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Chapter 2

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2.1 Adverse Drug Reactions

Adverse drug reactions and adverse drug events can have a detrimental effect on patients well being and the overall health care system. A comprehensive ongoing ADR program in a hospital can help to complement organizational risk management activities, assess the safety of drug therapies, measure ADR incidence rates over time, and educate health care professionals regarding drug effects and increase their level of awareness regarding ADRs.

2.1.1 Epidemiology of ADRs

Epidemiologic studies show that 17-36% of patients admitted to hospitals will experience an ADR. Furthermore, 3-5% hospital admissions may be due to ADRs. In a study conducted by Food and Drug Administration (FDA) determined that, of the 26,753 spontaneously reported ADRs, 24% were serious; of which 18% resulted in hospitalization and 6% were leading to death.
According to Anne Lee, as many as 5% hospital admissions may be attributed to adverse drug reactions. 5 to 10% of hospital inpatients experience an adverse drug reaction during their stay. Fatal adverse drug reactions may occur in about 0.1% of medical inpatients and 0.02% of surgical inpatients. The epidemiology of ADRs in the Indian population is not known as very few studies have been reported. Malhotra et al. assessed 4,764 consecutive visits of patients to medical emergency at the Postgraduate Institute for Medical Education and Research, Chandigarh, India, were for adverse drug events. They reported that 5.9% of all visits to the medical emergency department were deemed to be drug related. Adverse drug reactions accounted for 45% of events. A recent study from All India Institute of Medical Sciences (AIIMS), New Delhi, in which both inpatients and outpatients were included, indicates that 22.3% of the patients experienced adverse drug reaction and a vast majority of these were dose-dependent and potentially preventable.

2.1.2 Classification of ADRs

Rawlins and Thompson devised a convenient method of classifying adverse drug reactions in 1977. They categorized all ADRs as Type A or Type B reactions.

Type A (Augmented)

- Arising from the exaggerated but normal pharmacological action of a drug.
- They are common and predictable.
- Based on pharmacology of the drug.
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- Dose dependent reactions.
- Have high morbidity but low mortality.

E.g., Bradycardia caused by propranolol, atropine induced dry mouth.

Type B (Bizzare)

- Aberrant side effects unrelated to the normal pharmacology of the drug.
- They are unpredictable and uncommon.
- Not dose dependent reactions
- Have low morbidity but high mortality.

E.g., Anaphylaxis due to penicillin, Steven Johnson syndrome due to carbamazepine.

2.1.2.1 Some of the Limitations of above classification has been identified

1. The inclusion criterion for this classification is not clear. Some adverse reactions do not fit comfortably in this. For e.g., cancer patients taking immunosuppressants, develop reactions at injection sites.

2. In this classification Type B reactions are effectively classified as ‘everything that is not Type A’. This renders Type B reactions as a highly heterogeneous group with little in common, ranging from allergic skin reactions to extravasation to some forms of cholestasis.
3. Drug interactions involve the interplay between at least two different etiology of adverse reactions arising from a single chemical entity. Hence they should not be included.

4. Therapeutic failure is not an adverse reaction in the traditional sense and cause is often not clear. Known contributing factors include inappropriate choice of drug, non-compliance, under dosage, formulation failure or an idiosyncratic lack of response.

5. According to this classification intentional overdose by the patient causes symptoms described as “toxicity” rather than “adverse effect”. As they arise at doses that are not used clinically they should be excluded.

6. Rawlins and Thompson state that mortality is likely to be higher with Type B reactions than Type A. This would not appear to be the case in practice.

7. This classification state that only Type A reactions are dose dependent. The greater the dose used, more likely an individual would often suffer from reaction concerned.

2.1.3 Modification of the Classification

Wills et al. proposed a new classification. In this they retain Type A or Type B as such and eight new categories were proposed. This classification makes it clear that adverse reactions should refer to events involving a single agent (i.e., not drug interaction) 8.

Type A (Augmented)

- Arising from the exaggerated but normal pharmacological action of a drug.
- They are common and predictable.
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- Based on pharmacology of the drug.
- Dose dependent reactions.
- Have high morbidity but low mortality.

Type B (Bugs)
- Pharmacologically predictable.
- Involves interaction with a micro-organism.
- Improves if medicine withdrawn.

E.g., Sugar-containing medicines promoting dental caries, antibiotics causing overgrowth of resistant bacterial species in intestine.

Type C (Chemical)
- An irritant reaction depending on the chemical nature of drug or excipient.
- Related to drug concentration.

E.g., Pain at the site of injection.

Type D (Delivery)
- Caused by method of administration or nature of formulation.
- Improves if medicine withdrawn or method of delivery changed.
- Not dependent on chemical or pharmacological properties of a drug or excipient.

E.g., Infections at the site of an injection, cough after use of dry powder inhaler.

Type E (Exit)
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- Pharmacologically predictable.
- Begins only when medicine stopped or dose reduced.
- Improves if medicine reintroduced.

e.g., Causative drugs are opioids, benzodiazepines.

Type F (Familial)
- Only occurs in those genetically predisposed.
- Improves if medicine withdrawn.

e.g., Patients with glucose-6-phosphate dehydrogenase deficiency may experience haemolysis when exposed to quinine.

Type G (Genetotoxicity)
- Causes irreversible genetic damage.

e.g., Teratogenic agents damage genetic material within the foetus.

Type H (Hypersensitivity)
- Requires activation of immune system.
- These are the most common after Type A reactions.
- Improves if medicine withdrawn.
- Not predictable or dose dependent.

Type U (Unclassified)
- Unknown mechanism of occurrence.

e.g., Drug induced taste disturbance, muscular adverse effects of simvastatin.
2.1.4 Predisposing Factors

Age

- Geriatric and paediatric patients are more susceptible to adverse drug reactions.
- Elderly are always at risk because of altered physiological functions and often they are on multiple drug treatment.
- Young children, particularly neonates, handle and respond to a drug in different way than adults.

E.g., Reye’s syndrome with aspirin and hepatotoxicity with sodium valproate.

Gender

- In general, women appear to be at greater risk of ADRs than men.
- Increased drug exposure dose not account for the difference.

E.g., Reactions involving gastrointestinal tract.

