



## Adverse Drug Reactions related to mortality and morbidity: Drug-drug interactions and overdoses – Angella Angiji

### ABSTRACT:

Adverse drug reactions (ADRs) are a contributing factor to morbidity and mortality resulting to 6.5-10.9% hospital admissions and mortality rates of 0.15-2.9%. A considerable number of reported ADRs are preventable particularly those caused by drug interactions and overdoses. Preventive measures such as adhering to RMPs, awareness ongoing training for healthcare professionals and patients could help reduce the prevalence of ADRs.

### INTRODUCTION

Adverse drug reactions (ADRs) are an acknowledged factor contributing to morbidity and mortality universally. In literature, an estimated 6.5% of hospitalizations in Europe result from ADRs, and 6.7% for serious ADRs and 10.9% including non-serious in the US (Lazarou, Pomeranz, & Corey, 1998). Overall ADR related mortality rates range from 0.15-2.9% (Mouton et al., 2015). In 2005, drugs were the leading cause of death estimated at 739, 936 per year (Null, Dean, Feldman, & Rasio, 2005). The socio-economic healthcare costs associated with ADRs are very high, £466m/year in UK annually (Pirmohamed et al., 2004), and A\$946 200 in Australia (Chan, Nicklason, & Fial, 2001) are related to ADR hospital admissions. A significant percentage of ADRs are considered preventable with varying estimates of 40-77% in literature (Dormann et al., 2003; Farcas et al., 2010). Overdoses contributed to average 30% of ADRs while drug-drug reactions (DDIs) 4-32% (Alexopoulou et al., 2008; Dormann et al., 2003). ADRs have caused withdrawal of 28 drugs from the US market between 1976 and 2007 (Wilke et al., 2007). Factors contributing to ADR prevalence and/or susceptibility include: increase in the number marketed drugs, type of drug, increase in aging population, pregnancy, gender, disease state, genetics, ethnicity,

polypharmacy, and urbanization (Hinson, Roberts, & James, 2010; Shepherd, Mohorn, Yacoub, & May, 2012; Tan et al., 2016). Type A are commonly reported (predictable and dose dependent), as such are preventable by either dose adjustment or avoiding drug interactions. Various disciplinary groups continue to address the ADR burden i.e. pharmacovigilance, pharmacology, and pharmacoinformatics (pharmacogenetics). An ADR is defined by the World Health Organization (WHO), as any noxious, unintended or undesired effect of a drug that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy. Notice this definition, does not include special situations such as misuse, drug abuse, overdose, lack of drug efficacies or medication errors. ADRs are classified into two major groups: type A are predictable reactions from the known pharmacological action of the drug, and usually dose-dependent, while type B (idiosyncratic); are unpredictable and independent of the dose e.g. allergic reactions. Other minor categories include: type C which are chronic and are dependent on dose and time, type D which are delayed reactions, type E covers withdrawal and type F for unexpected failure of therapy (Hinson et al., 2010).

## METHODS

A comprehensive search of freely available articles was conducted in the following databases: EMBASE, Hertfordshire University Online Library, Leiden University Online library, Google scholar, EMA and FDA website. Search criteria used: 'adverse drug reaction' OR 'drug related problems' OR 'side effect' OR 'adverse event' OR 'morbidity' OR 'mortality' OR 'drug interaction' OR 'overdose'. Only articles published between 2000-2017 in English were included. The titles and abstracts were first reviewed for inclusion/exclusion based on methods and results to ensure quality. Articles included reviews, retrospective, or prospective

## RESULTS

ADRs that resulted in and/or were experienced during hospitalization have been extensively studied universally. Table 1 gives a summary of the results. ADR-related emergency room visits and/or hospital admissions prevalence varies in literature, with estimates of 3% in the Netherlands and Germany, 6.5-8.8% in the UK (Ahern, Sahm, Lynch, & McCarthy, 2014; Pirmohamed et al., 2004), 5.8% in Italy (Franceschi et al., 2008), and 12.8% in Greece (Alexopoulou et al., 2008) also see Figure 1. Mortality rates due to ADRs have been estimated from 0.1-2.9% (Mouton et al., 2015; Pirmohamed et al., 2004). A retrospective eight year (1999-2006) study conducted in the US of >2 million deaths revealed 2341 (0.1 per 100,000) as ADR-related deaths (Shepherd et al., 2012). The observed variations can be attributed to study type, populations, ADR classification and causal relationship assessment definitions, and differences in hospital settings. More than 50% of ADRs were classified as type A, these suggests a considerable percentage of ADRs could be preventable. There is also worldwide variation in the reported figures for preventability of ADRs in the literature ranging from 40-77%. DDIs, and overdose

