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LEADING ARTICLE

Importance of Publishing Adverse Drug Reaction Case Reports: Promoting Public Health and Advancing Pharmacology and Therapeutics

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Abstract This article, which encourages physicians to publish case reports of adverse drug reactions (ADRs), is a review of how well-documented published case reports have contributed to promoting public safety and health and thus served to advance basic pharmacology. The origin of a number of regulatory guidelines can ultimately be traced to safety concerns triggered by such reports. It illustrates how case reports of ADRs, when coupled with simultaneous monitoring of drug pharmacokinetics, have also led to further investigations resulting in major advances in pharmacology, especially pharmacogenetics, mechanisms of drug–drug interactions and modulation of drug metabolism during inflammatory co-morbidities. Published case reports differ significantly from spontaneous case reports since they enjoy quality-compliant peer review and an immediate wider visibility among the readership, triggering others to report similar cases, and ultimately leading to prescribing restrictions on or withdrawals of the drug from the market depending on the risk. Therefore, the reporter should not be discouraged by (a) the unusual or bizarre nature of the reaction; (b) the interval, however long, from commencing drug administration to the onset of the suspected reaction; (c) however well-known the drug or the period for which it has been on the market; and (d) any pressure not to publish. Case reports should be published in reputable journals that are searchable through databases such as PubMed.

Key Points

Well-written published case reports, when widely accessible, enhance diagnostic and therapeutic practices by sharing 'real-world' experiences.

The origin of many regulatory guidelines and actions on drugs can be traced to published case reports that have triggered the uncovering of some major drug disasters.

Published case reports have frequently led to further investigations culminating in some major advances in pharmacology and therapeutics.

Introduction

This article provides a perspective on the clinical, regulatory and public health importance of publishing case reports of adverse drug reactions (ADRs), however unusual or unexpected the suspected reaction may be or implausible the association may appear at first. Since pre-approval clinical trials have their well-recognised limitations in uncovering rare, serious or long-term adverse effects, published case reports are vital in assessing the overall safety of drugs. With a view to stimulating publication of case reports, this paper summarises, with some examples, how case reports have played a crucial role in uncovering some major drug disasters and shaping much of the current regulatory framework for developing, evaluating and approving medicines and monitoring their clinical safety. Indeed, some case reports have proved to be valuable preludes to major discoveries in pharmacology and improving drug use.

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Published Case Reports Versus Spontaneous Reports

Published case reports and spontaneous reports submitted to the regulatory authorities are often mistaken as being equivalent, containing essentially the same information but with different degrees of detail. However, published case reports differ significantly from spontaneous reports submitted to national reporting systems in two important aspects: they enjoy quality-compliant peer review and an immediate wider visibility among the readership.

Publication of case reports also draws early attention to an interaction between a drug and another drug or an herbal product and are a valuable resource for information on interactions of drugs with surgical outcomes, failures of therapy, fraudulent products, and other clinical and pharmacovigilance issues of interest in resource-poor settings. Case reports often explain the nuances of how the causal diagnosis was suspected/made, what investigations were useful and how the adverse event was managed together with comments on the success of treatment. With an increasing trend towards reviewing previous literature, case reports also add an extra dimension to monitoring drug safety. The guideline on what constitutes a good case report of an ADR for publication has already been promulgated and the recommendations therein do not bear repeating here [1]. As early as 1990, Haramburu et al. [2] reported a comparison of 500 spontaneous reports and 500 published case reports and determined that the criteria for causality were more often of positive value in published ADR reports, and these were more reliable since publication implied the occurrence of a clear-cut reaction, which has been evaluated by a critical peer review process. Plessis et al. [3] have recently reported that more than one-third of the 321 spontaneous reports of serious ADRs from manufacturers to the national authority did not include information usually considered essential to evaluate a causal relationship. A well-documented initial publication of an ADR report may well trigger other readers to report similar cases (see "Published Case Reports, Major Drug Disasters and Regulatory Outcomes" below for a selection of case histories).

Published case reports can also help with clinical management of difficult cases. Physicians can quickly search databases such as PubMed for reports of similar cases, in contrast to time-consuming searches of national databases of spontaneous reporting systems which, not infrequently, include many poorly documented and/or duplicate cases. Furthermore, signals of disproportionate reporting from national spontaneous reporting databases need to be refined for sense before they could be utilised for clinical decision-making. Published case reports also provide clinically valuable information on switching patients to alternative medications within the same drug class [4, 5].

