1. Introduction

Drugs are therapeutic tools with benefits to the patients and at times they produce undesired effects along with the desired effect. Even though they are intended to cure, prevent or diagnose diseases, they can cause morbidity and mortality when improperly used. Thalidomide disaster of 1960s increased the interest in monitoring, detecting and preventing adverse drug reactions (ADRs) of drugs (Bemt & Egberts 2007).

In early 1960s, several developed countries across the world including United Kingdom (UK), United States of America (USA), Australia, Italy, New Zealand and West Germany established national level programs for collecting reports of ADRs, and many more countries have done so subsequently (Rawlins, Breck & Wood 1989).

In India, Pharmacovigilance program was initiated only in early eighties. Under the leadership of Drug Controller General of India, five centers were involved in monitoring and reporting ADRs (Dhikav, Singh & Anand 2004). In the early 1990s, Drugs Controller General of India (DCGI) has established ADR reporting and monitoring program with six regional centers for reporting and monitoring of ADRs. Since its inception, the national pharmacovigilance centre, located in All India Institute of Medical Sciences (AIIMS), New Delhi, collected reports of ADRs from all the six regional pharmacovigilance centers. Later, Indian Council of Medical Research (ICMR), through its research program, had identified and supported twelve teaching hospitals across the country for few years for reporting and monitoring of ADRs (Gogtay, Mangalvedhekar & Kshirsagar 2000; Nerurkar, Nadkar & Bichile 1998).

Definitions

Adverse reactions to drugs are defined as ‘a response to a drug which is noxious and unintended and which occurs at doses normally used in man’ (Edwards & Aronson 2000).

Adverse drug event (ADE) is defined as the harm caused by the use of drug. In a sense ADRs are also adverse events with causal link to drugs (Nebeker, Barach & Samore 2004). Normally ADEs don’t have established causal relationship to the adverse incident suspected of a drug.

While explaining certain sections of ADRs, literature related to both ADRs and ADEs are used since both of them have similar risk factors and identification procedure.
Incidence of ADRs in hospitalized patients

The incidence rates of ADRs differ widely across different Studies. ADRs in hospital in-patients are generally divided into two types viz: Those who develop ADRs during hospitalization period and those who are admitted to hospital due to ADRs. There are reports on both groups of patients from across the world. Many of such studies are from developed countries like US and UK.

Incidence of ADR report ranged from 1.9 to 37.3%. This wide variation was attributed to different methodology adopted to collect information on ADRs (van den Bemt et al. 2000). Two prospective studies from UK showed that 6.5% of patients admitted to hospital experienced ADRs. The figure for incidence in North America was reported close to half of this value. This discrepancy was attributed to methodological problems in pooling data (Davies et al. 2007)

Risk factors for ADRs

Risk factors for ADRs evaluated in the literature include age, sex, number of prescribers, number of concomitant medications, and number of co-morbid conditions. These risk factors are discussed in the following section.

Age

Age is considered as risk factor for analysis, pediatric group was focused because of their immaturity of enzyme systems and elderly group was considered because of combination of physiologic and pharmacokinetic factors which makes them vulnerable for ADRs (Ajayi, Sun & Perry 2000).

There is higher risk of ADRs among the neonates of neonatal intensive care units and usually they are critically ill, receive multiple drug therapy, immature organ system and altered response to drugs (Knight 1994). Study of ADRs in this population is far less when compared to adult population. There was a report by Mitchell et al that out of around 3000 admissions, only 0.2 percent were due to ADRs (Mitchell et al. 1988). A surveillance program of pediatric outpatients recorded ADRs in 473 (11.1 percent) of 4,244 separate courses of drug therapy (Kramer et al. 1985; Mitchell et al. 1988). These studies have shown less frequency of ADRs among neonates and children.
Increasing age was mentioned as a reason for ADRs. Committee on drug safety in UK which receives spontaneous reports on ADRs received 24 percent of their reports for elderly in 1965 and it rose to 35 percent in 1983. This showed the association between elderly age group and ADR reports (Castleden & Pickles 1988).

**Gender**

Studies have reported a difference in ADR frequencies between males and females. Findings of many studies have suggested a propensity for females to experience more reactions (Martinez-Mir et al. 1999; Tran et al. 1998). Reasons postulated for this difference included difference in drug pharmacokinetic and pharmacodynamic properties, lower lean body mass, a reduced hepatic clearance and difference in activity of cytochrome P450 (Drici & Clement 2001; Harris, Benet & Schwartz 1995; Rademaker 2001)

A study by Gray et al may be considered as an important study for identifying female gender as a risk factor for ADRs since it took into consideration all the confounding variables. The multivariate analysis employed in this study found that females were 2.26 times more likely to have ADR than males in the study population (Gray, Mahoney & Blough 1999).