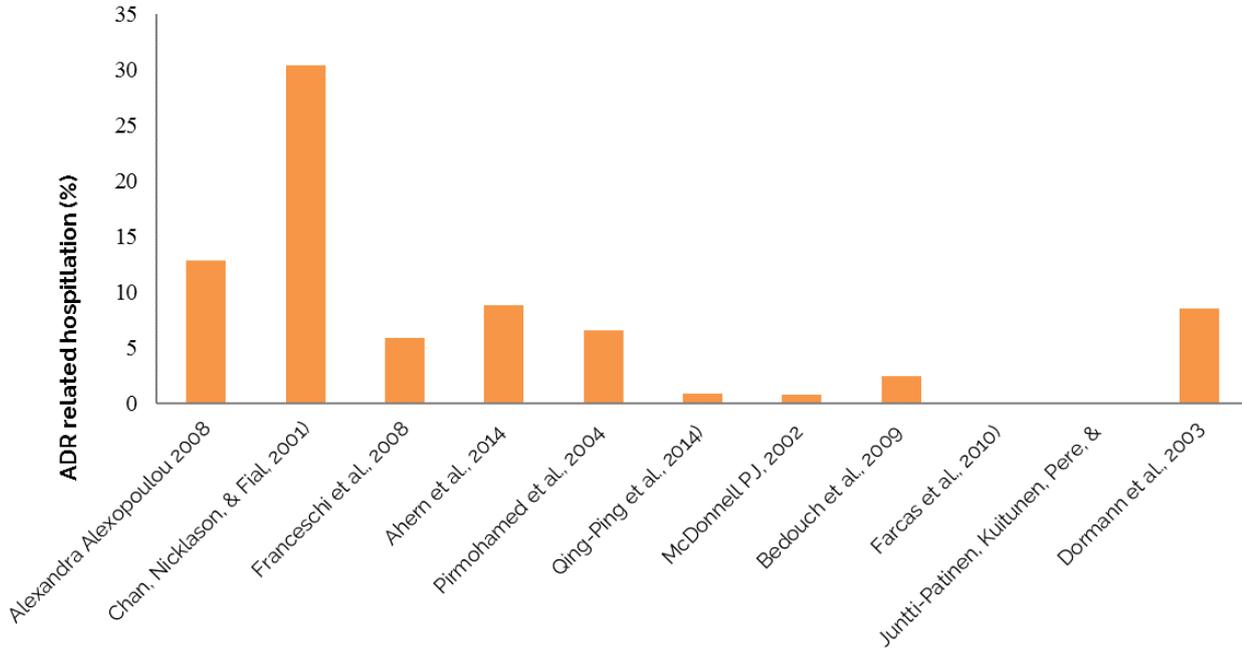
observational studies that discussed ADRs in any kind of setting such as hospitals, outpatient clinics etc. Studies which were included focused on ADRs of more than one specific drug measuring all ADRs regardless of location. These included studies performed within clinical settings (i.e. within hospital settings including both in and outpatient basis) that did not focus on ADRs related to one specific medicinal product or condition or ADR but which measured all ADRs regardless of the use of the medicine anywhere in the world. There was no restriction to the definition of ADRs.

contributions to ADRs ranged between 4.90-32.3% and 12.8-39% respectively (Alexopoulou et al., 2008; Dormann et al., 2003; Farcas et al., 2010). In regards to causality assessment, a higher percentage of ADRs were evaluated as definitely, probably or possibly related to the suspect drug in comparison to un-assessable and not related ADRs. The most commonly implicated drugs were: NSAIDs, diuretics and Beta-blockers (Table 2). NSAIDs, aspirin, anti-neoplastics and anti-psychotics were implicated in ADRs of the youngest patients while ACEi, diuretics, anti-arrythmics were implicated in those of the oldest patients (Alexopoulou et al., 2008). The costs associated with ADR burdens are enormous. In the UK only, this was estimated in 2004 to cost £466m (€706 million, \$847 million) per year in 2004 (Pirmohamed et al., 2004). Shockingly ADRs still remain the main reason for drug withdrawals. 462 drugs were withdrawn from the market due to ADRs between 1953 and 2013. 18% of the drugs were involved with hepatotoxicity, 17% immune-related reactions, 14% cardiotoxicity, 11% haematological toxicity, 13% carcinogenicity, 11% drug

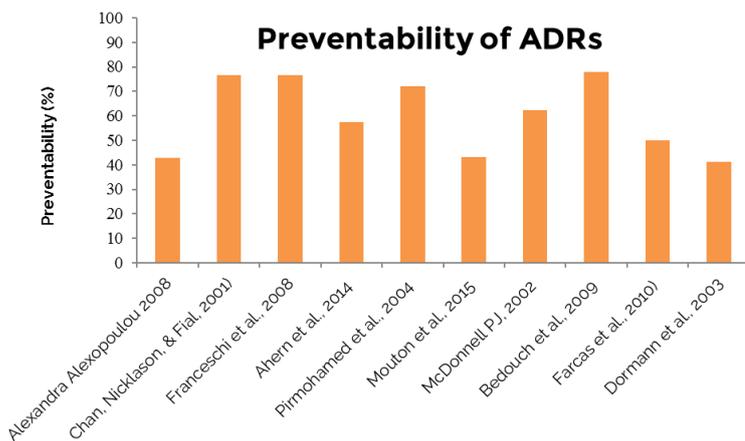
abuse and dependence. Death lead to 25% drug withdrawals (Onakpoya, Heneghan, & Aronson, 2016). An example

of a high profile drugs withdrawn from the market is Vioxx (Tan et al., 2016).