Many academically managed databases of drug information rely heavily on published case reports to maintain the completeness and currency of their databases. For example, a large number of drugs from diverse pharmacological and therapeutic classes are reported to prolong the QT interval of the surface electrocardiogram (ECG), pre-disposing a patient to potentially fatal ventricular tachyarrhythmias. The number of drugs involved, uncertain or questionable associations between a drug and its QT liability, and the potential consequences of drug-induced QT interval prolongation led the Arizona Centre for Education and Research on Therapeutics (AZCERT) to establish a database of QT-prolonging drugs (CredibleMeds; https://crediblemeds.org/) with categorisation of clinical risk with each drug. Medical literature is an important source of information for this database. AZCERT investigators monitor biomedical research publications of relevance by reviewing monthly reports generated by the National Library of Medicine's National Centre for Biotechnology Information and AZCERT scientists review a list of approximately 80–150 newly published articles each month that are captured with the relevant search terms and each publication is carefully scrutinised [6].

Although spontaneous reporting systems are the backbone of national pharmacovigilance systems, published case reports can assist with an immediate and better understanding of real-life situations and also assist with refinement of signals from databases of spontaneous reports. Often, regulatory authorities search for published case reports to help them refine a signal. The date of publication could also help with the refinement of a safety signal. As far as the case reports on ADRs are concerned, some journals recommend that authors report the case(s) to the national regulatory authority when accepting it for publication. However, reporting the same case to the national authority and publishing it in a journal carries the risk of duplication when the literature report is picked up by the authority or, as part of its mandatory surveillance and reporting requirements, by a pharmaceutical company. More often than not, the duplication can be readily identified during routine pharmacoepidemiological check, but it might be prudent for authors of case reports to add a declaration in the published report clarifying whether the case has already been reported to a particular country's national authority database.

Given the valuable role they play in monitoring drug safety, it is unfortunate that case reports, together with spontaneous reports, are generally ranked the lowest on evidentiary hierarchy, which typically categorises randomised controlled trials (RCTs), systematic reviews and meta-analyses of trials as constituting the strongest forms

of evidence. Published case reports do have their own limitations, which they share with spontaneous reports, regarding computation of incidence but in the context of ADRs or uncommon events, RCTs may not be the best sources of information for several well-known reasons, such as limited sample size, duration of therapy and restricted and highly selective eligibility criteria [7].

Historical and Current Perspectives on the Benefits of Published Case Reports

The utility of published case reports has attracted much discussion [8–10]. Following an evaluation of 63 case reports of ADRs published in 1997, Loke et al. [9] concluded that published case reports of suspected ADRs are of limited value as suspicions were seldom subjected later to confirmatory investigation. In response, Vandenbroucke [11] argued that this conclusion was flawed and too quick to dismiss the value of case reports, and Russmann [12] also countered that in contrast to many reports of limited quality and relevance that end up being buried in spontaneous reports databases, published case reports of suspected ADRs undergo peer review for quality and relevance. van Puijenbroek [13] also challenged the conclusion reached by Loke et al. [9], arguing that case reports published in journals closely represent the events that occur in clinical practice, there being no other sound alternatives that provide this 'real-world' information, and that case reports should not be blamed for a lack of numerical information considered so desirable for decision-making. Interestingly, a recent study by Onakpoya et al. [14] reported that confirmatory studies were conducted in 57 (69%) of the 83 instances of drug withdrawals due to a case report of a potentially fatal ADRs and there was evidence of an association in 52 (63%) of these. These investigators also identified two or more confirmatory studies for 36 of the 57 products.

Aronson [7] has also discussed why individual case reports of suspected ADRs should not necessarily be regarded as being evidentially poor and why anecdotal reports form a major source of information about suspected ADRs. As reported by Aronson [7], the numbers of case reports published in bioscience journals have been increasing gradually over the years between 1965 and 2010, and the numbers of case reports of adverse events have been increasing at a rate greater than that for other types of case reports.