In an analysis of 48 cohort studies in UK by Martin et al, it was concluded that the overall age standardized relative risk of an ADR in females compared with males was 1.6 (95% CI = 1.5-1.7). This sex difference was observed in all age groups over 19 years old (Martin et al. 1998).

**Polypharmacy**

In practice polypharmacy has been defined as using more than a certain number of drugs irrespective of the appropriateness of drug use (Masoodi 2008). Some available studies did not find association between polypharmacy and ADR (Gandhi, Seger & Bates 2000; Veehof et al. 1999). But there are number of studies which suggested the possible association between increased drugs and adverse events. Ebbesen et al reported a study which assessed drug related deaths. They reported that higher number of drugs administered was associated with higher frequency of fatal ADEs (Ebbesen et al. 2001). It was also suggested that drug interactions might play a part in this phenomenon since rates of reactions to
individual drugs were dependent upon the number of drugs given concurrently (May, Stewart & Cluff 1977)

**Multiple pathologies as a risk factor for ADRs**

Multiple disease conditions were identified as an independent risk factor for drug complications. In a report by Gandhi *et al* the number of medical problems was identified as significant clinical correlates of patient-reported drug complications in a univariate analyses (Gandhi, Seger & Bates 2000). Carbonin *et al* reported that taking more than four drugs (OR = 2.94, 95% - CI 2.38-3.62) as well as having more than four medical problems (1.78, 95% CI - 1.29-2.45) remained significant predictors of total ADRs (Carbonin *et al*. 1991). Multiple illnesses can result in altered drug handling capacity (Bates *et al*. 1999; Young, Wurtzbacher & Blankenship 1997). The pharmacodynamic and pharmacokinetic changes resulting from insufficiency of organs can result in increased risk of an ADR (Harris, Benet & Schwartz 1995).

**Multiple physicians as a risk factor for ADRs**

Number of studies has shown that with increasing number of prescriber increases the chance of inappropriate combination of drugs leading to further complications. A cross sectional retrospective database study looked at two measures of physician involvement: prescribing physicians and number of physicians providing care. They reported that the number of prescribing physicians was more strongly associated with the risk of a potentially inappropriate drug combination than the number of physicians providing medical care (Tamblyn *et al*. 1996). In a study by Green *et al*, they reported the number of prescribing physician was independent risk factor for developing ADEs (Green, Hawley & Rask 2007).

**Methods for Identifying ADRs**

Number of methods is available to collect data on ADRs. Method of ADR identification method influences the ability to perform causality assessment and calculation of incidence.

**Spontaneous voluntary and solicited reporting**

Spontaneous or voluntary reporting method was an important method of ADR reporting in the post approval stages (Fletcher 1991; Venulet & ten Ham 1996) Spontaneous reporting system relies on the willingness of health care professional to report a reaction to a
regulatory agency or within their organization. Since spontaneous reporting is targeted all
the treated population, it helps to collect data on a large scale and it is undoubtedly
inexpensive compared to many other methods (Begaud et al. 1994; Venulet & ten Ham
1996).

Spontaneous reporting has some important limitations that affect the ability to assess
causality. Underreporting seriously affects the ability to calculate true incidence of ADRs
(Begaud et al. 1994). Spontaneous monitoring system cannot capture adverse effects that
manifest themselves as a highly prevalent disease or with a long delay between exposure
and clinical manifestation (Moore, Psaty & Furberg 1998).

**Chart review**

Chart review is an important method of screening medical records to identify adverse
events related to drugs. Prospective screening of medical records is called intensive
surveillance/monitoring. When performed retrospectively, it was often done through

Some researchers developed a list of target indicators or trigger tools that would flag those
records that were highly suspected of having an ADR. These trigger tools were even linked
to electronic data bases and have shown to increase the detection of adverse events by 50
folds compared to traditional method of reporting (Rozich, Haraden & Resar 2003).

**Diagnostic coding**

International Classification of Diseases, Clinical Modification (ICD-CM) defines certain
adverse event codes. These codes are assigned to case records with adverse events. The
case records with specific diagnostic codes can be further reviewed by researchers to
validate proper coding and verify a causal relationship. (Schumock, Thornton & Witte 1991)

**Screening of laboratory tests**

Screening of laboratory values for identifying drug related adverse effects offer an
alternative method in data record screening. Certain conditions like agranulocytosis,
aplastic anemia, liver injury, hyponatremia and rhabdomyolysis were identified as drug
induced ADRs using these screening systems. Such screening method can be even
automated making it easier to screen the lab report records. (Ramirez et al. 2010; Tavassoli et al. 2007)

**Integrated computerized surveillance**

Advances in computerized medical records opened up new methods for detecting ADRs. These computerized surveillance systems could screen predetermined signals from medical and pharmacy records and integrate them effectively. Such systems enhance the detection rate of adverse events (Classen et al. 2005; Kilbridge et al. 2006; Kilbridge & Classen 2006).

