Signals of muscle relaxant drug interactions associated with unintentional traumatic injury: A population-based screening study

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Introduction

- Use of muscle relaxants is rapidly increasing in the United States (US).
- Little is understood about the role of drug interactions in the known association between muscle relaxants and unintentional traumatic injury, a clinically important endpoint with substantial morbidity, disability, and death.

Objective

- To assess potential associations between concomitant medications taken with muscle relaxants and hospital presentation for unintentional traumatic injury

Methods

Database & Study Design

- Data: Optum Clinformatics
- Design: A semi-automated high-throughput pharmacoepidemiologic screening analyses using a series of bi-directional self-controlled case series studies
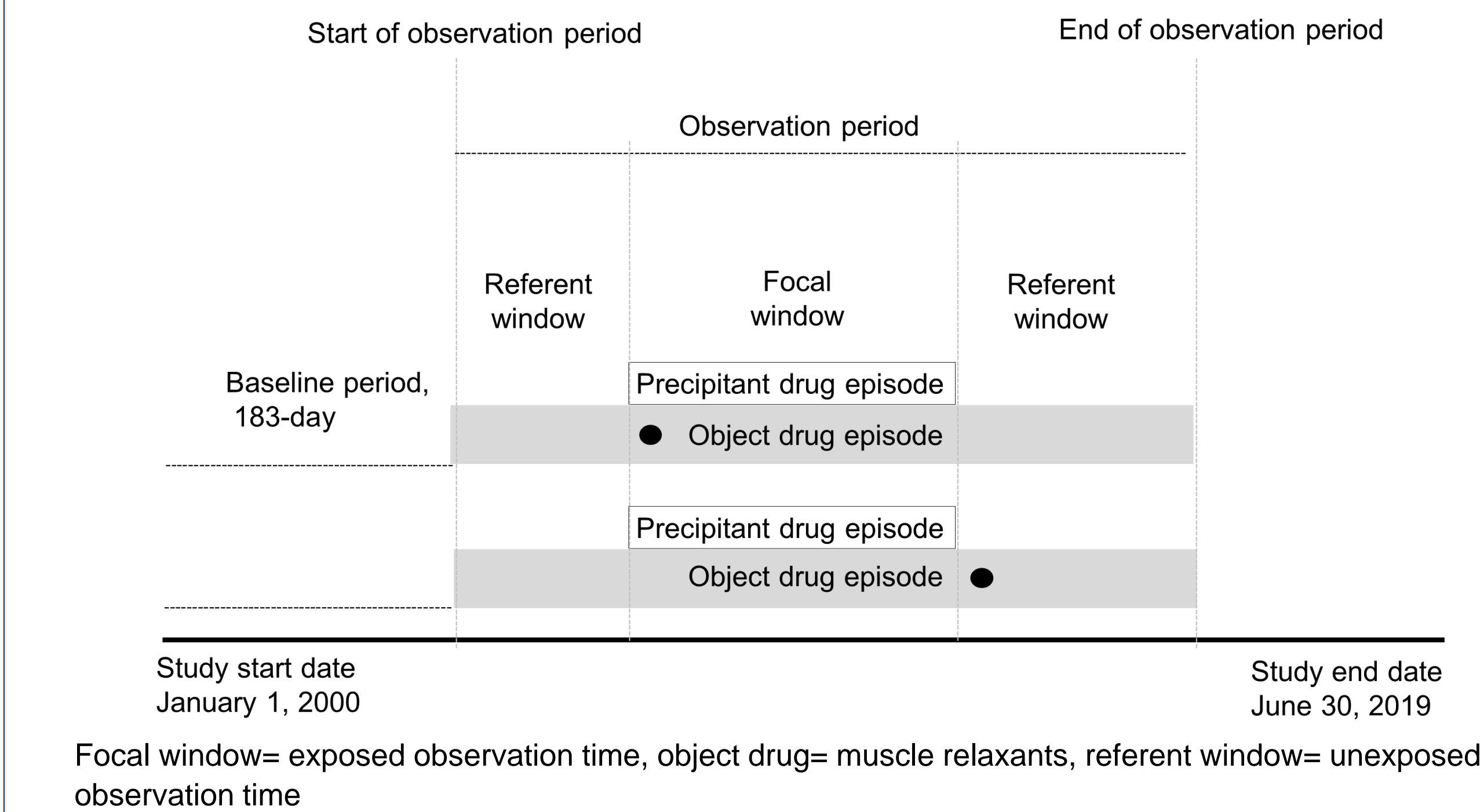
Figure 1. Eligibility for cohort entry
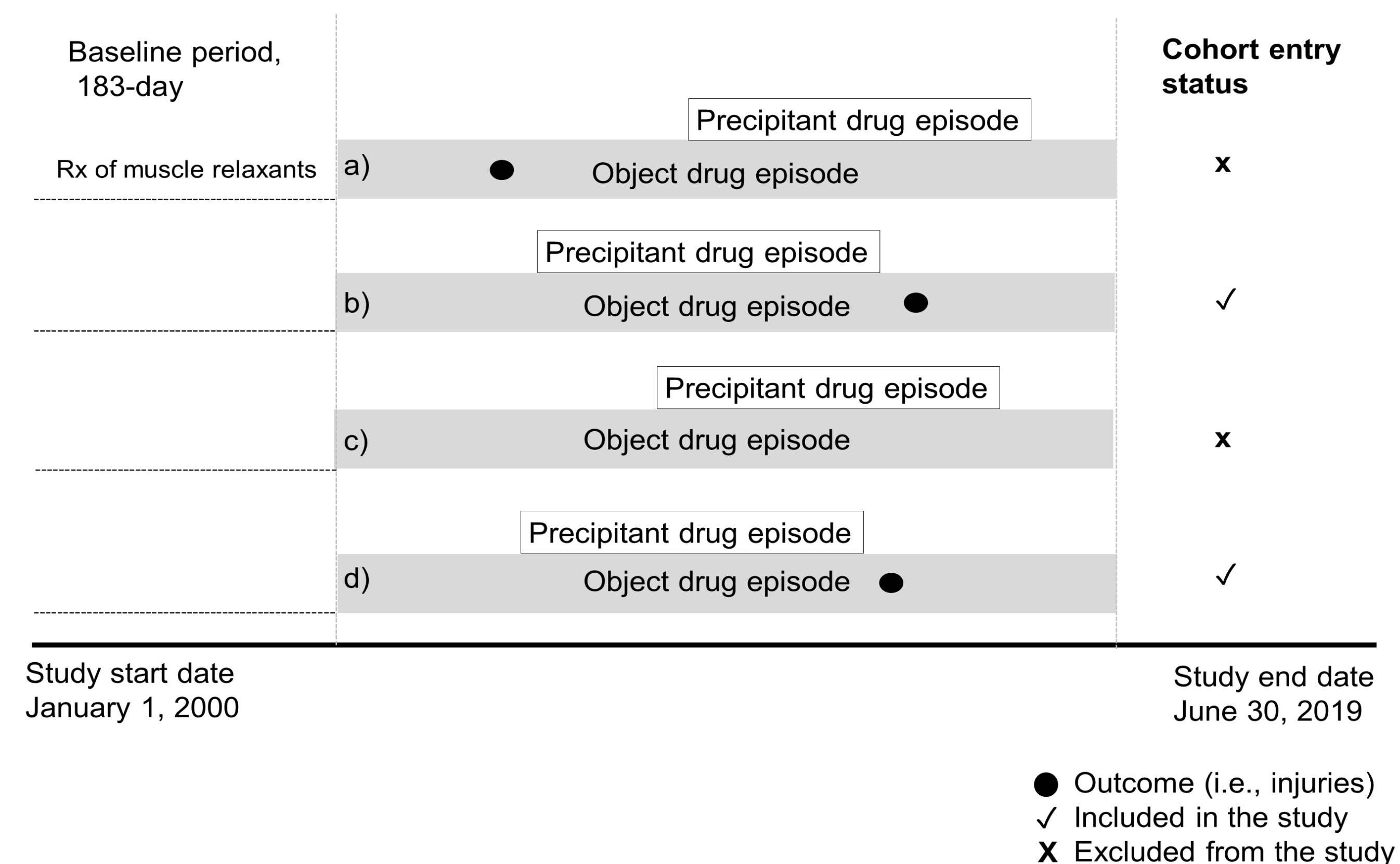
The figure illustrated scenarios of cohort entry
Patient a was not included because of use of a muscle relaxant during the baseline period.
Patients b and d were included given the absence of prior use of muscle relaxants and presence of injuries.
Patient c was not included since the patient did not experience an injury during the observation period.