It is often said that one report is an event, two are a coincidence but the third denotes a potential association that requires further investigation for its significance [15]. Therefore, case reports can be considered as hypothesis-generating tools and can have a profound influence on public safety and the future marketing prospects of the drug concerned. A high index of suspicion is all that is required and the reporter should not be discouraged by (a) the unusual or bizarre nature of the reaction; (b) the interval, however long, from commencing drug administration to the onset of the suspected reaction; (c) however well-known the drug is or long the period for which it has been on the market; and (d) speaking from experience, any pressure not to publish. For innovative, often first-in-class, drugs, knowledge regarding their safety at the time of their approval is often even less extensive and such drugs may require a tighter scrutiny post-approval. As illustrated in "Case Reports of Thalidomide-induced Phocomelia led to Early Drug Regulation" and "Published Case Reports, Major Drug Disasters and Regulatory Outcomes" below, a number of major drug disasters were uncovered following publication of seminal first reports, leading to regulatory actions against the drug and promulgation of regulatory guidelines as well as legislation.

It is worth adding a caution regarding where the case report is published. Most reputable journals are open to accepting ADR case reports, especially if the ADR and the drug are new. An internet search (with the search phrase "journals with 'case reports'") reveals that there is now an ever-burgeoning number of journals, at least two to three for every specialty/subspecialty, devoted to publishing case reports. While the majority of these relate to unusual presentations of or interventions in patients, case reports of ADRs are certainly not excluded. More critically, however, many of these journals are open-access journals with publication processing fees and are not searchable through PubMed queries. Furthermore, a recent report has also challenged the quality of publications in a few of these journals [16]. Case reports submitted as Letter to the Editor can also be difficult to search for. *Drug Safety Case Reports* is one of the few online-only, open-access journals specifically dedicated to publishing ADR case reports.

Case Reports of Thalidomide-Induced Phocomelia Led to Early Drug Regulation

Any discussion on the safety of drugs and its profound implications for the need to regulate medicines must begin with thalidomide-induced phocomelia and neuropathy. The epidemic of phocomelia in the late 1950s following the introduction of thalidomide to the market in November 1957, and the regulatory/legislative consequences for drug development, are all too well-known and have been briefly reviewed previously [17]. Thalidomide illustrates not only the significance of initial recognition and reporting of an apparently bizarre and previously unrecognised ADR, but also the rapid surge in the rate at which similar reports follow once the clinicians are sensitised to a potential

association. The first child afflicted by thalidomide-induced damage (to the ears) was born on 25 December 1956 but the first case reports of an apparently new type of congenital defect (phocomelia) were reported by Weidenbach in 1959; subsequently, other sporadic cases also began to appear in the literature. However, strong evidence suggesting that these foetal abnormalities had a common exogenous cause emerged only in September 1960, when Kosenow and Pfeiffer, at a meeting of the German Paediatric Association, presented details of two cases of children born with severe skeletal malformations together with various other deformities [18]. While these physicians realised that their cases were highly unusual, they did not refer to any increase in similar cases, nor did they consider what the aetiology of these malformations might be. Shortly there after, in December 1960, Florence, a Scottish general practitioner, published a letter entitled "Is Thalidomide to Blame?" in the *British Medical Journal* describing neuropathy [19]. Four of his patients had complained of paraesthesia of the hands and feet, coldness of the extremities and nocturnal cramps in leg muscles. He questioned whether these symptoms could be due to thalidomide as all four had received the drug. This was the first report of thalidomide neuropathy in the medical literature but others soon followed [20]. In September 1961, there was a sudden increase in cases of phocomelia and Lenz, a German paediatrician, noted that 50% of these patients had taken thalidomide. On 11 November 1961, for the first time, Lenz suspected thalidomide to be the cause of this outbreak of limb and ear malformation in Western Germany, and by 16 November he felt sufficiently certain as a result of his continuing investigations to warn (by a telephone call) the manufacturer of the drug. However, it was not until December 1961 that McBride more firmly suggested this association in a brief letter published in *The Lancet* [21]. McBride inquired "have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?" Case reports started to appear at an alarming rate, and what might be described as an epidemic of thalidomide-induced phocomelia galvanised governments across the world into re-examining or enacting legislative controls on regulation of drugs [17], and later led to investigation of a drug for its teratogenic potential as one of the principal requirements for marketing it. Critically, however, thalidomide was never approved in the USA, which was spared the tragedy. Kelsey, a medical officer at the US Food and Drug Administration (FDA) charged with evaluating the US application for thalidomide during early 1960s, tenaciously resisted extraordinary pressure from the sponsor for its approval. Her refusal to approve thalidomide was initially based on, among other reasons, case reports of thalidomide-induced neuropathy. She requested that the sponsor further clarify the mechanisms and the impact of this ADR [22]. While the sponsor was dealing with this request, an ever-increasing frequency of phocomelia reports overshadowed any concerns regarding neuropathy. Therefore, the USA was spared the teratogenic tragedy, in part due to the initial case reports of thalidomide-induced neuropathy. Following this tragedy, Bowles urged ADR reporting as a factor in accreditation of pharmacists [23]. Related to the early case reports of thalidomide and congenital defects, it is also worth remembering that valproate-induced neural tube defects were also first signalled in a case report series in 1982 [24].