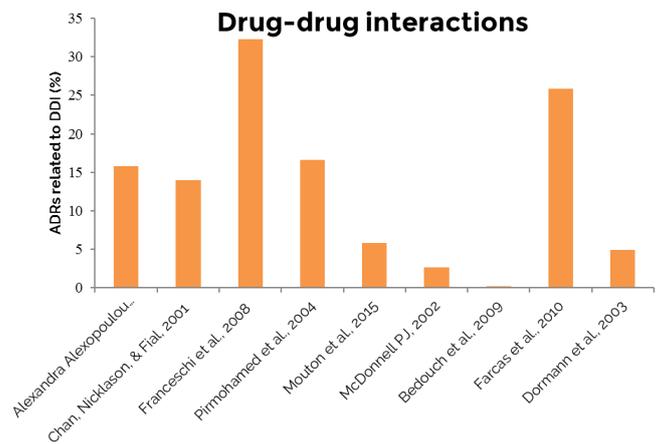
### Prevalence of ADRs related to Admissions or ER visits



### Preventability of ADRs



### Drug-drug interactions



**Figure 1: Top: % of hospital admissions due to ADRs, bottom left: % ADR that are potentially preventable, bottom right: % of ADR caused by DDI.**

**Table 1: Summary of all results**

| Article<br>Type of study<br>Country  | ADR related admissions (%)                          | Fatal (%)                           | Preventability                                       | Non-preventable (%)                          | Relatedness  | Drug interactions   | Overdose                                 |
|--|---|-------------------------------------|--|--|--|---------------------|--|
| Alexandra Alexopoulos 2008<br>Prospective<br>Greece                            | 12.8%<br>Type A (89.2%)<br>Type B (10.8%)           | Not specified                       | Possible (24.3%)<br>Definite (18.6%)                 | 57.1   | Definite or probable (74.3%)<br>Possible (25.7%)                 | 15.80%              | Not specified                            |
| (Chan, Nicklason, & Fial, 2001)<br>Prospective<br>Australia                    | 30.4%<br>Type A (96.7%)<br>Type B (3.3%) only 1 ADR | 6 deaths<br>(4 were<br>preventable) | Definitely (53.4%)<br>Possible (23.3%)               | 23.30%                                       | Definite (20%)<br>Probable in (41.4%)<br>Possible in (31.4%)     | Not specified       | Not specified                            |
| Franceschi et al. 2008<br>Prospective<br>Italy                                 | 5.80%   | Not specified                       | Definitely (45.1%) ,<br>Possible (31.4%)             | Unavoidable (18.6%)<br>Unclassifiable (4.9%) | Definite (6.8%)<br>Probable (91.2%)<br>Possible (2.0%)           | Potentially (32.3%) | Not specified                            |
| Ahern et al. 2014<br>Prospective<br>Ireland                                    | 8.80%   | Not specified                       | Overall 57.3%<br>Definitely (5.3%)<br>Possibly (52%) | Unavoidable (33.3%)<br>Unclassified (9.3%)   | Definite (4%)<br>Probable (28%)<br>Possible (68%)                | Not specified       | Excluded from<br>study                   |
| Pirmohamed et al. 2004<br>Prospective<br>UK (England)                          | 6.5%<br>Type A (95%)                                | 0.15%                               | Definitely (9%)<br>Possibly (63%)                    | Unavoidable (28%)                            | Definite (1.8%)<br>Probable (68.8%)<br>Possible (29.4%)          | 16.60%              | Excluded from<br>study                   |
| (Qing-Ping et al., 2014)<br>Retrospective<br>China                             | 0.81%   | 0%                                  | Not reported   | Not specified                                | Not reported   | Not specified       | Not specified                            |
| Moulton et al., 2015<br>Retrospective<br>South Africa                          | Not specified                                       | 2.90%                               | 43%  | Not specified                                | Definite (4 cases)<br>Probable (10 cases)<br>Possible (55 cases) | 5.80%               | Not specified                            |
| McDonnell PJ, 2002<br>Retrospective<br>US                                      | 0.76%   | Not specified                       | 62.30%   | Not specified                                | Not reported   | 26%                 | Not specified                            |
| Bedouch et al., 2009<br>Prospective<br>France                                  | 2.40%   | Not specified                       | 78%  | Not specified                                |  | 16.70%              | 12.8                                     |
| Farcas et al., 2010)<br>Prospective study<br>Romania                           | Overall 5.07<br>Type A (87.5%)<br>Type B (12.5%)    | Not specified                       | Potentially 40.18%<br>Definitely (9.82%)             | 50%  | Definite (8.57%)<br>Probable (74.29%)<br>Possible (17.14%)       | 25.90%              | Not applicable<br>Excluded from<br>study |
| Juntti-Patinen, Kuitunen, Pere, &<br>Neuvonen, 2006)<br>Prospective<br>Finland | 2.3%<br>Type A (85%)<br>Type B                      | 0.6                                 | Not reported   | Not specified                                | Definite (2.3%)<br>Probable (                                    | Not specified       | 39%                                      |
| Dormann et al., 2003<br>Prospective<br>Germany                                 | 8.50%   | 1 death                             | 41.20%   | Not specified                                | Possible (46.1%)<br>Probable (43.1%)<br>Definite (10.8%)         | 4.90%               | 39%                                      |

