The combination of poor quality evidence on potential drug-drug interactions (PDDIs), and a general lack of PDDI knowledge by prescribers, results in many thousands of preventible medication errors each year. While many sources of PDDI evidence exist to help improve prescriber knowledge, they disagree substantially in their coverage, accuracy, and agreement. Four clinical drug information sources agreed on only 2.2% of 406 PDDIs considered to be "major" by at least one source, and three sources listed only one quarter of 59 contraindicated drug pairs. Difficulties with synthesizing evidence and gaps in the scientific knowledge of PDDI clinical relevance underlie such disagreement. Excessive alerting of PDDIs that have little potential clinical significance frustrates clinicians and can lead them to respond inappropriately, but sufficient evidence to properly rank such alerts rarely exists**. Addressing these issues is urgent** as United States healthcare organizations consider PDDI screening in their strategies to achieve the effective use of electronic health records.

RESEARCH OBJECTIVES AND AIMS:

Research Objective: *Problem* – There are currently many gaps in the scientific knowledge base on the clinical relevance of PDDIs. *Solution* - We will prioritize PDDIs involving warfarin, statins, and psychotropics by the need for pharmacoepidemiologic investigation. We will then investigate the feasibility of using the large-scale observational data available in the IMEDS laboratory to 1) establishing the risk of exposure to PDDIs, and 2) develop population-specific adverse event prediction models that include PDDI exposure as a risk factor.

SCOPE/PROPOSED APPROACH:

The Table lists the tasks, inputs, goals, and output of the proposed project. The principal investigator is currently leading a National Library of Medicine funded project titled "Addressing gaps in clinically useful evidence on drug-drug interactions" (1R01LM011838-01). An important part of this funded project is to update and extend an existing PDDI knowledge base to provide current information on warfarin, statin, and psychotropic pharmacokinetic drug-drug interactions. Once completed, we will use the knowledge base as a reference standard for investigating the feasibility of using large-scale observational data for establishing the risk of exposure to PDDIs. We will also review the literature and work with clinical experts to identify the most important adverse events in patients exposed to each drug, and use this information to guide the development of population specific adverse event prediction models that include PDDI exposure as a model feature.

IMPACT:

The proposed work will contribute to public health by making more effective use of PDDI evidence, filling in important gaps in drug safety knowledge, and spurring innovations in pharmacovigilance and pharmacoepidemiology. We will publish all results in journals in accordance with IMEDS policies, make source code publicly available, and share all data with interested researchers in accordance with all applicable Federal guidelines.

Table. IMEDS PDDI research activities and tasks.

Tasks	Input	Goals	Output
1. Build an exemplar PDDI assertion knowledge base for warfarin, statin, and psychotropic PDDIs	The preliminary work mentioned in the proposal text	Develop an exemplar knowledge base that would be extendable to other drug classes and interaction mechanisms	A knowledge base for warfarin, statin, and psychotropic PDDIs containing complete and up-to-date evidence supporting the existence of the interactions and potential ADE/ADR associations
2. Explore the feasibility of using large-scale observational data to establish the risk of exposure to PDDIs	The knowledge base for warfarin, statin, and psychotropic PDDIs developed in activity #1.	Extend methods developed during the OMOP experiments to work with drug-drug interaction investigations and explore the effect on PDDI-event risk associations of varying outcomes, datasets, and methods across a range of PDDIs.	Information on the potential strengths and limitations of various methods and datasets across a range of PDDIs involving warfarin, statin, and psychotropic drugs.
3. Develop population specific adverse event prediction models that include PDDI exposure as a model feature.	The knowledge base for warfarin, statin, and psychotropic PDDIs developed in activity #1.	Develop a variety of machine learning algorithms to predict important adverse events for patients exposed to PDDIs affecting the three drug classes.	Knowledge on the usefulness of including PDDIs as a feature in machine learning adverse event prediction algorithms

EXPERIENCE:

Team (Please refer to as the Translational Informatics Applied to Drug Safety (TRIADs) Investigator Group):

- (Principal Investigator) Richard D Boyce, PhD, Assistant Professor, Department of Biomedical Informatics, University of Pittsburgh
- Philip Empey, PharmD, PhD , Assistant Professor, School of Pharmacy, University of Pittsburgh
- Subashan Perera, PhD, Associate Professor, School of Medicine, University of Pittsburgh
- Matthias Samwald, PhD, Postdoctoral researcher, Section for Medical Expert and Knowledge-Based Systems, Medical University of Vienna

Preliminary work: Three studies establish our experience with PDDI assertions for drugs in the statin and psychotropic classes.(1–4) These same studies led to the development of the Drug Interaction Knowledge Base (DIKB), an evidence-focused knowledge base designed to support pharmacoepidemiology and clinical decision support.(5) The DIKB contains quantitative and qualitative assertions about drug mechanisms and pharmacokinetic drug-drug interactions for over 60 drugs; primarily psychotropics and statins. A Linked Data version of the DIKB(6) (under development) is the only PDDI knowledge base we are aware of that uses the SWAN scientific discourse ontology(7) to link each assertion about a drug property to both supporting and refuting evidence from the scientific literature, drug product labeling, and FDA guidance documents.

In prior work, we have developed a taxonomy of drug interaction evidence(2) and a novel knowledge representation technique(8) that identified 41 PDDIs involving 16 drugs, including 6 statins.(1) All 41 PDDIs were supported by pharmacokinetic drug-drug interaction studies involving humans. We also predicted 31 novel PDDIs based on the pharmacokinetic properties of the 16 drugs and found the clinical relevance of thirteen novel PDDI predictions to be supported by case reports evaluated using the Drug Interaction Probability Scale.(9) The study validated our novel knowledge-based approach on a narrow set of drugs. As part of our effort to expand our PDDI knowledge representation methods to a larger set of drugs, we conducted studies that synthesized and contrasted psychotropic pharmacokinetic PDDI information written in both product labeling and the scientific literature.(3,4)

The principal investigator is also currently the principal investigator of a project funded by the National Institute on Aging (K01AG044433) that has the long-term goal of developing an effective informatics intervention that prevents harm to nursing home residents from drug-drug interactions while avoiding known issues with drug-drug interaction alerting such as alert fatigue. Part of this K01 project involves extracting, translating, and loading data from five nursing home in Western Pennsylvania into the OMOP common data model. This has given experience with the same data model and standard vocabulary used in the IMEDS lab.

Timeline: We expect the project to last four years starting in May of 2014 and going until May of 2018. We will acquire exempt Institutional Review Board Approval for all activities prior to beginning them. Over the first year of this four-year project, we will build extend the PDDI knowledge base and conduct preliminary research in the IMEDS lab to establish the prevalence and incidence of exposure to PDDIs in the knowledge base. In years 2 through 4, we will explore the feasibility of using large-scale observational data to establish the risk of exposure to PDDIs and develop population specific adverse event prediction models that include PDDI exposure as a model feature. All throughout the project, we will disseminate research results throughout the project by submitting manuscripts to journals, presenting at relevant conferences, and maintaining a public project web page.

Expected use of the IMEDS resources: Our use of the IMEDS lab over the first two years is expected to be periodic, focused on understanding the different data sets and determining how to best operationalize studies that include PDDIs as an independent variable. We expect our use of the IMEDS lab to increase in Years 3 and 4 as we implement the studies.

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