Multiple Drug Therapy

The incidences of adverse drug reactions are increasing with multiple drug use. This suggests that the effects of multiple drug use are not simply additive but it is a synergistic effect.

Intercurrent Disease

- Patients with renal, hepatic and cardiac disease may have altered drug-handling capacity.
- In such patients one may have difficulty in attributing causality in view of other disease or alternative cause of event.
e.g., Increased adverse reactions of co-trimoxazole in HIV-positive patients.

**Pharmacokinetic Variables**

- There is great variation in how people respond to drugs.
- The dose required to produce a given pharmacological effect varies between individuals.

e.g., Patients with decreased hepatic and renal function may show considerable changes in drug deposition, leading to adverse drug reaction.

**Race**

- Ethnic differences may affect drug handling and render some individuals more at risk of ADRs.
- Genetic factors are often responsible.

e.g., Glucose-6-phosphate dehydrogenase deficiency (G6PD) is more prevalent in African people.

**Pharmacogenetics**

- Genetic polymorphism altering drug metabolism are important causes of Type A reactions.

e.g., G6PD deficiency leading to haemolysis by certain oxidant drugs like sulphamethoxazole, nitrofurantoin and primaquine.

**Allergy**

- True allergic reactions are immunologically mediated effects.
- Patients with a history of atopic or allergic disorders are at greater risk.

e.g., Allergic reactions vary from rash to severe bronchospasm and hypotension associated with anaphylaxis.
2.1.5 Surveillance Methods for ADRs [8][10][11]

Case reports
Published case reports have been vital in alerting the health professionals to new and serious adverse drug reactions. E.G., Halothane induced hepatitis.

Advantages

- Good for studying rare effects with high power.
- Very simplistic method.
- Serve as an alerting mechanism for clinicians, investigators and others health professional.

Disadvantages

- Case reports are weakest form of evidence for causation.

Case control studies
These involve comparing drug exposure among cases of particular condition, which may be drug induced, with a control group. e.g., Reye’s syndrome with aspirin.

Advantages

- Excellent for validation and assessment.
- Can study multiple disorders.

Disadvantages

- It is expensive and will not detect new effects.

Cohort studies
These are prospective studies, and study the fate of a large group of patients
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taking a particular drug. These studies compare the adverse events in group of patients taking the drug of intent, with a comparative group.

Advantages

• Large group of population can be studied.

• Good at detecting the adverse effects of a drug.

Disadvantages

• Very large numbers are required.

• These are costly and take a long time to generate results.

Case series

This is a group or cluster of case reports that may be generated by a single clinician, group of clinicians, a hospital, pharmaceutical company or a regulatory agency.

Advantages

• These allow a closer examination of the problem and likelihood of causality is enhanced.

• A large data can be generated.

Disadvantages

• They are expensive.

• Provide little insight into the rate of occurrence or extent of the problem.

• Occasionally may produce a false alarm when the relationship is strictly spurious.
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Prescription event monitoring
This includes recording all patients exposed to selected drugs. The patients or their physicians can then be approached by means of questionnaire to record any or selected record.

Advantages

• Large cohorts can be studied.

• Allows the follow up of exposed patients over a long period.

Disadvantages

• Validation of data is always a problem.

• Take a long time to produce results.

Spontaneous reporting system
This concept came into importance after the thalidomide tragedy. The goal of this method is to identify potential adverse effects of medications. Physicians were requested to report their earliest suspicions, either uncertain or incomplete.

Advantages

• Allows characterization of ADRs in actual population.

• Able to detect rare ADRs.

• Early detection of signals is possible.

• Covers the whole life cycle of the drug.

• Do not interfere with the prescribing habit of the practitioners.

Disadvantages
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- Under-reporting is always a problem.
- It is difficult to establish causation using these systems.
- The information obtained is often incomplete, unverified and inadequate.

2.1.6 Causality Assessment

It is assessment and classification of the likelihood of a causal relationship between a drug and a suspected adverse reaction.

2.1.6.1 Scales for causality assessment

- Naranjo’s ADR probability scale (Appendix-1)
- WHO probability scale (Appendix-2)
- Karch and Lasagna scale (Appendix-3)

2.1.6.2 WHO causality categories

Certain

A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/likely

A clinical event, including laboratory test abnormality, with a reasonable time
sequence to administration of the drug, unlikely to be attributed to concurrent
disease or other drugs or chemicals, and which follows a clinically reasonable re-
sponse on withdrawal (dechallenge). Rechallenge information is not required to
fulfill this definition.

**Possible**
A clinical event, including laboratory test abnormality, with a reasonable time
sequence to administration of the drug, but which could also be explained by
concurrent disease or other drugs or chemicals. Information on drug withdrawal
may be lacking or unclear.

**Unlikely**
A clinical event, with laboratory test abnormality, with a temporal relationship to
drug administration which makes a causal relationship improbable, and in which
other drugs, chemicals or underlying disease provide plausible explanations.

**Conditional/Unclassified**
A clinical event, including laboratory test abnormality, reported as an adverse
reaction, about which more data are essential for a proper assessment or the ad-
ditional data are under examination.

**Unassessible/Unclassifiable**
A report suggesting an adverse reaction which cannot be judged because informa-
tion is insufficient or contradictory, and which cannot be supplemented or verified.

Noel et al. conducted a study to determine the number of cutaneous adverse
drug reactions in hospitalized patients in a tertiary care centre in Bangalore. It was a prospective study over a period of one year. A total of 56 patients were diagnosed to have cutaneous ADRs. They used WHO probability scale. Only drugs having certain and probable causal association with reaction were considered for analysis. One patient had certain causal association while 45 patients were categorised for probable association.

The most common type of ADRs were maculopapular rash (35%), followed by toxic epidermal necrolysis (20%), and Steven Johnson syndrome (15%). The most common drugs implicated for cutaneous reactions were antiepileptics (44%), chemotherapeutic agents (32%) and NSAIDs (11%) respectively.

Vargas et al. conducted a study to determine the frequency of adverse drug reactions in intensive care units and to evaluate their effect on the length of stay. They performed a prospective study to detect ADRs in 420 patients hospitalized in ten predetermined beds in the ICU of hospital between March and December 1996. Ninety six different ADRs were detected in 85 of the 420 patients seen, 8 ADRs were severe, the suspected medication had to be discontinued in 51 cases and new drugs were necessary to manage the ADRs in 73 cases. Each ADR was related to a 2.38-day increase in the length of stay. Although this estimation was reduced to 1.76 days.