Published Case Reports, Major Drug Disasters and Regulatory Outcomes

In order to promote efficient drug development, regulatory authorities often consider whether to issue a guideline on some specific aspect of drug development. However, events may unfold that provide the necessary impetus and urgency for drafting the guideline. The origin of a number of regulatory guidelines can ultimately be traced to safety concerns initially signalled by case reports.

Benoxaprofen

Benoxaprofen is a novel non-steroidal anti-inflammatory drug that was approved in 1980. The drug was launched amidst massive publicity, with marketing described as "explosive" [25]. The resulting uptake of the drug in clinical practice was overwhelming, heralding a flood of ADR reports that included hepatotoxicity and a variety of cutaneous reactions [26, 27]. The first two case reports of hepatotoxicity and deaths associated with benoxaprofen appeared in April and May 1982 when Taggart and Alderdice [28] and Goudie et al. [29] reported a total of eight cases of elderly women who developed cholestatic jaundice while taking benoxaprofen, six of whom died. Many other reports soon followed, and before long there were 61 fatalities associated with benoxaprofen-induced hepatotoxicity and the drug was suspended from the market on 3 August 1982 with immediate effect [30]. A number of risk factors predisposing to benoxaprofen-induced cholestasis were identified. Fatal reactions occurred predominantly in the elderly. Later, a study by Kamal and Koch [31] revealed that the mean elimination half-life of benoxaprofen was 101 h in these elderly patients, which was substantially greater than the reported half-life of 30–35 h in normal younger adults. This experience, together with that with other drugs, led the US FDA to issue a guideline in 1989 requiring sponsors to study the pharmacokinetics of drugs in the elderly if the drug is likely to be used by this population. This guideline was later

superseded by an internationally harmonised guideline [32]. Given the regulatory concern about the potential for altered pharmacokinetics of drugs (and, therefore, the clinical response) in other subpopulations, it is tempting to speculate that the subsequent guidelines recommending subset analysis in other subpopulations (such as in females, different ethnicities, and patients with hepatic or renal dysfunction) may indirectly owe their origin to the altered pharmacokinetics of benoxaprofen in the elderly. Published case reports of hepatotoxicity abound [33], and hepatotoxicity is one of the major reasons for market withdrawal or restricted use of many drugs [26, 34]. Not surprisingly, authorities have issued guidance on pre-approval characterisation of drugs regarding their hepatotoxic potential [35].

Torsadogenic Drugs

Clinical trials with prenylamine, an effective antianginal drug introduced in the early 1960s, had not signalled a risk of torsades de pointes (a potentially fatal ventricular tachyarrhythmia) during its use. However, reports linking prenylamine with syncope, prolongation of the QT interval, ventricular tachycardia, ventricular fibrillation and torsades de pointes began to appear from 1971 onwards [36]. Despite warnings and advice to increase the dose more gradually, reports of these ventricular tachyarrhythmias continued to appear. By 1988, 158 cases of polymorphous ventricular tachycardia were reported in association with prenylamine. Some of these events had a fatal outcome and the drug was withdrawn from the market worldwide in 1988 [37].

