older people taking medicines with anticholinergic properties are at an increased risk of experiencing adverse events [1–6]. Anticholinergic medicines bind to the muscarinic receptors, and the decreased cholinergic neurotransmission impacts both peripheral and

Dr. Mohammed S. Salahudeen, PharmD, MBA
School of Pharmacy, University of Otago
PO Box 56
Dunedin 9054 (New Zealand)
E-Mail mohammed.salahudeen@otago.ac.nz

central body systems [3, 7–10]. Peripheral anticholinergic adverse effects mainly include constipation, urinary retention, dry mouth, blurred vision, peristaltic reduction and tachycardia. The central anticholinergic adverse effects of clinical interest are cognitive impairment, confusion and delirium [11–14]. The risk of anticholinergic adverse events has been found to increase with age, pre-existing cognitive impairment, polypharmacy, comorbidities and cholinergic neuronal degeneration, and it is influenced by individual pharmacokinetic and pharmacodynamic variability [2, 8, 10, 15, 16].

The frequency of adverse drug reactions reported in older adults (≥ 65 years) is 7-fold higher than in younger adults [17]. Epidemiological studies have reported that 20–50% of the older population are routinely exposed to medicines that possess anticholinergic properties [18, 19]. Recent literature has highlighted that up to 40% of all institutionalised older people take medicines with known anticholinergic activity [2, 20]. Similarly, it has been reported that among hospitalised older people, the prevalence of those taking anticholinergic medicines increased significantly (7.2 ± 3.5 vs. 5.7 ± 3.1 ; $p < 0.001$) during their hospital stay [21].

The cumulative exposure to multiple medicines with anticholinergic properties is widely referred to as anticholinergic (ACh) burden [10, 12]. Numerous studies have reported ACh burden to be an important predictor of cognitive and physical impairment in older populations [1, 15, 22–26]. A higher ACh burden is associated with greater risks of morbidity and mortality, a longer length of hospital stay, institutionalisation and functional and cognitive decline in older people [3, 7–9, 12, 27–34]. Reducing the ACh burden can cause significant improvements in short-term memory, delirium, behaviour, daily-living and quality of life [7, 15, 28, 35]. Our recent systematic review identified two cohort studies [36, 37] that demonstrated an improvement of cognitive performance after the discontinuation of anticholinergic medicines [10]. A retrospective study by Nishtala et al. [15] found that a significant interaction exists between age ≥ 65 years and the exposure to medicines with anticholinergic properties [15]. In their study, Hilmer et al. [28] found a relationship between higher anticholinergic exposure and impaired physical function after adjusting for age, sex, race and comorbidities.

The current model assumes that the antimuscarinic response contributed by each drug is linear and additive [28]. However, there is a need to further explore the effect of anticholinergic events using nonlinear models which may reflect receptor binding more closely. Studies involving population-level data examining the exposure to anticholinergic drugs and adverse events are limited. Furthermore, clinical evidence implicating anticholinergic adverse events and the influence of associated patient characteristics in a nonlinear framework is lacking. To provide additional insights into the relationship between anticholinergic drugs and the influence of patient characteristics, we proposed a model-based approach to predict anticholinergic-type adverse events (central and peripheral adverse events) in this study. The main objective of this study was to explore the relationship between effects of important patient characteristics and the occurrence of anticholinergic-type events.

Methods

Data Source and Study Population

This retrospective population-level study included hospitalised individuals in 2010 identified from the national health data collections maintained by the Ministry of Health of New Zealand [38, 39]. Pharmaceutical collections are used by the Pharmaceutical Management Agency (PHARMAC) and the Ministry of Health of New Zealand to administer payment to pharmacists for dispensing medicines that are publicly funded under the national medicines budget managed by PHARMAC. Data on dispensed medicines were obtained from the phar-

maceutical collections for 2010. Demographic characteristics such as sex, date of birth, ethnicity and district health board of domicile were also extracted from the pharmaceutical collections. Patient information from the pharmaceutical collections was matched with hospital event data from the National Minimum Dataset using unique encrypted National Health Index numbers. We captured all medicines dispensed 14 days prior to the date of hospital admission to identify possible associations with outcomes of interest. Diagnoses in the National Minimum Dataset are coded using the International Classification of Diseases and Related Health Problems, 10th revision, Australian modification (ICD-10-AM). We identified ICD-10 codes for delirium (F05), constipation (K59) and urinary retention (R32, R39) from the coded diagnosis to capture anticholinergic events.