Another study carried out by Hurwitz and Wade in seven wards of Belfast City hospital found that the incidence of ADRs were 118 (10.2%) of the 1,160 patients who received drug therapy. The median age was 56 years, the youngest was 11 years and the oldest was 93 years. Of the 129 reactions to drugs that occurred,
4 were severe, 103 were moderate and 22 were mild.\textsuperscript{17}

Hurwitz conducted a study to collect the information on predisposing factors in ADR. Of 1,160 patients 118 developed ADRs of which 68 were females and 50 males, with median age being 60 years. Reports revealed 27 patients had a history of previous reactions, 19 patients were having allergic disease, 6 patients who developed reactions had diabetes and 4 patients had jaundice.\textsuperscript{18}

Lazarou et al. conducted a meta-analysis of 39 prospective studies at United States hospitals over a period of 32 years to obtain ADR incidences. Four electronic databases were searched from 1966 to 1998. They considered those patients admitted to the hospital due to an ADR (ADRAd) and those experiencing an ADR while in the hospital (ADRIn). The incidence of serious ADRIn was 2.1% of hospitalized patients while the incidence of serious ADRAd was 4.7%. The incidence of fatal ADRIn was 0.19% of hospitalized patients and the incidence of fatal ADRAd was 0.13%. Combining ADRIn and ADRAd, the overall incidence of serious ADRs was 6.7% of hospitalized patients and the overall incidence of fatal ADRs was 0.32%. The incidence of ADRIn of all severities was 10.9% of hospital patients. The overall incidence of ADRIn plus ADRAd for ADRs of all severities was 15.1% of hospital patients.\textsuperscript{21}

In another survey of ADRs carried by Hurwitz in ward of two Belfast hospitals for 52 weeks found that 2.9% of 1,268 patients were admitted due to adverse reactions to drugs taken for therapeutic purpose and 2.1% were admitted because of self-poisoning. Patients admitted because of ADRs had a median age of 60 years and those because of self-poisoning had a median age of 27 years.
20 were men and 17 women were admitted for ADR while 10 men and 17 women were admitted for self-poisoning. Of those admitted for ADRs 11 were of life-threatening severity and rest were moderate. 6 patients were admitted because of overdosage.\textsuperscript{19}

Troyen et al. as part of an interdisciplinary study of medical injury and malpractice litigation estimated the incidence of adverse events, defined as injuries caused by medical management and of the subgroup of such injuries that resulted from negligent or substandard care. They reviewed 30,121 randomly selected records from 51 randomly selected acute care, non psychiatric hospitals in New York State in 1984. They developed population estimates of injuries and computed rates according to the age and sex of the patients as well as the specialties of the physicians. Adverse events occurred in 3.7% of the hospitalizations and 27.6% of the adverse events were due to negligence. Although 70.5% of the adverse events gave rise to disability lasting less than six months, 2.6% caused permanently disabling injuries and 13.6% lead to death. They concluded that there is a substantial amount of injury to patients from medical management, and many injuries are the result of substandard care.\textsuperscript{20}

Raschetti et al. analysed the contribution of ADEs to the overall number of referrals or visits at an emergency department, to determine the proportion of more severe episodes requiring hospital admission and to characterize the different causes of drug-related visits or admissions. Among the 5497 patients who visited the Emergency Department over 1 year, 235 (4.3%) experienced an ADE, 45 of these (19.1%) were subsequently hospitalized, among whom there were five deaths. Dose-related therapeutic failures were the main cause of the drug-related
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admissions (55.6%), whereas ADRs caused the most frequent drug-related visits to the emergency-department (63.8%). Twenty-five (1.4% of total admission) of the 45 ADE-related admissions were evaluated as preventable, contributing by more than 61% of overall length of hospital stay.\textsuperscript{21}

Nicholas et al. conducted a study to assess the frequency and cost of drug reactions causing or prolonging hospitalization. All patients admitted to an internal medicine ward over 6 months were evaluated to identify serious ADRs. The number of drug classes on admission or at the time of the ADR was counted. All 329 patients were evaluated: 212 male, 117 female, mean age 57.2 and range 17-95 years. They stayed a total of 3720 hospital days. 298 had no ADR; 31 had ADRs. In 10, the ADR caused admission. 3% of the admissions were related to ADRs. In addition, 6.6% of hospitalized patients had significant ADRs. Between 5 and 9% of hospital costs were related to ADRs. In 24 of the 31 patients with ADRs (77%), these were related to the pharmacological properties of the involved drugs, and may possibly have been avoidable.\textsuperscript{22}

Munir et al. conducted a study to ascertain the current burden of ADRs through a prospective analysis of all admissions in two general hospitals in Merseyside, England. 18,820 patients aged more than 16 years admitted over six months were assessed for cause of admission. There were 1225 admissions related to an ADR, giving a prevalence of 6.5%, with the ADR directly leading to the admission in 80% cases. Overall fatality was 0.15%. Most reactions were either definitely or possibly avoidable. Drugs most commonly implicated in causing these admissions included low dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs (NSAIDs), the most common reaction being gastrointestinal
bleeding. They concluded that burden of ADRs on the National Health Society (NHS) is high, accounting for considerable morbidity, mortality and extra costs.\textsuperscript{3}

Gurwitz et al. studied the incidence and preventability of ADEs and potential ADEs in nursing homes. A cohort study was performed on all long-term care residents of 18 community-based nursing homes in Massachusetts during a 12-month observation period. Potential drug-related incidents were detected by stimulated self-report by nursing home staff and by periodic review of the records of nursing home residents by trained nurse and pharmacist investigators. From 28,839 nursing home residents of observation in the 18 participating nursing homes, 546 ADEs (1.89 per resident-months) and 188 potential ADEs (0.65 per 100 resident-months) were identified; of the ADEs, 1 was fatal, 31 (6%) were life-threatening, 206 (38%) were serious, and 308 (56%) were significant. Overall 51% of the ADEs were judged to be preventable, including 171 (72%) of the 238 fatal, life-threatening, or serious events and 105 (34%) of the 308 significant events. They concluded that ADEs are common and often preventable in nursing homes.\textsuperscript{23}