**Table 2: Most common drugs and ADRs per reference**

| Article<br>Type of study<br>Country  | Drugs   | ADRs   |
|--|---|--|
| Alexandra Alexopoulou 2008<br>Prospective<br>Greece                          | NSAIDS<br>Aspirin<br>Oral hypoglycemic<br>Diuretics<br>Oral anticoagulant   | Hemorrhagic<br>Metabolic<br>Renal<br>Dermatological<br>Gastrointestinal<br>Hematological   |
| Chan, Nicklason, & Fial, 2001<br>Prospective<br>Australia                    | ACEi<br>Diuretics<br>Beta-blockers<br>Calcium antagonist<br>NSAIDS  | Falls and falls + postural hypotension (20)<br>Pulmonary oedema/heart failure (14)<br>Delirium (12)<br>Acute renal failure (6)<br>Stroke (5)<br>Palpitations (4)     |
| Franceschi et al., 2008<br>Prospective<br>Italy                              | NSAIDs (23.5%),<br>Warfarin (20.6%),<br>Low-dose Aspirin (2.9%),<br>Amiodarone (3.9%),<br>ACE inhibitors (3.9%),<br>Antibiotics (2.9%).   | Gastrointestinal disorders (47.1%)<br>Platelet, bleeding and clotting disorders (19.6%)<br>Cardiovascular disorders (12.7%).   |
| Ahern et al., 2014<br>Prospective<br>Ireland                                 | ACE inhibitor e.g. Ramipril (9)<br>Beta-blocker e.g. Bisoprolol (9)<br>Diuretics (22)<br>Aspirin (5)<br>Wafarin (4)   | Dehydration,<br>Hyponatraemia<br>Acute kidney injury<br>GI bleeding<br>Gastritis.  |
| Pirmohamed et al., 2004<br>Prospective<br>UK (England)                       | NSAIDs (29.6%)<br>Diuretics (27.3%)<br>Wafarin (10.5%)<br>ACEi (7.7%)<br>Antidepressants (7.1%)<br>Beta-Blockers (6.8%)<br>Opiates (6.0%)   | Gastrointestinal bleeding (15 deaths)<br>Intracranial haemorrhage (5 deaths)<br>Renal failure (5 deaths)<br>Perforated duodenal ulcer (2 deaths)                     |
| (Qing-Ping et al., 2014)   | Antibiotics (34.94%)<br>Digestive system drugs (16.9%)<br>Traditional Chinese medicines (15.59%)  | General disorders (30.56%)<br>Gastrointestinal disorders (17.71%)<br>Respiratory system disorders (5.29%)<br>Central and peripheral nervous system disorders (4.64%) |
| Mouton et al., 2015<br>Retrospective<br>South Africa                         | Antivirals for systemic use (19)<br>Antimycobacterials (15)<br>Diuretics (9)<br>Antithrombotic agents (7)   | Renal failure<br>Drug-induced liver injury<br>Haemorrhage<br>Gastrointestinal bleeding   |
| McDonnell PJ, 2002)<br>Retrospective<br>US                                   | Chemotherapy<br>Anticoagulants<br>Antidiabetic agents   | Not reported   |
| Bedouch et al., 2009<br>Prospective<br>France                                | Cardiovascular drugs (22.2%)<br>Antibiotic/anti-infective (13.3%)<br>Analgesic/antiinflammatory drugs (11.3%)<br>gastrointestinal drugs (11.2%)<br>psychotropic drugs (9.6%)<br>antithrombotic agents (6.3%). | Not reported   |
| Farcas et al., 2010)<br>Prospective study<br>Romania                         | Cardiovascular agents (37%)<br>Anticoagulants (21%)<br>NSAIDs (11%)   | Gastrointestinal system (17.86%)<br>Metabolic system (13.39%)<br>Vascular system (11.61%)<br>Hepatic system (9.82%)<br>Renal system (8.93%)                          |
| (Juntti-Patinen, Kuitunen, Pere, & Neuvonen, 2006)<br>Prospective<br>Finland | Antibiotics<br>Cardiovascular drugs<br>NSAIDs   | Gastrointestinal symptoms (17 cases)<br>Haemorrhage (16 cases)<br>Cardiovascular symptoms (14 cases)<br>Skin disorders (13 cases)                                    |
| Dormann et al., 2003<br>Prospective<br>Germany                               | cardiovascular agents (16.8%)<br>gastrointestinal drugs (16.2%)<br>Diuretics (9.5%)<br>Analgesics/NSAIDs (6.2%)<br>Respiratory medications (6.0%).  |  |