Overall, all hospitalised individuals aged ≥ 65 years living in New Zealand who were receiving at least one prescription medicine during the period starting on January 1, 2010 to December 31, 2010 were included in this study. Individuals with missing data on one or a combination of the following variables were excluded from the dataset: age, sex, medicine and medicine strength/dose. In this study, delirium, constipation and urinary retention were examined for anticholinergic adverse effects. Delirium is the most common cause of acute cognitive dysfunction in hospitalised older people, and it is mediated by the antagonism of centrally acting muscarinic receptors [40, 41]. These adverse effects were chosen because they reflect typical adverse pharmacological effects linked to central or peripheral muscarinic receptors associated with drug properties. Several studies have highlighted constipation and urinary retention as frequently occurring adverse anticholinergic effects in older people [7, 42, 43].

A validated weighted comorbidity index [Charlson comorbidity index (CCI)] was used for the measurement of comorbidity burden [44]. It provides a weighted score of a subject's comorbidities which can be used to predict short- and long-term outcomes. Compared to other comorbidity indices, the CCI score can be assigned to the majority of patients and is readily available. Studies have shown that the CCI score predicts hospitalisation, adverse outcomes as well as mortality [45–47]. The extracted data were rearranged into NONMEM version 7.2 with the G95 FORTRAN compiler-readable format using MATLAB version R2013b.

Approval to undertake this study was provided by the Human Ethics Committee of the University of Otago, New Zealand (approval No. HD14/10).

Exposure to Anticholinergic Medicines

Numerous medicines possess anticholinergic activity, but many of them are unlikely to cause significant clinical symptoms when given as monotherapy [48]. Our study focused on the use of medicines with relevant central and peripheral anticholinergic effects. Hence, the study considered medicines that have been identified as carrying a mild, moderate or severe risk of anticholinergic properties. Anticholinergic exposure was defined based on a list of medicines with known anticholinergic activity from the expert-opinion rating scales [49]. From this exposure, ACh burden was defined in this study as the sum of all anticholinergic medicine(s) taken by an individual.

Patient Characteristics and Modelling

The dataset comprised various patient characteristics such as medicines with anticholinergic properties (ACh burden), age, sex, non-anticholinergic medicines (non-ACM), CCI, ethnicity and number of hospital admissions during the study period. In this study, the total of all medicines is a continuous variable equivalent to the sum of all non-ACMs and the number of all anticholinergic medicine(s) (ACh burden). We were interested in ACh burden, and hence defined the other part of the total number of medicines as non-ACM. The study considered both linear and nonlinear logit models to evaluate the patient characteristics. The linear

models were constructed based on a stepwise forward addition of patient characteristics from the structural model to define the maximum number of important characteristics. The nonlinear model building was performed by adding patient characteristics into three different locations to predict various effects. In all models, second-level interactions were considered for testing variables of different patient characteristics.

