Skeletal Muscle Relaxant Drug-Drug-Drug Interactions and Unintentional Traumatic Injury: Screening to Detect Three-Way Drug Interaction Signals

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Abstract

Background and Purpose. Skeletal muscle relaxants (SMRs) are commonly co-prescribed with potentially interacting medications that may contribute to increased risk of unintentional traumatic injury (hereafter, injury). While prior research has investigated clinical outcomes for some pairwise drug interactions involving SMRs, drug interactions involving more than two drugs, such as drug triads (3DIs), largely remain unexamined. We sought to identify SMR 3DI signals associated with injury via automated high-throughput pharmacoepidemiologic screening of 2000–2019 healthcare data for members of commercial and Medicare Advantage health plans. Experimental Approach. We performed a self-controlled case series study for each drug triad consisting of an SMR base pair (i.e., concomitant use of an SMR with another medication), and a co-dispensed medication (i.e., candidate interacting precipitant) taken during ongoing use of the base pair. We included patients aged [?]16 years with an injury occurring during base pair-exposed observation time. We used conditional Poisson regression to calculate adjusted rate ratios (RRs) with 95% confidence intervals (CIs) for injury with each SMR base pair + candidate interacting precipitant (i.e., triad) versus the SMR-containing base pair alone. Key Results. Among 58,478 triads, 29 were significantly positively associated with injury; confounder-adjusted RRs ranged from 1.39 (95% CI=1.01–1.91) for tizanidine+omeprazole with gabapentin to 2.23 (95% CI=1.02–4.87) for tizanidine+diclofenac with alprazolam. Most identified 3DI signals are new and have not been formally investigated. Conclusions and Implications. We identified 29 SMR 3DI signals associated with increased rates of injury. Future etiologic studies should confirm or refute these SMR 3DI signals.

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