## DISCUSSION

Polypharmacy is commonly observed in patients with concomitant pathologies and in the elderly population (Bushardt, Massey, Simpson, Ariail, & Simpson, 2008). Patients taking more drugs due to concomitant pathologies are more likely to experience ADRs (Franceschi et al., 2008). The use of multiple drugs has been associated with inappropriate prescribing and/or inadequate monitoring (Mouton et al., 2015; Rambhade et al., 2012). Mouton (2015) demonstrated that 52% of preventable ADRs, most were because the drug was considered to be inappropriate for the patient or due to inadequate monitoring (Mouton et al., 2015). Consistently, a retrospective study conducted in Temple University Hospital found half of the preventable ADRs resulted from inappropriate dosing due to inappropriate prescribing due to failure to correct for dosage based on patient age-related renal function or interacting drug (overdose). One-third (33%) of preventable ADRs was due to patient non-compliance, and 2% to drug allergy. Antidiabetic therapy and NSAIDs had the highest percentage of admission due to patient non-compliance (McDonnell, Jacobs, Monsanto, & Kaiser, 2002). In Italy, 21.8% had received an inappropriate prescription or contraindicated, 41% were not monitored during treatment, and 37.2% had not received a prescription for an effective gastroprotective drug concomitantly with NSAID or low-dose aspirin (Franceschi et al., 2008). These results reflect a need for careful monitoring and prescribing from physicians. This could be prevented by implementing computerized systems tracking of prescriptions using patient specific risk factors (Dormann et al., 2003).

DDI represents an important percentage of preventable ADRs in ER visits and hospital admission. Polypharmacy is a major risk factor for DDI with the rate of DDI exponentially increasing in patients taking 4 or more drugs (Juntti-Patinen,

Kuitunen, Pere, & Neuvonen, 2006; Kennedy, 2016).

A drug interaction refers to an effect of one drug being affected or altered by the presence of another drug, or a particular food or drink. Drug interactions with food and drinks are out of the scope of this review. Two main types of interactions that can occur between drugs: pharmacodynamic (agonists or antagonist) or pharmacokinetic interactions (absorption, distribution, metabolism, and excretion). A drug interaction can also occur during formulation due to incompatibility. An interaction may affect efficacy (decrease or increase) or safety (increase drug toxicity). For an interaction to be clinically relevant, it requires to have a narrow therapeutic index or a steep concentration-response curve. These conditions are not met for most interactions (Rang, Dale, Ritter, Flower, & Henderson, 2012). Three prospective studies reported varying results of ADRs potentially related to DDI i.e. 16.6% of ADR admissions were due to DDI in the UK (Pirmohamed et al., 2004), and 32.3% in Italy (Franceschi et al., 2008), and 16.7% in France (Bedouch et al., 2009). Drugs interactions implicated were NSAID/Aspirin, aspirin and warfarin (UK). Aspirin and warfarin caused gastrointestinal bleeding (Pirmohamed et al., 2004). A retrospective study in the US, reported 26% ADR potentially involving DDIs (McDonnell et al., 2002). It is impossible to remember or predict all possible DDIs, however, there are several medical judgment support tools providing information on drug interactions and their ADRs. These include: search tools for interactions of chemicals (STITCH), translational bioinformatics, signal detections by data mining databases, manually annotated targets and drugs online program (MATADOR), Psychoactive drug screening program (PDSP), and IntAct (Tan et al., 2016). Bioinformatics data may not always be clinically relevant. Additionally, the FDA provides physicians

with guidance on how to prevent ADRs induced by DDI using 'the stepwise approach' as follows: 1) taking good medication history using 'AVOID Mistakes' (**A**llergies, **V**itamins and herbs, **O**ld drugs, **I**nteractions, **D**ependence and **M**endel) 2) understanding of which patients and drugs are at risk, 3) checking readily available reference documents, 4) consulting other health care professional and 5) use of up-to-date computerized databases (U.S. Food and Drug Administration, 2015).

Medications errors, off label use, misuse and abuse are potential causes of ADRs that are usually excluded from ADR studies. Iatrogenic deaths in the US cause up to 7.8 million deaths per 10years, and medication errors were estimated at 14% fatality rate, (Null et al., 2005). A few studies have included ADRs related to overdoses, drug-drug interactions, and drug-alcohol combination. Prospective studies conducted in Germany and Finland both found overdose to contribute to about 39% of ADRs (Dormann et al., 2003; Juntti-Patinen et al., 2006). In France the estimate was much less, overdoses contributed to 12.8% ADRs (Bedouch et al., 2009). The Finnish group found overdose as the main cause of ADRs (39.2%), psychotic and antidepressants were common drugs involved. This was mostly due to drug-ethanol combination. Drug allergy represented 4.9% of ADRs, DDI (4.9%), and contraindications (17.1%). ADR detection rate was 51%, and depended on causality assessment and severity of an ADR i.e. physicians were more aware of severe or definite ADRs while mild and possibly related were usually not recognized (Dormann et al., 2003). As can be seen, these ADRs might have been prevented by adhering to indications, contraindications and/or implementing computerized systems tracking of

prescriptions using patient specific risk factors. Note that ADRs prevention is also essential to ensure compliance as patients are likely to stop their drugs or take them less frequently if they experience an ADR which can be detrimental for some high risk patients.

