

# **Using Biomedical Knowledge to Identify Plausible Signals for Pharmacovigilance**

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The need to monitor unintended effects of approved drugs has been highlighted by several recent high-profile events in which fatal side effects of drugs were detected after their release to market. Notoriously, the Cox-2 inhibitor Rofecoxib (Vioxx) was withdrawn from market on account of evidence suggesting that treatment with the drug increased the rate of coronary artery disease, and recently new evidence has emerged suggesting the commonly used antibiotic Azithromycin (Zithromax) may cause fatal arrhythmias. In an effort to mitigate the morbidity and mortality resulting from such undetected side effects, regulatory bodies such as the Food and Drug Administration (FDA) have instituted spontaneous reporting systems to systematize post-marketing surveillance. However there is evidence that under-reporting of adverse drug events (ADEs) is widespread. Automated monitoring of events documented in the Electronic Health Record (EHR) as free text or structured data has been proposed as a path toward earlier identification of meaningfully correlated drug-event pairs. As these pairs must ultimately be reviewed by domain experts to assess their implications, there is a pressing need to develop methods to selectively identify plausible drug-event pairs within the large pool of correlations to be found in clinical data. In the proposed research, we will develop and evaluate models of biological plausibility, based on knowledge extracted from the biomedical literature and using methods of hyperdimensional computing for efficient search and inference across multiple concepts and relations simultaneously. These methods will be used to selectively identify plausible drug-event pairs found in structured clinical data, and extracted from unstructured data using natural language extraction. The developed methods will be evaluated formatively, for their ability to rediscover known side effects from the biomedical literature, and summatively for their ability to improve the precision of effects attributed to a set of known drugs using statistical methods alone. In addition we will evaluate their ability to predict recent FDA warnings, using historical data and knowledge. If successful, the proposed research will provide the means to identify automatically plausible drug-event pairs for regulatory purposes, mitigating consequent morbidity and mortality. In addition, the methods will provide a generalizable approach that can be used to apply knowledge derived from the biomedical literature to interpret clinical data. PUBLIC HEALTH RELEVANCE: The need to monitor unintended effects of medications has been highlighted by several high-profile events in which fatal side effects of approved drugs were detected after their release to market. In the proposed research, we will develop and evaluate methods to identify automatically biologically plausible adverse drug events found within clinical patient records, using knowledge extracted from the biomedical literature. If successful, these methods will provide the means for earlier detection of harmful drug effects, limiting consequent morbidity and mortality.