Lagnaoui et al. to increase the knowledge base conducted a study of the frequency, hazard function, avoidability, and cost of ADRs as a cause for admission in internal medicine, or when occurring after admission. The study was based on all admissions to an internal medicine unit over a 4-month period. Patients were intensively followed in order to assess any ADR occurring during the hospital stay. Causality, direct costs and preventability were assessed. Of the 444 admissions, 156 ADRs occurred in 116 patients (26.1% of all admissions); 95 (21.4%) of these had ADRs at admission which were the reason for admission
in 32 (7.2%). Twenty-one patients (4.7%) were presented with 26 ADRs during hospitalization. The in-hospital ADR incidence rate was 10.1 percent for 1000 patient per day. The cost of ADRs leading to hospitalization was estimated at Euro 11,537 per hospital bed per year. Eighty percent of ADRs could be considered preventable. They concluded that ADRs in hospitalized patients are common and often preventable. Since most ADRs occurred before admission, prevention strategies should preferentially target primary health care providers.

Gurwitz et al. reported 1523 adverse drug events, of which 27.6% were considered preventable. The overall rate of adverse drug events was 50.1% per 1000 person per year. Of the adverse events 578 were categorized as serious, life threatening, or fatal. Most of the adverse events resulted in symptoms of more than one day in duration. The drug classes involved were cardiovascular drugs (24.5%), diuretics (22.1%), nonopioid analgesics (15.4%), hypoglycemics (10.9%), and anticoagulants (10.2%).

Wenchen et al. conducted a study to evaluate outpatient ADRs leading to hospitalization during 1997 to 1998. A total of 191 patients were included, of those 56% were female and 45% of the patients were 75 years or older. The average length of stay for study patient was 8 ± 10.3 days. Major therapeutic classes implicated were antidiabetics 27.8%, anticoagulants 15.2%, anticonvulsants 10%, β-blockers 7.9%. Organ systems most commonly involved were endocrine 30.9% and cardiovascular 24.1%.

Samuel et al. conducted a study to introduce an ADR monitoring programme at two hospitals in South India over six months. In total, 152 ADRs were documented. The percentage of patients with a reported ADR at each of the three
centers was 3.5, 3.7 and 2.3. The gender of patients with reported ADRs was 53.9% male and 46.1% female. Most of the patients had a type “A” reaction (72%). Using Naranjo’s probability scale, 25.7% of ADRs were categorized as “probable” and 74.3% as “possible”. Of the ADRs reported in the two hospitals, 31.1% related to unplanned medications and 68.8% occurred during the hospital stay.

Chatterjee et al., conducted a one year prospective and observational study on adverse cutaneous drug reactions in outpatient clinic of a tertiary care hospital. The incidence of ACDR in developed countries range from 1-3% among inpatients whereas in developing countries like India some studies peg it to 2-5% of the inpatients, but there is lack of comprehensive data amongst out patients. Therefore the objectives of the study were:

1. Assess the incidence of ACDR amongst out patients attending the Dermatology department.

2. Assess causality and identify the offending drugs.

3. Identify any potential risk factors.

All patients who attended the Dermatology OPD of the hospital from 1st May 2002 to the 30th April 2003 were screened. A total of 27,726 patients attended the Dermatology OPD during the study period of one year. The incidence of ACDR was 2.66% (739) of the total patients screened. This study showed that female patients have contributed more of ACDR when compared to male patients. The common offending drug groups were antimicrobials (34.10%), anticonvulsants (32.88%) and anti-inflammatory drugs (21.51%). This study concluded that the
incidence of drug induced adverse skin reactions at dermatology out patient setting is 2.6%. Since previous studies were principally done amongst hospitalized patients this study provides data about the magnitude of this clinical entity in an out patient setting.

Filomena et al. conducted and reported a study on Hospital based intensive monitoring of antibiotic induced adverse events in a university hospital. The prospective study aimed to evaluate the frequency and type of adverse reaction to antibiotics and predisposing risk factors in inpatients. Data were collected over a 3-week period. There was no follow-up. 171 forms were analyzed (125 adults: 39.5% male, 60.5% female; 46 children:50% male, 50% female). Cefazolin (19.9%), chloramphenicol (18.6%), ceftriaxone (15.4%) and netilmicin (12.9%) were the most widely used antibiotics. Adverse events were reported in four adults and three children. One leucopenia subsequent to trimethoprim/sulfamethoxazole, two cases of nephrotoxicity caused by netilmicin plus teicoplanin, and by cefotaxime, one episode of severe diarrhoea and one case of skin rashes subsequent to ceftriaxone, one case of neurotoxicity after chronic isoniazid administration, and one angioneurotic edema due to piperacillin and in one of the patients, with ceftriaxone-induced skin rash was reproted. They concluded that the concomitant administration of antimicrobial drugs increased the risks for ADRs. After this study some antimicrobial agents have been eliminated from the list of drugs available at that hospital.

Padmini Devi et al. conducted a five year study in a South Indian hospital, on drug induced upper gastrointestinal disorders requiring hospitalization. Case reports of patients in the Department of Gastroenterology (from January 1998 to
December 2002) hospitalized with diagnoses of drug induced upper GIT disorders were analyzed retrospectively. Out of 101 cases identified over the study period, 8 were categorized as certain, 87 as probable and 6 cases as possible. The certain and probable cases (95) were analyzed. The drug class most commonly implicated with adverse drug reactions was non steroidal anti-inflammatory drugs (NSAIDs) (76.8%). Among individual drugs, aspirin was most commonly involved (32.6%). Results of endoscopy revealed gastric erosions (40.2%), combination of gastric ulcer and gastric erosions (16.1%), gastric ulcer (15.0%), duodenal ulcer (13.8%). They concluded that NSAIDs especially aspirin was implicated in maximum number of patients. A male preponderance was noticed which seems to be due to the association with risk factors like chronic smoking and alcohol consumption, more common in males in an Indian setting.\textsuperscript{29}