Age and gender as contributing factors to ADRs are controversial topics in literature. Some studies found no significant effects of age on ADR susceptibility (Mouton et al., 2015), while others found the ADR group to be significantly older, than the non-ADR group (Ahern et al., 2014; Pirmohamed et al., 2004). Paediatrics and the elderly are closely monitored and special interest age groups in drug use and development. This is because there is little or no information on the safety of most drugs in these populations for ethical reasons. Pharmacokinetics and pharmacodynamics are known to differ with age. For example: delayed gastric emptying in neonates and infants, and deteriorating organ functions in the elderly (Hinson et al., 2010; Schmucker, 2005). A reduction in renal function can cause drug toxicity due to reduced excretion, particularly for drugs with low therapeutic index. In addition, there is an increase in medication use as one ages. Females have been found to be more sensitive to ADRs than male patients (Lopez-Gonzalez, Herdeiro, Piñeiro-Lamas, & Figueiras, 2014; Qing-Ping et al., 2014). In contrast, ADR deaths were found to be more common in males than females (Shepherd et al., 2012) while other studies found no significant differences (Ahern et al., 2014; Alexopoulou et al., 2008). The differences can be accredited to gender specific factors, such as hormonal and immunological factors, differences in pharmacokinetics, and patterns of drug use. In addition, the type of drugs used differ between males and females.

Genetic variation caused by polymorphism can affect sensitivity of an individual to ADRs. In future (era of

precision medicine), whole genome profiling for single nucleotide polymorphism (SNPs) could be prediction technique for ADRs (Rang et al., 2012). Already about 10% of labels (in the EU and US) do contain information related to genetics and drug responses. About 30% of ADRs are estimated to be preventable using genetic testing and gene-ADR associations, however, only 20% have been found to be clinically relevant. Several pharmacogenetics technique are now available which enable prediction of drug responses through genetic content. Examples include microarrays for genetic testing, candidate gene approach, genome wide association (GWAS) and next-generation sequencing. Genetic testing can also be an important tool in ADR diagnosis, identification of patients for close monitoring and/or drug use exclusion). However, these techniques are limited by sample size, lack of pharmacogenomics knowledge, clinical relevance and poor phenotyping strategies. Successful examples of the genetic approach include: the link between glucose-6-phosphate dehydrogenase (G6PD) polymorphisms and haemolytic anaemia abacavir hypersensitivity and HLA-B\*57:01 (Pirmohamed, Ostrov, & Park, 2015; Wilke et al., 2007). Besides genetics, ethnic differences can be predictions for ADR sensitivity e.g. Chinese population are more sensitive to cardiovascular effects of propranolol, than Caucasians or Afro-Caribbeans (Rang et al., 2012).

Other factors affecting ADR sensitivity include pregnancy, and environmental factors. Most drugs and herbal remedies are not recommended for use during pregnancy, and lactation due to little or no information on pharmacokinetics and pharmacodynamics. This is because of physiological changes in pregnancy, and safety of neonates (lactation). Changes during pregnancy that may affect drug responses include: reduced albumin concentration, increased cardiac output leading to increased glomerular filtration (Rang et al., 2012). It has been estimated

80% of pregnant women take between 3-8 prescribed or purchased over the counter drugs. The trouble with this type of exposure is that it affects mother or father, or the fetus and may even further affect generations to come. The thalidomide tragedy is perhaps the best example of this category. A trend towards a higher risk of ADRs in rural areas is reported which might be linked to access to healthcare (Shepherd et al., 2012).

In order to ensure safety of medicine, European and US regulatory authorities have adopted a proactive risk based approach rather than the reactive approach. The US/FDA version is the Risk Evaluation and Mitigation Strategies (REMS) (Lis, Roberts, Kamble, J Guo, & Raisch, 2012). Since November 2005, companies seeking an European Union (EU) marketing authorization are required to submit a Risk Management Plan (RMP) to the European Medicines Agency (EMA) at the time of marketing authorization application. Note that since this is relatively new, some medicines may not have RMPs, in this case it is likely that one will be required with any application involving a significant change in marketing authorization. RMPs contains two main parts i.e. safety specifications and pharmacovigilance (PV) plan. An essential part of a RMP is the proposed pharmacovigilance activities which may be clinical trials, post-authorization safety studies and/or spontaneous reporting depending on the risk of profile of the drug (European Medicines Agency, 2016; Giezen et al., 2009).