Additional exploration was possible with the nonlinear model, which resembles a pharmacological binding model (which consider drug(s) binding to the receptor), and patient characteristics could be incorporated to test whether they (1) increased the risk of events independent of ACh burden (i.e. they pose a risk even in the absence of ACh burden) by adding patient characteristics to the baseline (β_0), (2) increased the maximal anticholinergic effect of ACh burden (i.e. an overall greater effect is seen with ACh burden) by adding an interaction of patient characteristics on E_{max} or (3) increased the apparent potency of the ACh burden (i.e. greater effects were seen for a given ACh burden value) by adding a patient characteristics on ACH_{50} that provides 50% of the maximal effect. The following logistic models were used to describe the linear and nonlinear predictors:

Linear Framework

$$\log_e \left\{ \frac{\pi}{1 - \pi} \right\} = \beta_0 + \beta_1 X_1 + \dots + \beta_n X_n, \quad (1)$$

where,

$$\log_e \left\{ \frac{\pi}{1 - \pi} \right\} \quad (2)$$

represents the log odds (logit) for reporting adverse anticholinergic effects, X_n represents the presence or absence of the n -th variable, β_n represents the parameter estimate and β_0 represents the intercept (base probability).

Nonlinear Framework

$$\log_e \left\{ \frac{\pi}{1 - \pi} \right\} = \beta_0 + E_{max} \frac{ACh \text{ burden}}{(ACH_{50} + ACh \text{ burden})}. \quad (3)$$

Here, E_{max} is the maximal effect that can be achieved, and ACH_{50} is the *ACh burden* that provides 50% of the maximal effect. In this modelling framework, we can consider the influence of patient characteristics on β_0 (the intercept), E_{max} (the maximal effect) and ACH_{50} (the apparent ACh burden potency).

All logit expressions were transformed using the expit function ($e^x / (1 + e^x)$) for a standard logistic regression. Model building for the linear and nonlinear frameworks was carried out from the base model (a model that considered intercept only).

Statistical Analysis

The data were analysed using logistic regression (in this case expanded to generalised nonlinear models) for all three anticholinergic events (delirium, constipation and urinary retention) using the software NONMEM (version 7.2). The NONMEM (nonlinear mixed effects modelling) software is a regression program that can accommodate repeated measurement data, where each individual may contribute multiple observations. Since some individuals contributed to more than one occasion (number of hospital admissions), the subject-specific

Table 1. Characteristics of the study population

	Total dataset population	Delirium	Constipation	Urinary retention	For total events
Patients	2,248	48	80	20	–
Total events	148 (6.6)	48 (2.1)	80 (3.6)	20 (0.9)	148 (6.6)
Male	1,020 (45.4)	17 (35.4)	27 (33.8)	12 (60.0)	56 (37.9)
Female	1,228 (54.6)	31 (64.6)	53 (66.2)	8 (40.0)	92 (62.1)
Age, years ^a	79±8.0	85±6.7	82±8.6	84 9.6	84±8.3
Total medicines	3.48±2.5	5.88±2.8	5.89±3.0	5.45±2.5	5.74±2.8
Occasions ^b	1.10±0.4	1.08±0.3	1.05±0.2	1.00±0.0	1.04±0.2
CCI	1.10±0.3	1.42±1.5	1.16±1.4	1.10±1.3	1.23±1.4
Ethnicity					
European	1,855 (82.5)	46 (95.8)	64 (80.0)	17 (85.0)	127 (85.8)
Māori	158 (7.0)	2 (4.2)	8 (10.0)	2 (10.0)	12 (8.1)
Pacific	109 (4.8)	0	1 (1.3)	0	1 (0.7)
Asian	82 (3.6)	0	6 (7.5)	1 (5.0)	7 (4.7)

The values are given as mean ± SD for continuous variables and as numbers (%) for nominal data.

^a The subjects' age ranged from 65 to 102 years. ^b The total number of occasions is based on the number of hospital admissions during the study period.

random effects were also considered. In this framework, a second-order conditional estimation method (the Laplacian option) was used in NONMEM.

Patient characteristics with a statistically significant effect were incorporated in the model, which significantly reduced the unexplained between-subject variability (in circumstances where this was estimated), and the Akaike information criterion was used in this study for model selection [50]. Continuous data from the patient characteristics (such as age) were normalised in the model by the mean population value to derive a stable conversion of data with less variance. The analysis continued with the stepwise forward addition of patient characteristics from the structural base model to define the maximum number of important patient characteristics. The structural model was then revised by considering interaction terms to provide the final model.