Kenneth et al. conducted a study on adverse events due to discontinuations in drug use and dose changes in patients transferred between acute and long term care facilities. The objective of this study was to identify medication changes during transfer between hospital and nursing home and adverse drug events caused by these changes. Participants were residents of 4 nursing homes in the New York City metropolitan area admitted to 2 academic hospitals. The results of this study showed, the total 122 admissions the mean numbers of medications altered during transfer from nursing home to hospital and hospital to nursing home were 3.1 and 1.4 respectively. Most changes in drug use were discontinuations, followed by dose changes and class substitutions. Although most medication changes (8/14) implicated in causing ADEs occurred in the hospital, most ADEs (12/14) occurred in the nursing home after nursing home readmission. This study states that medication changes are common during transfer between hospital and
nursing home and are a cause of ADEs. Research is needed on interinstitutional patient care and system interventions designed to prevent ADEs.\textsuperscript{30}

## 2.2 Drug-Drug Interaction

### 2.2.1 Overview of Drug Interactions\textsuperscript{31}

To prevent or detect drug interactions, the physician needs to identify risk factors in the individual patients. The medications that are most likely to be involved in interactions must also be evaluated.

Jerry et al. assessed the incidence and preventability of adverse drug events among older persons in the ambulatory clinical setting. There were 1523 identified adverse drug events, of which 27.6\% (421) were considered preventable. The overall rate of adverse drug events was 50.1 per 1000 person per years, with a rate of 13.8 preventable adverse drug events per 1000 person per year. Of the adverse drug events, 578(38.0\%) were categorized as serious, life threatening, or fatal; 244 (42.2\%) of these more severe events were deemed preventable compared with 277 (8.7\%) of the 945 significant adverse drug events. Errors associated with preventable adverse drug events occurred most often at the stages of prescribing 89 (21.1\%) also were common. Cardiovascular medications (224.5\%), followed by diuretics (22.1\%), non-opoid analgesics (15.4\%), hypoglycemic (10.9\%), and anticoagulants (10.02\%) were the most common medication categories associated with preventable adverse drug events. Electrolyte/renal (26.6\%), gastrointestinal tract (21.1\%), hemorrhagic (15.9\%), metabolic/endocrine (13.8\%) and neuropsychiatry (8.6\%) events were the most common type of preventable adverse drug events.\textsuperscript{32}
Daniel et al. reported the prevalence of 25 clinically important potential drug-drug interactions (DDIs) in a population represented by the drug claim databases of a pharmacy benefit management company (PBM) studied. The number of DDIs ranged from 37 for pimozide and azoles anti-fungal to 1,27,684 for warfarin and non-steroidal anti-inflammatory drugs. The highest prevalence and highest case-exposure rate occurred with the warfarin-NSAID combination. The combination with the lowest overall prevalence differs from the combination with the lowest case-exposure rate. Number of cases, prevalence, and case-exposure rate for both sexes generally increased with age. An estimated 3,74,000 plan participants were exposed to a clinically important DDI during a 25-month period. Between 20% and 46% of prescription drug claims were reversed for a medication with a drug interaction when a warning about the interaction was sent to the pharmacy.

Philip reported that, of 793 retrieved citations, 120 contained original reports on 186 interactions. The weighted kappa statistics was 0.67, representing substantial agreement. Of 86 different drug and food appraised, 43 reported level evidence. Of these, 26 drugs and food interact with warfarin. Warfarin’s anticoagulant activity was potentiated by 6 antibiotics (cotrimoxazole, erythromycin, fluconazole, isoniazid, metronidazole and miconazole); 5 cardiac drugs (amioderone, clofibrate, propafenone, propranolol and sulfinpyrazone); phenylbutazone; piroxicam; alcohol (only with concurrent liver disease); cimetidine and omeprazole. Three patients had a hemorrhage at the time of audio potentiating interactions (caused by alcohol, isoniazid, and phenylbutazone). Warfarin’s anticoagulant effect was
inhibited by 3 antibiotics (griseofulvin, rifampicin, and nafcillin) drug active on
the central nervous system (barbiturates, carbamazepine and chlordiazepoxide),
cholestyramine; sucralfate.

Richard et al. stated in their poster that the records for 94(41%) of the 230
patients identified were reviewable. The gatifloxacin (n=40) and control (n=54)
groups did not differ significantly in percentage of male patients (50% and 41%,
respectively), mean age (76 and 77 years), mean fine score (an indication of
disease severity)(107 and 109), or percentage of patients taking drugs known
to interact with warfarin (13% to 16%). More gatifloxacin-treated patients had
INR values greater than 3.0 (55% versus 37%) (p= 0.083) and required a de-
crease in their preadmission warfarin maintenance dosage (38% versus 18%)
(p=0.19).gatifloxacin recipients were significantly more likely than control pa-
tients to require a warfarin dose to be withheld during concomitant antimicrobial
therapy (60% versus 33%) (p=0.05).

Anthony et al. stated in his case study about a 66-year old man who had a
cerebrovascular accident in 1991 taking warfarin to prevent embolism. He had
a deep vein thrombosis in November 1995 and March 1996. The man also had
hypertension, coronary artery disease, diabetes mellitus, peripheral vascular dis-
ease and had undergone below-knee amputation of his right leg. Medication in
addition to warfarin included fosinopril sodium (5 mg daily), hydrochlorthiazide
(25mg daily), glipizide (10mg twice daily), regular insulin (sliding scale doses)
and diphendramine hydrochloride (25 mg p.r.n.). At the dose of warfarin sodium
42.5 mg/wk, the patients INR had been 2.53 to 3.13(goal, 2.5-3.5) for the past 10
months. To better control his diabetes, was started with acarbose therapy: 25mg
daily in week 1, 25mg twice daily in week 2, and then 25mg three times daily in
week 3. Four day before starting acarbose therapy, his INR was 3.09. After two
weeks of acarbose therapy the patients INR increased to 4.85. other than recent
addition of acarbose, there was no apparent factor that would have contributed
to the elevated INR. There had been no change in patients diet, ethanol use, non-
prescription use, or complication with medication regimens. Doses of warfarin
were withheld for one day and then resumed at the lower dosage of 40mg/wk;
subsequently the endocrinologist discontinued acarbose. Seven days after acar-
bose therapy was stopped the INR was 2.84 . Fortunately, the patient did not
have a bleeding episode as a result of high INR.