Methods

Figure 2. Study design

Focal window= exposed observation time, object drug= muscle relaxants, referent window= unexposed observation time
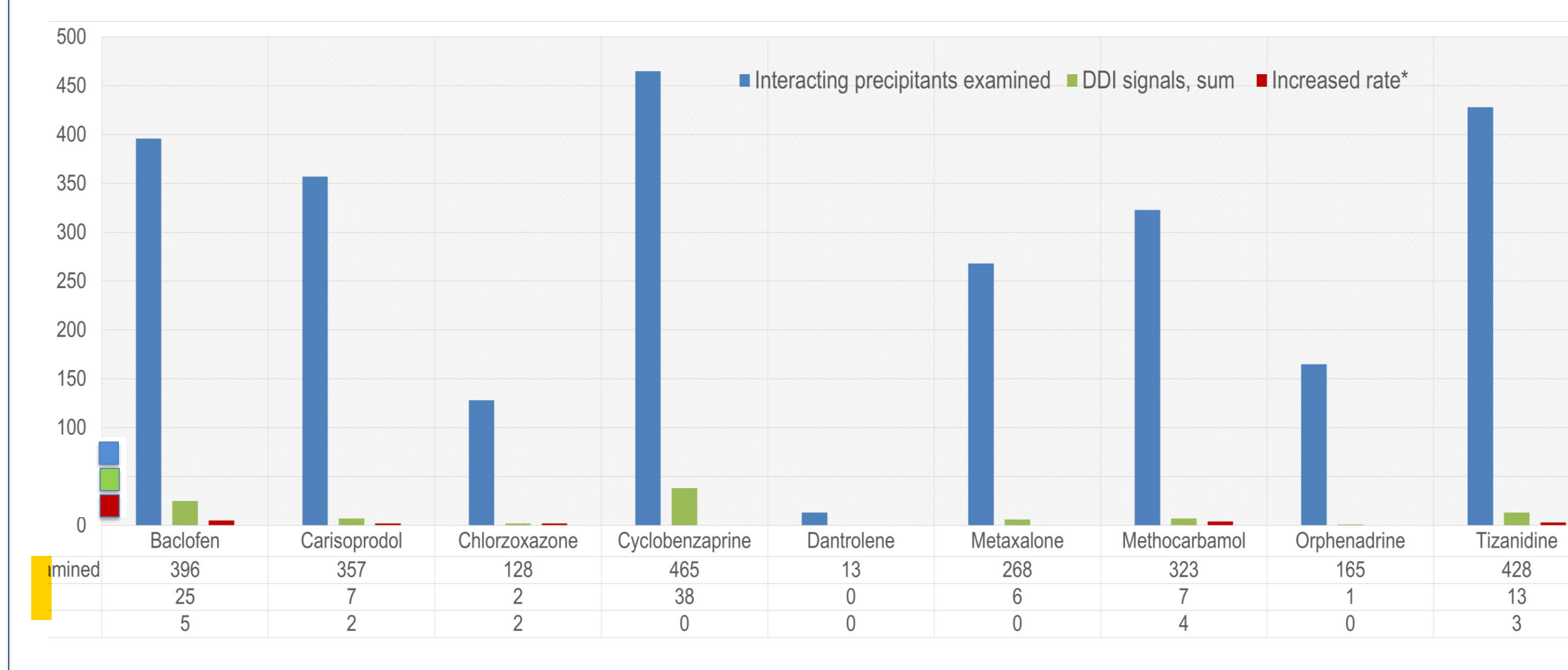
Study outcomes

- Primary: unintentional traumatic injury
- Secondary: typical hip fracture and motor vehicle crash, examined separately

Statistical analysis

- Within each cohort, we compared the occurrence of the outcome during the focal window vs. referent window
- We used conditional Poisson regression models to estimate the rate ratios (RRs) adjusting for time-varying confounders while accounting for multiple estimation via semi-Bayes shrinkage.

Results

Figure 3. Summary of potential signals of DDIs with muscle relaxants

DDI = drug-drug interaction

* Lower bound of the 95% confidence interval for the RR of interest excluded the null value

Results

Table 1. Confounder adjusted rate ratio after semi-based shrinkage of muscle relaxant drug interaction signals, given statistically significantly increased rates of unintentional traumatic injury by therapeutic category of precipitant drug

Object drug	Precipitant drug	Precipitant drug therapeutic category	Adjusted RR	95% CI	
Baclofen	morphine§	CNS	1.46	1.13	1.87
	sertraline	CNS	1.29	1.04	1.62
	atropine	GI	1.70	1.05	2.74
	diphenoxylate	GI	1.79	1.10	2.91
	sitagliptin	Endocrine and metabolic	1.67	1.07	2.60
Carisoprodol	varenicline	CNS	**2.11**	**1.18**	**3.75**
	lansoprazole	GI	1.72	1.02	2.90
Chlorzoxazone	cephalexin	Anti-infective	**2.03**	**1.00**	**4.13**
	methylprednisolone	Endocrine and metabolic	1.76	1.02	3.06
Methocarbamol	lamotrigine	CNS	**2.28**	**1.14**	**4.55**
	ondansetron	CNS	1.49	1.08	2.05
	levothyroxine	Endocrine and metabolic	1.43	1.05	1.94
	dexlansoprazole	GI	**2.03**	**1.01**	**4.10**
Tizanidine	amiodarone	CVD	1.65	1.04	2.62
	digoxin	CVD	1.91	1.13	3.23
	oxybutynin	Renal and genitourinary	1.51	1.12	2.02

CI= confidence interval; CNS= central nervous system; CVD= cardiovascular diseases, GI= gastrointestinal; RR= rate ratio
§ Drug interaction with impact on object documented in Micromedex
Rate ratios > 2.00 were bolded to highlight N = 4 potential signals that may warrant particular attention in future etiologic work

Conclusion

- In this population-based analysis, we utilized the self-controlled case series design as a screening method to detect signals of DDIs of muscle relaxants.
- Our analysis identified one anticipated and several new signals of muscle relaxant DDIs associated with unintentional traumatic injury.
- Future studies should seek to confirm or refute these potential interactions.