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Adverse drug reactions

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Editors' View

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Effective and potent medications have provided some of the most significant advances in human health in history, but in the pithy argot of the American frontier 'there ain't no such thing as a free lunch'. Potent therapies are likely to have the potential for forceful adverse effects, and indeed the history of the Therapeutic Revolution demonstrates this clearly. The therapeutic benefits of the sulphonamides were realized quickly after they were marketed, and almost as quickly their potential to produce major adverse events was recognized [1]. For the following nine decades investigators, clinicians and regulators have struggled with the balance of the double-edged sword of efficacy *vs*. toxicity and the burden of adverse drug events, as eloquently described by Sir Alasdair Breckenridge in this themed issue exploring frontiers in Adverse Drug Reactions (ADRs) [2]. While problems associated with ADRs are frequently considered in the context of the individual patient, in fact the issues are much broader and apply to clinicians, drug regulatory agencies, industry and indeed more broadly to society in general. As an illustration, in 2014 the NHS spent £14 billion on prescription medications. It been estimated that one in seven in-patients sustains an ADR as a consequence of these medications, increasing hospital stay and often requiring additional medication [3, 4]. It is therefore incumbent on us to understand better both aspects of this two edged sword, to deliver therapy that is both effective and safe.

The problem of ADRs is not unique to any particular population group or age range, as demonstrated by Alleqaert & van den Anker in the case of infants and by Davis & O'Mahony with respect to the elderly [5, 6]. In the case of these two distinctly different populations factors such as polypharmacy and alterations in drug clearance place them at an increased risk for adverse effects associated with therapy. These manuscripts emphasize the need for vigilance for ADRs for clinicians who care for these patients. The risks associated with polypharmacy are also clearly articulated in the work of Saedder *et al*., who found in a review of more than 85 000 patients that the total number of drugs prescribed is the single most consistent risk factor for ADRs [7].

Of importance, the work of Moulton *et al*. demonstrates that the problem of ADRs is not only an issue for the developed world. In the case of their work evaluating drug-related mortality in four hospitals in South Africa, death from ADRs, with drug-related deaths in 2.9% of all hospital admissions, appears to be more common than in the studies conducted in the developed world [8]. While the burden of ADRs is often couched in terms of cost or days of hospitalization, Del Pozzo-Magana *et al*. demonstrate that ADRs appear to have a direct and deleterious impact on health-related quality of life, an under-appreciated effect that is not well understood in terms of both burden and how to address this best, notably for patients with chronic disease [9]. As well, the work of Chan *et al*. reminds us that not only do our patients often use complementary and alternative medicines, but that ADRs can also occur to these therapies [10].

This raises the question of how to approach this problem. In addition to recognition and vigilance, improved methods of signal detection are urgently needed. The conventional drug development process is excellent at detecting common and important ADRs in the population for which the drug was developed, but given real-world patterns of drug utilization better methods for detection of rare adverse events and for detection of ADRs in populations for which the drug was not evaluated prior to marketing are urgently needed [1]. Black *et al*. report on the potential for the use of electronic medical records (EMRs), an increasingly common component of care, for the detection of ADRs [11]. While EMRs are a common part of medical care and are more and more commonly used for ADR signal detection, the performance of these systems as assessed by guidelines for data linkage is poor, and more consistent definition of study design and reporting is needed if routine clinical EMRs are to achieve their potential in signal generation. Chan *et al*. explore the possibility of the use of databases to detect rare adverse events, a long-standing problem when ADRs are rare but very severe [12]. The use of databases for signal generation is discussed, with the caveat that signal generation then requires a separate and rigorous causality assessment.

In terms of future perspectives Li considers the potential for translational bioinformatics to pharmacology to inform drug discovery and drug safety research [13]. This approach, which informs and is complementary to

conventional pharmacology studies, remains somewhat underdeveloped, in large measure due to lack of training on how to conduct these studies and a relative lack of highly qualified personnel. Personalized or precision medicine is frequently cited as a development with potential for enhancing patient safety. Goulding *et al*. have reviewed randomized clinical trials of genotype-guided drug dosing to determine if there is hope or merely hype in this approach, and in an analysis of more than 1900 patients have concluded that there is in fact evidence for real-world effectiveness of genotype-based drug dosing for warfarin in enhancing therapeutic benefit and reducing risk [14]. Elzagallaai *et al*. demonstrate that there is increasing hope for the potential for *in vitro* approaches to diagnose and potentially prevent serious ADRs [15]. While many challenges remain before this approach enters the clinical mainstream these studies provide insights as to the potential pathogenesis of selected serious ADRs.

The two edged sword of therapeutics, effectiveness *vs*. toxicity, remains as much of an issue now as ever. In an era in which therapy is increasingly complex and costly, innovation in drug safety pharmacology offers patients, clinicians, regulators and industry the promise of being better able to diagnose, treat and, ultimately, prevent adverse consequences of drug therapy.

Competing Interests

There are no competing interests to declare.

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