The 95% confidence interval for the adjusted odds ratio (aOR) values was estimated using a parametric bootstrap in which 10,000 parameter values were simulated in MATLAB under the posterior distribution from the NONMEM parameter estimates. The confidence interval was then taken as the 2.5th and 97.5th percentiles of the simulations.

Results

The study sample consisted of 2,248 older hospitalised individuals. The incidence rates of anticholinergic-type adverse events in the dataset for delirium, constipation and urinary retention were 2.1, 3.6 and 0.9%, respectively. The mean age (± SD) of the study population was 79 ± 8 years. A detailed summary of the patient characteristics is given in table 1. The overall incidence rate of all events in the dataset was 6.6%, and the baseline estimate from logistic regression estimated an average incidence rate of the three events of 2.2%. However, considering the Akaike information criterion, the complexity of the multivariate model, the biological plausibility and the pharmacological mechanism, the non-linear model was preferred over the linear model. A detailed summary of both the linear

Table 2. Particulars of the anticholinergic medications identified from the study population (n = 69)

System	Therapeutic class	Medicines with anticholinergic activity	Frequency
Cardiovascular system	Diuretic	furosemide (H, L)	981
		chlortalidone (L)	6
	Beta-blocker	metoprolol (L)	939
		atenolol (L)	63
	Nitrate	isosorbide (L)	237
	Antiarrhythmic	digoxin (H, L)	309
	Calcium channel blocker	diltiazem (L)	216
		nifedipine (L)	9
	Platelet inhibitor	dipyridamole (L)	147
ACE inhibitor	captopril (L)	3	
Anticoagulant	warfarin (L)	477	
Respiratory system	Xanthine	theophylline (M, L)	6
Neurological system	SSRI	citalopram (L)	486
		fluoxetine (L)	114
		paroxetine (H, M, L)	78
	SNRI	venlafaxine (L)	21
	Antidepressant	amitriptyline (H)	414
		imipramine (H)	15
		dosulepin (dothiepin) (M)	33
		clomipramine (H)	15
		nortriptyline (H, M)	135
		doxepin (H)	27
		bupropion (L)	3
		mirtazapine (L)	3
		Antipsychotic	quetiapine (H, M, L)
	risperidone (L)		138
	prochlorperazine (M, L)		126
	haloperidol (M, L)		93
	olanzapine (H, M, L)		27
	levomepromazine (H)		21
	fluphenazine (H, L)		3
	Antiparkinson	carbidopa (L)	54
		benztropine (H)	12
	Anxiolytic (Benzodiazepine)	temazepam (L)	123
		lorazepam (L)	117
		clonazepam (L)	72
		diazepam (L)	57
		triazolam (L)	54
		midazolam (L)	24
oxazepam (L)		12	
alprazolam (H, L)		9	
Anticonvulsant	valproic Acid (L)	42	
	carbamazepine (M, L)	33	
Antimanic	lithium (L)	18	

Table 2 (continued)

System	Therapeutic class	Medicines with anticholinergic activity	Frequency
Gastrointestinal/ genitourinary tract system	Antispasmodic	atropine (H)	3
	Antidiarrheal	loperamide (M, L)	45
	Antacid	ranitidine (M, L)	42
		cimetidine (M, L)	3
	Antihistamine	loratadine (M, L)	27
		cetirizine (M, L)	18
		promethazine (H)	6
		fexofenadine (M)	3
	Antiemetic	metoclopramide (L)	75
		domperidone (L)	63
Antimuscarinic (overactive bladder agent)	oxybutynin (H, M)	72	
Muscle relaxant		orphenadrine (H)	3
Immunosuppressant		cyclosporine (L)	6
Opioid	Narcotic analgesic	codeine (M, L)	162
		morphine (L)	132
		oxycodone (L)	102
		tramadol (M, L)	30
		methadone (M)	15
Miscellaneous	Biguanides	metformin (L)	480
	Corticosteroid	prednisone (L)	171
		dexamethasone (L)	54
		hydrocortisone (L)	18
	Anti-gout	colchicine (H, L)	36
	Antimetabolite	methotrexate (L)	6
COMT inhibitor	entacapone (L)	3	

n = 69, i.e. the total number of unique anticholinergic activity medicines captured in this study was adopted from one of our previous publications [49].