In 1990, Monahan et al. [38] reported the first association (exclusive of drug overdose) of symptomatic torsades de pointes occurring with the use of terfenadine in a patient who was taking the recommended prescribed dose of this drug in addition to cefaclor, ketoconazole and medroxyprogesterone. Investigations revealed excessive levels of parent terfenadine and a proportionate reduction in the concentrations of its metabolite, leading the authors to suggest inhibition of terfenadine metabolism by ketoconazole. This was later confirmed to be the case; whereas the parent drug prolonged the QT interval of the ECG and was torsadogenic, the metabolite was the therapeutically active moiety devoid of this toxic effect [39]. This report was followed by a number of other similar case reports, and together with reports related to other drug–drug interactions, ultimately led to the development of drug interaction guidelines in the European Union (EU) (in 1997) and USA (1999), both of which have now been updated [40, 41]. Not only that, but terfenadine was later removed from the market to be replaced in the USA by its therapeutically active metabolite fexofenadine in July 1996 (and later elsewhere). Just about this time, and 5 years after the first reports related to terfenadine, the unfortunate epic was repeated with cisapride, a gastric prokinetic agent, that proved to be highly torsadogenic, especially in combination with cytochrome P450 (CYP) 3A4 inhibitors including ketoconazole. Early publications of cases of cisapride-induced torsades de pointes in 1995 [42–44] were followed by an avalanche, culminating in 341 cases reports of assorted arrhythmias (including 117 of QT prolongation, 107 of torsades de pointes and 80 fatalities) and withdrawal of cisapride from the market in July 2000 [45].

Apart from terfenadine and cisapride, a number of other non-cardiac drugs were first reported in isolated published case reports to prolong the QT interval of the ECG, with or without inducing torsades de pointes. The drugs include thioridazine, levacetylmethadol, methadone, halofantrine, pimozide, astemizole, terodiline and sertindole among many others. The resulting concerns led the Committee on Proprietary Medicinal Products (CPMP), the EU scientific advisory body for human medicines, in December 1997 to adopt its seminal document "Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products" [46]. A few years later, together with further input from the US, Japanese, Canadian and Swiss authorities, the strategy described in the CPMP document ultimately evolved into two internationally harmonised guidelines (ICH S7B and ICH E14) issued in May 2005 [47, 48]. These guidelines require the sponsors to conduct, among other investigations, a thorough QT study dedicated to uncovering the effect of the drug on the QT interval.

Terodiline is a particularly interesting example since it vividly illustrates how, when prompted by published case reports and alerts from the regulatory authority, physicians begin to report similar cases they may have encountered previously but had not suspected the association [37]. This drug was first introduced in the UK for urinary urgency and frequency in July 1986. A report of the sudden unexpected death of a previously healthy 20-year-old man, following an overdose in 1987, first raised the suspicions of its proarrhythmic potential [49]. The first proarrhythmic reactions to clinical doses of terodiline were also reported to the UK regulatory authority in 1987, when there was one case of ventricular tachycardia and one of bradycardia [37]. Following its post-approval routine clinical use, the first three reports of torsades de pointes in association with terodiline were notified to the marketing authorisation holder during 1988–1989 and the fourth report was in 1990 [50]. The literature in early 1991 included additional reports of QT-interval prolongation and torsades de pointes [51–54]. By July 1991, there were a total of 21 reports of ventricular tachyarrhythmias (including 13 of torsades de pointes) [37]. Following a safety warning letter from the UK authority to physicians in July 1991, the total number

of reports increased to 69 by September 1991 [37, 55]. A majority of these 48 additional reports were retrospective cases in which the onset of terodiline-associated proarrhythmia had antedated the warning letter, illustrating clearly that these were simply not reported earlier because the association might have appeared too implausible to the prescribing community.

Practolol

As with thalidomide and the unique nature of the toxicity associated with its use, it was an atypical and previously unreported ADR (oculomucocutaneous syndrome) that first attracted concerns regarding the safety of practolol [56]. The oral formulation of this cardioselective β-adrenergic blocking agent without any local anaesthetic activity, indicated for a wide range of cardiac conditions including various tachyarrhythmias, was introduced in 1970. Early indications of an impending disaster included case reports of exfoliative dermatitis [57], systemic lupus syndrome [58], drug eruption [59], psoriasiform eruptions [60], skin reactions with eye signs consisting of atypical conjunctival shrinkage and xerosis [61], and keratoconjunctivitis sicca [62]. By November 1974, Felix et al. [63] reported a case series of 21 patients suffering from drug-induced rashes caused by practolol seen over the preceding 2 years. By the end of 1974, 187 reports of corneo-conjunctival damage, several hundred of psoriasiform or hyperkeratotic skin reactions, 25 of deafness, 14 of a syndrome resembling systemic lupus erythematosus and eight of an unusual form of sclerosing peritonitis were reported to the UK regulatory authority [64]. A seminal publication report of 27 patients in 1975 emphasised how the latency of skin and/or ocular effects may extend to several months [56], thus highlighting the long duration of therapy as being no barrier to suspecting a drug-associated ADR and publishing a good case report [65]. Similar changes were reported to be rare in association with atenolol, oxprenolol or propranolol [66–68]. Often referred to as the 'practolol disaster', the key early evidence of these unexpected and unusual reactions came from isolated case reports. A number of authors also reported a relatively novel autoimmune mechanism underpinning this toxicity. For example, serological studies in 22 patients presenting with ocular disease attributable to practolol revealed a raised incidence of antinuclear antibodies [69]. The indication of practolol was much restricted and it was withdrawn from general use in October 1975 [70].