Brian et al. explained in his case study of a 51 year-old admitted to hospital in
august 1997 for repeat femoral- popliteal arterial bypass grafting; the procedure
had first been performed in January 1997. He had received a mechanical aortic
valve in 1979 and was taking warfarin to prevent thromboembolism. During the
previous seven months, his INR had been stable on 2.4 and 3.3 (2.5-3.5), and the
weekly total of his daily warfarin sodium doses had been 45mg, he had a history
of severe peripheral vascular disease (with a transient ischemic attack), diabetes
mellitus, hypertension and depression. After the repeat bypass surgery, warfarin
sodium therapy was restarted at the previous dosage (total, 45mg/wk), and the
patients medication regimen was stabilized. He was transferred from the surgic-
ical ward to another floor for rehabilitation; his other oral medications included
famotidine 30 mg daily, glyuburide 5 mg daily, fosinopril sodium 20 mg daily,
hydrochlorthiazide 50 mg daily, doxepine 75mg twice daily, and dipyridamole 50
mg twice daily. He was also receiving 70/30 combination insulin 24 units subcu-
taneously in the morning and 50 units in the evening. About two weeks after the
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patient was transferred from the surgical ward, troglitazone therapy was started to improve the management of his diabetes. The troglitazone dosage was 200 mg daily orally for the first two weeks and 400 mg daily thereafter. The patient's INR was found to be 3.3 before 5 days of troglitazone therapy was started and 5.5 after 17 days therapy was started. There was no change in the patient's regimen other than addition of troglitazone and no change in diet or use of ethanol since hospital admission. Warfarin sodium was withheld for two days immediately after the high INR was reported and the dosage of warfarin sodium was further reduced to a weekly total of 32.5 mg. Seven after the last adjustment the patient's INR was 2.9, and eight days after it was 2.8. The patient now takes 400 mg daily and daily warfarin sodium totaling 32.5 mg/wk. The patient did not have bleeding or increased brushing while his INR was higher than desired.

Olga noted that a very large number of drug interactions have been reported with warfarin. The drugs may interact through pharmacodynamic or pharmacokinetic mechanisms. The former include alteration of bioavailability of vitamin K, affecting receptor sensitivity and affecting homeostasis via platelet functions. The pharmacokinetic interactions may be due to effects on warfarin absorption, protein binding and metabolism. Because of the possible serious consequences of interference with anticoagulant therapy, special care is required when any medication is added to patients on anticoagulant therapy. Patient monitoring should be more frequent in such cases. The optimum anticoagulant therapy should be aimed at an adequate balance between effective prevention of intravascular thrombosis and the production of unwanted bleeding. Interactions with warfarin are of particular importance not only because unexpected loss of anticoagulant control may have serious consequences, but also warfarin offers a useful mecha-
Cynthia studied that the interaction between amiodarone and warfarin has only been described in patients being followed up for relatively short time periods. The objectives of this study were to characterize the interaction between these two agents in a clinical situation over a longer period of time in a larger cohort of patients and to determine the relationship between the maintenance dose of amiodarone and the resultant need to adjust the dose of warfarin. At baseline prior to initiation of amiodarone, the warfarin dose was $5.2 \pm 2.6$ mg/d. The magnitude of the interaction between these two agents peaked at 7 weeks, which resulted in a 44% mean maximum reduction in the warfarin dose. The warfarin dose inversely correlated with the maintenance dose of amiodarone ($r^2 = 0.94$, $p < 0.005$). Minor bleeding episodes occurred in five patients (12%). For patients receiving amiodarone maintenance doses of 400, 300, 200, or 100 mg/d, it is recommended that the daily warfarin dose be reduced by approximately 40%, 35%, 30%, or 25%, respectively. The magnitude of the amiodarone/warfarin interaction is highly dependent on the maintenance dose of amiodarone. This relationship can aid clinicians in adjusting the dose of warfarin for patients receiving long-term amiodarone treatment.

Harder et.al. stated that coumarin derivatives combine three unfavorable properties, which make them prone to potential life threatening drug-drug interactions:

1. High protein binding
2. Cytochrome P450 dependant metabolism
3. A narrow therapeutic range
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There are 250 different compounds which are interacting with coumarins (mostly with warfarin). Julie stated that when the cyclooxygenase-2 (COX-2) inhibitors celecoxib and rofecoxib became available, many physicians at our institution were interested in using them because studies showed that they were associated with less gastrointestinal bleeding than traditional nonsteroidal anti-inflammatory agents. Gastrointestinal bleeding is of special concern in patients taking warfarin. Early studies found minimal changes in International Normalized Ratios (INRs) when COX-2 inhibitors were added to warfarin therapy. The package insert for celecoxib states that, in healthy subjects given warfarin 2-5 mg daily, “celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time(PT). However, in postmarketing experience bleeding events have been reported”. Rofecoxib’s package insert states, “Prothrombin time (measured as INR) increased in both single- and multiple-dose crossover studies in healthy individuals receiving both warfarin and rofecoxib. Administration of rofecoxib 25 mg once daily was associated with mean increases in INR of approximately 8%”. From March 1999 to March 2000, 28 patients in our ambulatory care anticoagulation clinic had been prescribed either celecoxib or rofecoxib after being stable on warfarin therapy. Thirteen of these patients had increases in their INR. Within this group of 13 patients, 6 had other possible causes for the increasing INR, such as decreased dietary vitamin K, increased alcohol consumption, or the addition of aspirin or an antibiotic drug. No other potential cause for the changing INR was identified in the 7 remaining patients. The average increase in the INR for these 7 patients was approximately 1.5 (a change of 50-60%). Five of the seven had INRs greater than 4.0, putting them at risk for bleeding. One patient did
have an episode of bleeding, which was reversed by an injection of phytonadione.

Barry et.al stated that warfarin is an established agent with a narrow therapeutic index whose effect is altered by many commonly used medications. The propensity for such interactions is well known, and recommendations on how to manage them has been documented in worldwide product labeling and various professional treatment guidelines. Despite its proven benefits in appropriate patients, warfarin must be given with great care.