Anticholinergic activity is indicated by L (low), M (moderate) or H (high). ACE = Angiotensin-converting enzyme; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; COMT = catechol-O-methyltransferase.

and nonlinear model buildings is depicted in online supplementary table S1 (see www.karger.com/doi/10.1159/000441718).

Table 2 summarises the frequencies of the most commonly prescribed medicines with anticholinergic activity identified from the study population. The anticholinergic activity of medicines is rated based on a published reference scale inferring high (H), moderate (M) and low (L) activity [49]. The most frequently used anticholinergic medicines are those for the treatment of cardiovascular and neurological disorders (table 2). The majority of the anticholinergic medicines identified had L anticholinergic activity (80%), including furosemide, metoprolol, citalopram, metformin, warfarin, digoxin, isosorbide and diltiazem. M to H activity anticholinergic medicines included amitriptyline, quetiapine, nortriptyline, prochlorperazine, haloperidol and paroxetine. L, M and H activity anticholinergic medicines were used for calculating the burden scores shown in table 2. Several anticholinergic activity medicines

Table 3. Patient characteristics of interest influencing anticholinergic adverse events derived from the final (nonlinear) model

Factors	aOR (95% CI)
ACh burden	3.21 (1.23–5.81)
Non-ACM	1.41 (1.31–1.51)
Age	1.08 (1.05–1.10)
CCI	0.84 (0.78–0.95)

ACh burden = Sum of total anticholinergic medicines; non-ACM = non-anticholinergic medicines; CCI = Charlson comorbidity index; aOR = adjusted odds ratio; CI = confidence interval.

available in the literature [49] were not applicable to the study population because either they are not available in New Zealand or they are funded by PHARMAC. A complete list of these medicines is outlined in online supplementary table S1.

The final model was a nonlinear model for predicting the probability of anticholinergic-type events. Those patient characteristics that were found to be influential were ACh burden, non-ACM, age and CCI (table 3). The main patient characteristic was ACh burden (aOR of an anticholinergic event was 3.21, 95% CI: 1.23–5.81, for those taking an average of 5 anticholinergic medicines compared to those taking 1; $p < 0.05$). It was a strong independent risk factor for developing an anticholinergic event. Other patient characteristics that were found to be significant included: non-ACM (aOR 1.41, 95% CI: 1.31–1.51) and age (aOR 1.08, 95% CI: 1.05–1.10). The CCI score was negatively associated with anticholinergic events (aOR 0.84, 95% CI: 0.78–0.95). The influence of ACh burden was nonlinear within the logit domain, and the estimated maximum probability (E_{max}) of an adverse anticholinergic event was 0.33, i.e. with an infinite number of ACh burden medicines. The patient characteristics non-ACM, age and CCI were found to influence the baseline risk of an anticholinergic event. In addition, CCI and non-ACM were found to influence the maximum risk of an anticholinergic event associated with ACh burden (i.e. they affected E_{max}). None of the patient characteristics appeared to modify the effect of risk posed by ACh burden drugs.

Discussion

This study examined and explored the relationship between patient characteristics associated with anticholinergic drugs and anticholinergic-type adverse events in older people. The evidence from the current study clearly supports the existing literature that higher ACh burden, polypharmacy, age and multimorbidity are independent risk factors for adverse anticholinergic events in older people [2, 7, 51–53]. Findings from a recent cross-sectional study conducted in Finland involving 621 older individuals showed a strong association between ACh burden and anticholinergic events [54]. In a cohort study conducted by Rudolph et al. [31], higher anticholinergic risk scores were associated with an increased risk of both peripheral and central anticholinergic adverse effects in older people. The study compared two cohorts, one retrospective (132 patients) and one prospective (117 patients); in both cohorts, the risk of anticholinergic adverse events increased significantly with higher anticholinergic risk scores. Compared to the retrospective cohort, the prospective primary-care cohort reported dry mouth and constipation more frequently with an evidence of a dose-response relationship [31].