Summary

The case histories in "Benoxaprofen", "Torsadogenic drugs" and "Practolol" described above illustrate how one or two published case reports can prompt others to report a similar drug-reaction association, ultimately resulting, if the frequency is high and/or the clinical consequences serious, in removal of the drug concerned from the market. Although only a few examples are discussed here, there are a number of other drugs with a similar fate. Novel chemical structures or mechanisms of action are no guarantee of improved safety or efficacy; indeed, perhaps, quite the contrary can be true for the first-in-class drugs. As stated very elegantly in an editorial in the *British Medical Journal*, "A drug with unusual properties may be expected to have unusual side effects—and both the frequency and nature of these effects have been surprising" [25]. In this context, drugs such as benfluorex, dexfenfluramine, metiamide, mibefradil, nomifensine, sitaxentan, temafloxacin, ticrynafen, troglitazone and zafirlukast come immediately to mind. Still, for many other drugs, the consequences arising from published case reports have been less draconian and have included severe prescribing restrictions or a change in dose. Failure of these initial measures to control the risk often lead to withdrawal of the drug from market.

Studies Evaluating the Contribution of Published Case Reports

To further emphasise the importance of issued case reports of ADRs, it is worth summarising various studies on the source of information leading to drug withdrawals, safety alerts from regulatory authorities and changes in product labelling. Many of these studies do not make a clear distinction between published reports and spontaneous reports, but those that suggest published case reports, explicitly or by implication, are summarised below.

In a study of 59 safety alerts issued by the US, Canadian, European and Australian authorities between 2010 and 2012, 36 (61%) were supported by published and unpublished post-marketing ADR reports and 11 (17%) of these relied on case report/case series. The sections of the drug label most frequently updated were the "Warnings and Precautions" and "Contraindications" ($n = 40$; 68%) [71]. In a survey of 22 products withdrawn from the Spanish market during 1990–1999, the evidence supporting the withdrawal came from published case reports in no less than ten instances [72]. Similarly, a total of 21 drugs were withdrawn in France for safety reasons between 1998 and 2004 and, among these, published or unpublished case reports constituted the sole evidence in 12 (57%) instances [73]. A follow-up study of a total of 22 active ingredients withdrawn from the same market between 2005 and 2011 revealed that in five (23%) instances case reports provided the sole evidence [74]. In another study of 19 drugs withdrawn from the EU market for safety reasons during the period 2002–2011, case reports were cited in 18 (95%) of

these, whereas case-control studies, cohort studies, RCTs or meta-analyses were cited in 12 (63%) of these withdrawals [75]. In the most recent study of 462 safety-related withdrawals worldwide from 1950 to 2014, case reports were used as evidence for withdrawals in 330 instances (71.4%) [76]. Mechanism-based reasoning accounted for 56 (12.1%) withdrawals. For products launched after 1950 ($n = 354$), case reports were used as evidence in 247 instances (70%). The corresponding figures for each decade since 1950 were 85% for the 1950s, 74% for the 1960s, 69% for the 1970s, 68% for the 1980s, 64% for the 1990s and 35% for the period 2000–2008 [76].