**Patient self-reporting**

Even though physicians ask their patients, about unwanted effects to a particular drug or therapy, they fail to document the incidences of ADRs. ADR might have been a reason for change of drug or dosage (Jarernsiripornkul et al. 2009; Jarernsiripornkul et al. 2002). Patient interview could potentially help to identify undocumented adverse events connected to drug in the medical record. Recall bias was the concern on this method (Palaian et al. 2006). Irrespective of the collection method, identification of patient risk factors for ADRs is essential for developing prevention methods (Blenkinsopp et al. 2007).

**Pharmacoeconomic impact of ADRs**

ADR affects the health care system and patients in many ways like: complication of existing therapy, prolongation of hospital stay and increased economic burden. ADR adversely affects the quality of life of patients and results in direct and indirect cost to the health care system and society (Gautier et al. 2003; Goettler, Schneeweiss & Hasford 1997; Janaje Munasinghe & Singer 2001).

Number of studies has assessed the cost of ADRs in variety of health care settings like primary to tertiary level health care centers and in general medicine to specialty care settings. The cost estimated for ADR depends upon the country where it is studied to the level of care and year of study (Gautier et al. 2003). The costs reported by number of studies estimate few million dollars at the institutional level to billions of dollars at the national level. ADRs represent significant burden to the health care systems around the world in terms of the resources it consumes to manage the condition and indirect costs associated with it (Goettler, Schneeweiss & Hasford 1997).
Predicting cost of ADRs

There is a need to understand ADRs and analyze it so as to reduce the cost of ADRs. Cost analysis of ADR raises important issue like perspective to be adopted in analyzing the ADRs. Social perspective is preferred in a pharmacoeconomic evaluation since it includes all the relevant costs (Lundkvist & Jonsson 2004). Health care costs associated with ADR has been reported in number of studies. These costs are essentially hospital costs, in particularly arising from an increase in length of stay caused by an ADR. Usually cost of excessive hospital stays was used to calculate the additional cost of ADR management for insurance companies or the health care system (Khong & Singer 2002; Moore, Psaty & Furberg 1998). A study from European study estimated that the occurrence of an ADR during hospitalization or leading to hospitalization is responsible for a mean cost of € 2800. In studies reported from US, the cost of individual ADRs were in the range of US$ 2000 to 4000 per patient (Bordet et al. 2001). Depending on the incidence and severity of ADRs, the cost per adverse effect avoided ranged from US$ 215 to US$ 35459 (Bates et al. 1997; Field et al. 2005; Rodriguez-Monguio, Otero & Rovira 2003). At the National level it has been reported that in-house ADEs alone have been estimated to be US$ 2 million in the US for departments of internal medicine hospital admissions and in Germany it has been estimated that ADR results in direct cost of 0.4 billion marcs annually (Schneeweiss et al. 2002). In a study by Ramesh et al from India showed that the average cost involved in treating ADRs was Rs. 690/- (US$ 15) per patient. The cost appears low to the patient as most of health care costs in the study hospital were covered under a charity fund and only minimal costs were directly borne by the patients. (Ramesh, Pandit & Parthasarathi 2003) In another study on the ADRs in an intensive care unit of a private hospital in India, it was reported that the management of an average ADR resulted in US$ 1537 (Pattanaik et al. 2009). In another study in which admissions due to ADRs were studied and these hospitalizations resulted in an average of US$ 150 per admission (Patel et al. 2007). Thus ADRs impose significant financial burden to health care systems in the developed countries and as well as developing countries like India.

Use of modeling techniques in pharmacoeconomics is becoming increasingly popular among health care organizations. The use of modeling techniques can assist decision-makers in making more informed clinical, policy, and medication decisions in real-world scenario (Sanchez & Lee 2000). Traditionally linear regression has been the technique of
choice for developing models in predicting costs associated with health care (Silber et al. 2005; Weiner et al. 2007).

Generalized linear models (GLM) are reported to be attractive for the regression of cost data because they provide parametric methods of analysis where a variety of non-normal distributions can be specified and the way covariates act can be altered. Unlike the use of data transformation in ordinary least-squares regression, GLM make inferences about the mean cost directly (Barber & Thompson 2004).

**Rationale for the study**

Indian council of Medical Research sponsored ADRs monitoring program was carried out in the study hospital. This study was carried out to identify and collect ADR data of in-patients of Medicine and Specialty disciplines. This study was planned to collect the data on ADR and use the data for further analysis of cost of ADRs and develop prediction models for severity and cost. Since this study was based on chart review process, it was envisaged to develop a list of indicator tools for screening charts which will simplify the chart screening process. The specialty units included in the study were Cardiology and Dermatology. Since there were no reported studies on cost and severity prediction models in Indian settings, it was envisaged to carry out such study. It was thought such work might help in drug safety research in this country in the direction of modeling and prediction.