A prospective study involving 532 older veterans reported that the prevalence of anticholinergic-type adverse events, such as dry mouth and constipation, was significantly higher in individuals using anticholinergic drugs [55]. The study highlighted that anticholinergic-type adverse events are rare events (0.8%), which mirrors the incidence rate of anticholinergic-type events in our study population (6.6%) [55]. A study conducted in the USA involving 833 older home-care patients found that polypharmacy, a common occurrence in nursing-home residents, increases the risk of adverse drug events and hospitalisation [56]. Similarly, in our study, non-ACMs were associated with anticholinergic-type events both as an interaction with CCI and as an independent predictor.

In this study, we anticipated a positive association between comorbidities and anticholinergic events, adjusted for the total medicine burden; and the finding of a negative association is counterintuitive. We speculate that the burden of disease may take precedence over reporting of anticholinergic events. A new-user design excluding prevalent users (first-time users) may provide a clearer picture of the relationships between anticholinergic exposure and anticholinergic events, and this could be an area for future research.

The implications of this research could help to identify important patient characteristics that influence ACh burden. A reduction in ACh burden may result in improved short-term memory, confusion, behaviour and delirium together with an enhanced quality of life and daily functioning of older people [7, 28, 35]. In the context of quantification of ACh burden, drug dosage and muscarinic receptor-binding affinity are important to be considered. There is no globally accepted tool to quantify ACh burden for commonly prescribed medicines with known anticholinergic properties [10]. There is a need to improve the quantification of ACh burden. The model-based approaches presented in this study illustrate a potential direction for a nonlinear binding model to estimate the relative ACh burden of medicines.

One of the major strengths of this study was the use of population-level data and allowing the characteristics to be associated with the outcome of interest in a nonlinear model framework. The patient characteristics were derived from national health collections in real settings; hence, selection bias was negligible and makes our findings relevant to clinical practice. The findings reported in this study are generalisable as it represents the population of older people in New Zealand captured by the nationwide prescription database (Pharms). However, our findings need replication in other samples of diverse clinical settings for longer periods. The study also recognises important limitations of real data. The most significant concern is the potential of confounding by indication, something which is inherent to all pharmacoepidemiological studies.

The study did not account for all anticholinergic events contained in the national minimum dataset. Accurate documentation of anticholinergic-type adverse events relies on rigid clinical coding guidelines. Among the 2,248 individuals analysed in this study, only 2.1% had a coded diagnosis of delirium, which is considerably less compared to other database studies [40]. This may have underestimated the risk posed by ACh burden. Since causality was not assessed, we were unsure whether any of the events were caused by anticholinergics. A retrospective study design may be subject to residual confounding by unmeasured factors. The possibility of protopathic bias could not be entirely ruled out, as many older individuals receive anticholinergic medicines for the management of urinary symptoms. However, the choice of 3 diverse events, delirium, constipation and urinary retention, that arise commonly from anticholinergic activity medicines but less frequently from a single pathology was an attempt to decrease the risk of confounding factors associated with adverse events. This may cause an overestimate of the true association (positive confounding) or an underestimate of the association (negative confounding). It should be noted that this does not eliminate the risk.

Conclusion

To our knowledge, this is the first study that examined population-level data in a nonlinear model framework to predict anticholinergic-type adverse events. This study evaluated the relationship between important patient characteristics and the occurrence of anticholinergic-type events. ACh burden was found to be an independent risk factor for predicting the probability of the anticholinergic-type events in older people. This study lends support to findings obtained from observational and experimental studies and reinforces the clinical significance of reviewing anticholinergic medicines in older people.

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Disclosure Statement

None of the authors have any conflicts of interest to declare.

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