Published Case Reports Triggering Advances in Pharmacology and Therapeutics

Currently, there is unparalleled interest and activity in promoting genotype-based precision medicine. When the adverse pharmacodynamic effect of a drug—that is, an ADR—is coupled with simultaneous studies of the pharmacokinetic parameters (drug concentrations and its half-life) of the drug and/or its metabolites, case reports of ADRs have triggered further investigations that have led to some major advances in pharmacology, especially pharmacogenetics and our understanding, mechanisms and predictions of drug–drug interactions. Studies during late-1950s correlating the pharmacokinetics of isoniazid to its therapeutic or toxic response had already established genetic polymorphism of N-acetyl-transferase [77], but a similar polymorphism in the clinically more important and relevant mixed-function oxidases (now known as CYP drug-metabolising enzymes) had long eluded discovery. Studies correlating ADRs with the pharmacokinetics of drugs such as debrisoquine, sparteine and phenytoin have uncovered genetic polymorphisms of CYP enzymes (e.g. CYP2D6 and CYP2C9). Debrisoquine is an orally active anti-hypertensive agent, introduced on the market in the early 1960s, and its most troublesome and dose-related ADR is postural hypotension. Its daily dose requirements ranged from 10 to 360 mg with wide inter-individual variation in dose-adjusted plasma concentrations. Studies in the mid-1970s identified a correlation between the hypotensive response to debrisoquine, its plasma concentrations and the amount of unchanged drug excreted in urine, which was highly variable (8–58% of dose). Postural hypotension was related to its dose, coupled with impaired metabolism of debrisoquine [78–81]. At about the same time, diplopia, blurred vision, dizziness and headache were reported in two subjects who were unable to metabolise sparteine, an oxytocic alkaloid [82]. These observations on debrisoquine and sparteine, correlating their toxicity to pharmacokinetics, led to the discovery of *CYP2D6* polymorphism. Similarly, in 1964, Kutt et al. [83] published a case report of phenytoin toxicity, associated with high serum concentration of phenytoin, in a 24-year-old male patient who was unable to effect normal para-hydroxylation of this drug. Family study revealed this defect to be present in his brother and mother. Vasko et al. [84] also described a similar family in which the presenting case was a 32-year-old woman who developed signs of phenytoin toxicity 10 days after a standard dose of 300 mg daily. Subsequent studies established CYP2C9 as the principal enzyme that metabolised phenytoin and resulted in the description of its genetic polymorphism. Both CYP2D6 and CYP2C9 metabolise a large number of drugs and their discovery has elucidated the pharmacological basis of many previously unexplained individual susceptibilities to ADRs, lack of efficacy and exaggerated pharmacological effects of prodrugs and drug–drug interactions. Similarly, following early published reports of toxic plasma concentrations of clozapine and theophylline with associated clinical toxicity during inflammation, proinflammatory cytokines have now been shown to be important modulators of the expression of various CYP drug-metabolising enzymes [85].

In turn, the discovery of *CYP2D6* polymorphism has resulted in more effective and safe use of drugs previously considered unsafe. A good example of this is genotype-guided therapy with perhexiline to mitigate the risk of neuropathy associated with its use [86]. Singlas et al. [87] reported a comparison of the pharmacokinetics of perhexiline in angina patients with and without signs of peripheral neuropathy. Compared to the latter, those with neuropathy had higher plasma concentrations of perhexiline, slower hepatic metabolism and a longer plasma half-life. This neuropathy was later shown to be associated with poor CYP2D6 metabolic phenotype [88, 89], and, although perhexiline has been withdrawn worldwide, it remains available in Australia for use in selected patients with *CYP2D6* genotype-based dosing recommendations [90].

Conclusions

Publishing case reports should not be perceived merely as an expedient means of enhancing a curriculum vitae in the misguided belief that they are subject to less rigorous peer review. Compared to the spontaneous reports of ADRs submitted to national regulatory authorities, published case reports enjoy quality-compliant peer review, an immediate wider visibility among the readership and include information that more often fulfil the criteria for causality. Publication of case reports also draw early attention to uncommon drug interactions as well as to ADRs which have a long latency and help with clinical management of

difficult cases since the physicians can quickly search databases such as PubMed for reports of similar cases. Many academically managed databases of drug information rely significantly on published case reports to maintain their databases. The utility of published case reports has attracted much discussion but there is now common ground that they are very valuable and have played a crucial role in uncovering major drug disasters. Directly or indirectly, published case reports have shaped much of the current regulatory framework and contributed significantly to regulatory decisions. As illustrated here, some case reports have proved to be valuable preludes to some major discoveries in pharmacology and improving drug use.

Compliance with Ethical Standards

This article does not contain any studies with human or animal subjects. This is a review of data in the public domain and Dr. Shah declares compliance with all ethical standards.

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