PV is a science dedicated to detection, assessment, understanding and prevention of adverse events. PV is very critical for drug safety because it covers the entire population within or outside clinical settings and enables continuous benefit-risk balance assessment throughout the commercial life a drug. Spontaneous reporting of ADRs is the basis of PV relying on healthcare professionals and patients reporting ADRs. The main disadvantage in PV is under-reporting (estimated at 94%) which

may be caused by unawareness of necessity to report ADRs, difficulty and uncertainty of causality assessment, failure to distinguish between ADRs and disease symptoms, lack of time and fear of being called upon (Lopez-Gonzalez et al., 2014; Onakpoya et al., 2016). Examples of databases devoted to drug safety include SIDER, a database containing marketed medicines and their recorded ADRs, Vaccine Adverse Event Reporting

System (VAERS), and Myocardial Infarction Drug-Target Interactome network (My-DTome). Government owned drug safety databases include FDA Adverse Event Reporting System (FAERS), European Medicines Agency (EMA), Japan Pharmaceutical Information Centre (JAPIC). And recently multiple -omics databases including Dr. PRODIS integrated DRugome, PRoteome, and DISeasome (Tan et al., 2016).

## CONCLUSION

ADRs remain a significant contributing factor to morbidity and mortality worldwide despite increased awareness, research, publication, past mistakes or experiences and stricter regulations. The figures are likely to increase if preventive measures are not exercised. Most reported ADRs are Type A (predictable and dose dependent) and as such could be prevented. Drug-drug interactions, and overdose contribute to a significant number of preventable ADRs. Preventive measures to the ADR prevalence and costs are: implementation and adhering to RMPs, training of healthcare professionals should focus on avoiding inappropriate drug prescribing and on the importance of routine laboratory monitoring, particularly monitoring renal function, communication between patients and physicians, educational interventions stressing the relevance of PV may have a positive impact on spontaneous ADR reporting, empowering patients through health care education and literacy. The most promising approach by far is precision medicine which combines genetic analysis with factors such as behavioural, functional, environmental and lifestyle information.

## REFERENCES

- Ahern, F., Sahm, L. J., Lynch, D., & McCarthy, S. (2014). Determining the frequency and preventability of adverse drug reaction-related admissions to an Irish University Hospital: a cross-sectional study. *Emergency Medicine Journal: EMJ*, 31(1), 24–9. <https://doi.org/10.1136/emmermed-2012-201945>
- Alexopoulou, A., Dourakis, S. P., Mantzoukis, D., Pitsariotis, T., Kandyli, A., Deutsch, M., & Archimandritis, A. J. (2008). Adverse drug reactions as a cause of hospital admissions: A 6-month experience in a single center in Greece. *European Journal of Internal Medicine*, 19(7), 505–510. <https://doi.org/10.1016/j.ejim.2007.06.030>
- Bedouch, P., Allenet, B., Grass, A., Labarère, J., Brudieu, E., Bosson, J. L., & Calop, J. (2009). Drug-related problems in medical wards with a computerized physician order entry system. *Journal of Clinical Pharmacy and Therapeutics*, 34(2), 187–195. <https://doi.org/10.1111/j.1365-2710.2008.00990.x>
- Bushardt, R. L., Massey, E. B., Simpson, T. W., Ariail, J. C., & Simpson, K. N. (2008). Polypharmacy: Misleading, but manageable. *Clinical Interventions in Aging*, 3(2), 383–389. <https://doi.org/10.2147/CIA.S2468>
- Chan, M., Nicklason, F., & Fial, J. (2001). Adverse Drug Events as a Cause Of Hospital Admission In The Elderly. *Intern Med J*, 199–205.
- Dormann, H., Criegee-Rieck, M., Neubert, A., Egger, T., Geise, A., Krebs, S., ... Brune, K. (2003). Lack of awareness of community-acquired adverse drug reactions upon hospital admission: Dimensions and consequences of a dilemma. *Drug Safety*, 26(5), 353–362. <https://doi.org/10.2165/00002018-200326050-00004>
- Ehmann, F., Caneva, L., & Papaluca, M. (2014). European Medicines Agency initiatives and perspectives on pharmacogenomics. *British Journal of Clinical Pharmacology*, 77(4), 612–617. <https://doi.org/10.1111/bcp.12319>
- European Medicines Agency. (2016). Guideline on good pharmacovigilance practices ( GVP ). Module V – Risk management systems (Rev 2), (April), 1–22.
- Farcas, A., Sinpetrean, A., Mogosan, C., Palage, M., Vostinaru, O., Bojita, M., & Dumitrascu, D. (2010). Adverse drug reactions detected by stimulated spontaneous reporting in an internal medicine department in Romania. *European Journal of Internal Medicine*, 21(5), 453–457. <https://doi.org/10.1016/j.ejim.2010.05.014>
- Franceschi, M., Scarcelli, C., Niro, V., Seripa, D., Pazienza, A. M., Pepe, G., ... Pilotto, A. (2008). Prevalence, Clinical Features and Avoidability of Adverse Drug Reactions as Cause of Admission to Geriatric Unit. *Drug Safety*, 31(6), 545–556. <https://doi.org/10.2165/00002018-200831060-00009>
- Giezen, T. J., Mantel-Teeuwisse, A. K., Straus, S. M. J. M., Egberts, T. C. G., Blackburn, S., Persson, I., & Leufkens, H. G. M. (2009). Evaluation of post-authorization safety studies in the first cohort of eu risk management plans at time of regulatory approval. *Drug Safety*, 32(12), 1175–1187. <https://doi.org/10.2165/11318980-000000000-00000>
- Hinson, J. A., Roberts, D. W., & James, L. P. (2010). Adverse Drug Reactions. *Pharmacology*, 196(196), 1–34. <https://doi.org/10.1007/978-3-642-00663-0>
- Juntti-Patinen, L., Kuitunen, T., Pere, P., & Neuvonen, P. J. (2006). Drug-related visits to a district hospital emergency room. *Basic and Clinical Pharmacology and Toxicology*,

