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Improving drug safety: From adverse drug reaction knowledge discovery to clinical implementation

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ABSTRACT

Adverse drug reactions (ADRs) are a major public health concern, causing over 100,000 fatalities in the United States every year with an annual cost of $136 billion. Early detection and accurate prediction of ADRs is thus vital for drug development and patient safety. Multiple scientific disciplines, namely pharmacology, pharmacovigilance, and pharmacoinformatics, have been addressing the ADR problem from different perspectives. With the same goal of improving drug safety, this article summarizes and links the research efforts in the multiple disciplines into a single framework from comprehensive understanding of the interactions between drugs and biological system and the identification of genetic and phenotypic predispositions of patients susceptible to higher ADR risks and finally to the current state of implementation of medication-related decision support systems. We start by describing available computational resources for building drug-target interaction networks with biological annotations, which provides a fundamental knowledge for ADR prediction. Databases are classified by functions to help users in selection. Post-marketing surveillance is then introduced where data-driven approach can not only enhance the prediction accuracy of ADRs but also enables the discovery of genetic and phenotypic risk factors of ADRs. Understanding genetic risk factors for ADR requires well organized patient genetics information and analysis by pharmacogenomic approaches. Finally, current state of clinical decision support systems is presented and described how clinicians can be assisted with the integrated knowledgebase to minimize the risk of ADR. This review ends with a discussion of existing challenges in each of disciplines with potential solutions and future directions.

Contents

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1. Introduction

Clinical benefits of prescription drugs do not only depend on their efficacy in treating diseases but also their safety and tolerability in patients. Each dispensed prescription carries its own risks for causing adverse drug reactions (ADRs), ranging the full spectrum of severity from cosmetic to severe morbidity and mortality [1,2]. ADR is estimated to cause over 2 million hospitalizations and more than 100,000 fatalities each year in the United States alone [3,4], with an estimated annual cost of $136 billion [5,6].

Between 1976 and 2005, severe ADRs have caused 28 drugs to be withdrawn from the United States market [7], with the top drug-induced toxicities being hepatotoxicity (21%, 6), nephrotoxicity (7%, 2), cardiotoxicity (7%, 2), torsades (21%, 6), and rhabdomyolysis (7%, 2). For example, Vioxx is approved by the Food and Drug Administration (FDA) in 1999 and gained widespread acceptance among physicians (prescribed to over 80 million people worldwide) in treating patients with arthritis and other conditions causing chronic or acute pain. Five years later, it was pulled off the market due to significantly increased risk of heart attack and stroke, becoming one of the most widely used drugs ever to be withdrawn [8,9].

Thus, early identification as well as precise prediction of ADRs is crucial for drug discovery and development and patient safety. ADRs are often classified as Type A and Type B where Type A reactions are typically dose-related, expressing an extended therapeutic effect of a drug, for example, hypotension with antihypertensive therapy and bleeding events with warfarin; Type B reactions are 'idiosyncratic', occurring only in susceptible individuals [10]. The etiology of variable drug responses is multifactorial, including both genetic (e.g., severe haemolytic anaemia can occur

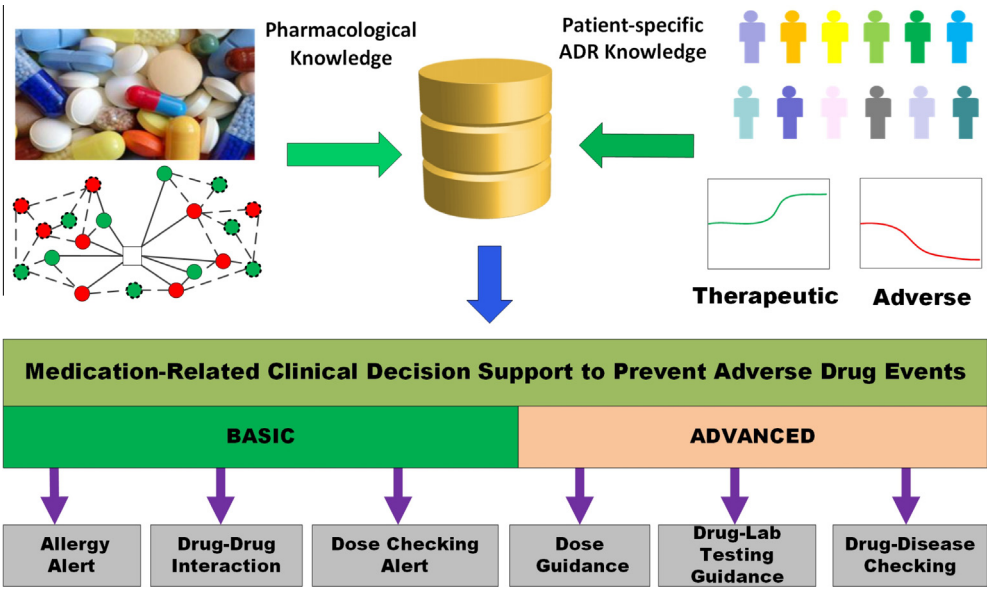

Fig. 1. Overview of the effort in ADR prevention from knowledgebase construction to clinical implementation.

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