A multiplicity of outcomes is possible when people use drugs. Most commonly the patient benefits from drug therapy; however adverse events ranging from minor side effects to death may occur. One of the consequences of multiple drug use is the risk of one drug influencing the activity, the availability or the effect of a second drug. This so-called drug interaction can be desired or result in adverse effects like reduced effectiveness or increased toxicity of the involved drugs. There are a number of mechanisms by which drugs interact with each other, and most of them can be divided in two general categories: pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic drug interactions occur when one drug affects the absorption, distribution, metabolism, or excretion of another. Pharmacodynamic drug interactions occur when two drugs have additive or antagonistic pharmacologic effects.

2.2.2 Epidemiology of drug interactions

The probability of a drug interaction increases exponentially in hospitalised and ambulant patients, with the number of drugs a patient is taking. Two developments cause an increase of polypharmaceutical combination therapies in
highly developed health care systems: First, an increased life expectancy which leads to an increase of chronic diseases and therefore leads to an enhanced demand for drugs, which is associated with the necessity of one individual patient to be treated by multiple practitioners or specialists. Second, due to chronic diseases long-term therapies and preventive actions become more important. The number of drugs taken at the same time is clearly higher in hospitalised patient settings [51, 55, 56, 57] than in ambulatory patients [57, 58, 59]. Epidemology of drug interaction studies assume a good compliance which may lead to an overestimation of drug exposure. In general the intake of over the-counter (OTC) drugs for self-medication is frequent [60]. In ambulatory patients the actual risk of drug interactions with self-medication is often not considered and might therefore be underestimated. The number of drugs used per defined period of drug therapy is clearly higher in hospitalised patients [51, 55, 56, 57] compared to ambulatory patients [57, 58, 60].
Egger et al.\cite{52} reported in a study at the University Hospital Basel that 53.8% of potential drug interactions at discharge resulted from a change of the medication during the hospital stay. Straubhaar et al.\cite{61} observed in a study at the University Hospital Basel that hospitalisation of patients with heart failure results in an increase in the number of drugs prescribed per patient and thereby, also in the number of potentially interacting drug combinations per patient. During the hospital stay a close medical monitoring combined with continuous nursing and therapeutic care is generally guaranteed. But this may profoundly change after discharge. Therefore, epidemiologic post-marketing surveillance investigations in ambulatory patients are of particular importance for drug safety.

In her thesis Käser assessed 22 potential drug interactions of clinical relevance (major and moderate) and 65 of 'possibly' clinical relevance (major, moderate and minor) per 100 outpatients per year. Reported incidences in outpatients range from 9.2% to 70.3% for drug interactions of any severity and from 1.2% to 23.3% for those considered of major relevance\cite{62,63,64}. This large range may be explained by investigations in different study populations or different definitions used for the clinical relevance of potential drug interactions.

Despite the high incidences of potential drug interactions the number of manifest adverse events is rather low\cite{32,65,66,67}. Studies so far have not provided conclusive data with respect to the frequency of prescribing interacting drugs and the occurrence of manifest adverse events caused by drug interactions in outpatients. Juurlink et al.\cite{68} recognised the need to examine clinical outcomes of drug interactions in a population-based fashion. They delivered data on three drug interactions that involve commonly used medications and that produce specific
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toxic effects. Elderly patients taking glyburide hospitalised for hypoglykaemia were more than 6 times as likely to be treated with co-trimoxazole, patients admitted with digoxin toxicity about 12 times more likely to be treated with clarithromycin and patients treated with angiotensine converting enzyme inhibitors (ACEI) admitted with hyperkalaemia were about 20 times more likely to have been treated with a potassium-sparing diuretic.

In the literature, the prevalence of potential drug interactions is often expressed as percentage of exposed patients. This fact does not consider that one patient may be affected by several potential drug interactions and that the prevalence is biased by the number of drugs taken together. Alternatively, the frequency of potential drug interactions can be expressed by the number of potential drug interactions relating to the number of possible double combinations of drugs which can be calculated according to the equation:

\[
\text{Number of drug pairs} = \frac{n(n - 1)}{2}
\]  

(2.1)

The frequency of clinical relevant potential drug interactions is about 6% and of highly relevant potential drug interactions below 2%.

2.2.3 Management of potential drug interactions

The identification of patients at risk and an accurate management of their drug therapy are important challenges for health care professionals to avoid serious clinical consequences caused by adverse drug reactions. This process of maximizing the benefits and minimizing the risks of a drug therapy for individual patients is complex and there are many steps where errors can occur. The mission
of healthcare providers is to provide systematic pharmaceutical care to reduce preventable drug-related morbidity and mortality. The Pharmaceutical Care Network Europe (PCNE) advanced this systematic approach. They classified drug-related problems (DRPs) according to their possible causes, possible interventions and the outcome of interventions. The PCNE classification was designed to be used in research as a process indicator in experimental pharmaceutical care studies and as an instrument to help health care professionals to document DRP-information in the pharmaceutical care process (Table 2.1). Amongst possible negative outcomes of drug therapies drug interactions pose an important problem. The possible causes of DRPs lie at prescribers’, pharmacists’ or patients’ level and interventions to prevent adverse outcomes due to DRPs installed at these levels. Any deviation from the intended beneficial effect of a drug therapy results in a drug-related problem. An optimal therapeutic outcome is only achieved with the absence of DRPs. Drug-related mortality and morbidity pose a major problem to health care. The rates of drug related hospital admissions found in two meta-analyses were up to 5.3% and Winterstein et al. found a median preventability rate of drug-related hospital admissions of 59%. The newspaper headline ‘Once a $76.6 billion headache, now a $177.4 billion migraine’ describes the increasing economic load caused by DRPs in USA between 1995 and 2000 after cost-of-illness analysis by Ernst and Grizzle. There is a need to reduce economic and medical burdens caused by DRPs by their identification, prevention and solution in a process of pharmaceutical care. A study of admissions to an Australian hospital found that drug interactions accounted for 4.4% of DRPs encountered.

According to the definition of PCNE a DRP is an event or circumstance in-
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volving drug therapy that 'actually' or 'potentially' interferes with desired health outcomes. According to this definition a drug interaction can be considered to be 'potential' in the constellation of patients' drug therapy or 'manifest' when leading to an adverse event. Drug interactions are often predictable based on an understanding of simple pharmacologic properties because they are caused by the same pharmacokinetic and pharmacodynamic principles that determine the behaviour of drugs in the body. Only few potential drug interactions do lead to 'manifest' outcomes and little information is available about the epidemiology of adverse outcomes. Most evidence is derived from case reports, volunteer studies, or investigations of potential drug interactions in hospitalised patients. It is very difficult for health care providers to predict the manifestation of a drug interaction. Hence, the statement 'Predicting drug interaction outcomes - do we do better than meteorologists?' by Hansten and Horn describes the incertitude in the process of pharmaceutical care, to minimise risk resulting from drug interactions.