98(2), 212–217. [https://doi.org/10.1111/j.1742-7843.2006.pto\\_264.x](https://doi.org/10.1111/j.1742-7843.2006.pto_264.x)

- Kennedy, C. (2016). Drug interactions Key points, 422–426. <https://doi.org/10.1016/j.mpmed.2016.04.015>
- Lazarou, J., Pomeranz, B. H., & Corey, P. (1998). Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. *The Journal of the American Medical Association*, 279(15), 1200–1205. <https://doi.org/10.1007/jama.279.15.1200>
- Lis, Y., Roberts, M. H., Kamble, S., J Guo, J., & Raisch, D. W. (2012). Comparisons of Food and Drug Administration and European Medicines Agency risk management implementation for recent pharmaceutical approvals: report of the International Society for Pharmacoeconomics and outcomes research risk benefit management working g. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 15(8), 1108–18. <https://doi.org/10.1016/j.jval.2012.06.019>
- Lopez-Gonzalez, E., Herdeiro, M. T., Piñeiro-Lamas, M., & Figueiras, A. (2014). Effect of An Educational Intervention to Improve Adverse Drug Reaction Reporting in Physicians: A Cluster Randomized Controlled Trial. *Drug Safety*, 38(2), 189–196. <https://doi.org/10.1007/s40264-014-0256-6>
- McDonnell, P. J., Jacobs, M. R., Monsanto, H. A., & Kaiser, J. M. (2002). Hospital admissions resulting from preventable adverse drug reactions. *Annals of Pharmacotherapy*, 36(9), 1331–1336. <https://doi.org/10.1345/aph.1A333>
- Mouton, J. P., Mehta, U., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., ... Cohen, K. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. *British Journal of Clinical Pharmacology*, 80(4), 818–826. <https://doi.org/10.1111/bcp.12567>
- Null, G., Dean, C., Feldman, M., & Rasio, D. (2005). Death by medicine. *Journal of Orthomolecular Medicine*.
- Onakpoya, I. J., Heneghan, C. J., & Aronson, J. K. (2016). Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. *BMC Medicine*, 14(1), 10. <https://doi.org/10.1186/s12916-016-0553-2>
- Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A. K., Walley, T. J., ... Breckenridge, A. M. (2004). Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *British Medical Journal*, 329, 15–19.
- Pirmohamed, M., Ostrov, D. A., & Park, B. K. (2015). New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity. *J Allergy Clin Immunol*, 136(2), 236–244. <https://doi.org/10.1016/j.jaci.2015.06.022>
- Qing-Ping, S., Xiao-Dong, J., Feng, D., Yan, L., Mei-Ling, Y., Jin-Xiu, Z., & Shu-Qiang, Z. (2014). Consequences, measurement, and evaluation of the costs associated with adverse drug reactions among hospitalized patients in China. *BMC Health Services Research*, 14(1), 1–9. <https://doi.org/10.1186/1472-6963-14-73>
- Rambhade, S., Chakarborty, A., Shrivastava, A., Patil, U. K., Rambhade, A., & Kumar Rambhade, S. (2012). A Survey on Polypharmacy and Use of Inappropriate Medications. *Toxicol Int. Jan Apr*;, 19(1), 68–73. <https://doi.org/10.4103/0971-6580.94506>

Rang, H., Dale, M., Ritter, M., Flower, R., & Henderson, G. . (2012). *Pharmacology. Rang and Dale's Pharmacology*.

Schmucker, D. L. (2005). Age-related changes in liver structure and function: Implications for disease? *Experimental Gerontology*, 40(8-9), 650-659. <https://doi.org/10.1016/j.exger.2005.06.009>

Shepherd, G., Mohorn, P., Yacoub, K., & May, D. W. (2012). Adverse drug reaction deaths reported in United States vital statistics, 1999-2006. *The Annals of Pharmacotherapy*, 46(2), 169-75. <https://doi.org/10.1345/aph.1P592>

Tan, Y., Hu, Y., Liu, X., Yin, Z., Chen, X. wen, & Liu, M. (2016). Improving drug safety: From adverse drug reaction knowledge discovery to clinical implementation, 110, 14-25. <https://doi.org/10.1016/j.ymeth.2016.07.023>

U.S. Food and Drug Administration. (2015). What does FDA do?

Wilke, R. A., Lin, D. W., Roden, D. M., Watkins, P. B., Flockhart, D., Zineh, I., ... Krauss, R. M. (2007). Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. *Nature Reviews. Drug Discovery*, 6(11), 904-16. <https://doi.org/10.1038/nrd2423>