A drug interaction that is likely to cause an adverse outcome in one patient may have no effect on another patient. Therefore, it gets more and more important to provide information about patient risk factors. Bergk et al. revealed that 11.6% of major or moderate potential drug interactions are only relevant in predisposed ambulatory patients. The variability among patients can be explained by the influence of a multiplicity of factors like e.g. advanced age, co-morbidities, pharmacogenetic influences. For e.g., the increased risk of hyperkalaemia in a patient treated with an ACEI and a potassium-sparing diuretic who also is a diabetic with renal impairment is obvious. A patient who is deficient in a cytochrome P450 isoenzyme (CYP) may be less likely to manifest an adverse
event caused by a drug interaction. For e.g., a CYP2D6 deficient patient may have an adequate therapeutic response with a low dose of a drug metabolised by CYP2D6 (e.g. simvastatin) compared with patients of normal or high CYP2D6 activity\textsuperscript{79}. When taking a potent CYP2D6 inhibitor (e.g. fluoxetine) there will be no interaction with simvastatin in the CYP2D6 deficient patient but there might be a substantial increase in serum simvastatin in patients with normal or high CYP2D6 activity\textsuperscript{80}. It is possible to determine a person’s genotype or phenotype for many of the CYP isoenzymes, but this is used primarily in research rather than as clinical tool for predicting drug response. As these procedures become more automated and less expensive, it is more likely that they used for clinical management, at least for selected patients\textsuperscript{80}.
Table 2.1: The basic Pharmaceutical Care Network Europe Classification (PCNE) scheme for drug related problems

<table>
<thead>
<tr>
<th>Code</th>
<th>Primary Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Problems</td>
</tr>
</tbody>
</table>
| P1   | Adverse reaction(s)  
Patient suffers from an adverse drug event |
| P2   | Drug Choice Problem  
Patient gets or is going to get a wrong (or no drug) drug for his/her disease and/or condition |
| P3   | Dosing problem  
Patient gets more or less than the amount of drug he/she requires |
| P4   | Drug Use/Administration Problem  
Wrong or no drug taken/administered |
| P5   | Interactions  
There is a manifest or potential drug-drug or drug-food interaction |
| P6   | Other |

<table>
<thead>
<tr>
<th>Code</th>
<th>Primary Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Causes</td>
</tr>
</tbody>
</table>
| C1   | Drug/Dose Selection  
The cause of the DRP can be related to the selection of the drug and/or dosage schedule |
| C2   | Drug Use Process  
The cause of the DRP can be related to the way the patient uses the drug, in spite of proper dosage instructions (on the label) |
| C3   | Information  
The cause of the DRP can be related to a lack or misinterpretation of information |
| C4   | Patient/Psychological  
The cause of the DRP can be related to the personality of the patient |
| C5   | (Pharmacy) Logistics  
The cause of the DRP can be related to the logistics of the prescribing or dispensing mechanism |
| C6   | Other |

<table>
<thead>
<tr>
<th>Code</th>
<th>Primary Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interventions</td>
</tr>
<tr>
<td>I0</td>
<td>No intervention</td>
</tr>
<tr>
<td>I2</td>
<td>At prescriber level</td>
</tr>
<tr>
<td>I2</td>
<td>At patient (or carer) level</td>
</tr>
<tr>
<td>I3</td>
<td>At drug level</td>
</tr>
<tr>
<td>I4</td>
<td>Other</td>
</tr>
</tbody>
</table>
‘The Swiss cheese model’ by James Reason\textsuperscript{[51]}, a British psychologist, has become the dominant paradigm for analysing medical errors and patient safety incidents. It was adapted by Hansten and Horn\textsuperscript{[52]} to the problem of drug interactions which systematically illustrates the avoidance/occurrence of an adverse drug reaction caused by a drug interaction. Because adverse drug reactions resulting from drug interactions are almost completely preventable, it is important to identify the steps at which prevention can take place\textsuperscript{[52]}. Perfect systems do not exist. The holes in the Swiss cheese represent gaps in the defenses shown below\textsuperscript{[51]}.

Adapted by Hansten and Horn\textsuperscript{[52]} from the ‘Swiss cheese model of accident causation’ by Reason\textsuperscript{[53]}. The hazard (in this case a drug interaction) must traverse the layers of defense for an adverse drug event to occur. In this case, the patients pharmacogenetic makeup protects against an adverse event. The holes in the cheese represent the gaps in defenses.

If managed adequately, many drug interactions do not result in clinical manifes-
tations. The risk of drug interactions often can be reduced by close monitoring, dose adjustment and/or coordinated sequence of administration. Bergk et al. \cite{69} revealed that only 25.3% of potential drug interaction of major severity offered no management options and should thus be avoided. Anyhow, Chen et al. \cite{84} found an incidence of 1.9 per 1000 patient years (95% confidence interval (CI) 1.5, 2.3) of prescribed potentially hazardous/contraindicated drug interactions. They identified multiple possible causes (e.g., lack of knowledge of the drug interaction or of the patient medication history) and system failures (e.g., incomplete medication records, communication between primary and secondary care or between the prescriber and the patient) for the dispensing of contraindicated drug combinations.

\subsection*{2.2.4 Drug Interaction Information Sources}

In the past 40 years more than 20,000 journal articles on drug interactions have been published. This flood of information has overwhelmed even the most dedicated and compulsive health care providers\cite{85}. No one can possibly memorise all the potential drug interactions that have been identified to date, and new interacting drug pairs are identified every month. To cope with this task drug interaction compendia in the form of books, computer or personal digital assistant (PDA) software or online databases are offered to health care providers. Studies revealing the prevalence of potential drug interactions often referenced in the US-database by Thompson Micromedex\cite{86} or the British Stockley’s drug interactions\cite{87}, which can be considered as standard information sources. In Austria, Germany and Switzerland a drug interaction database is implemented in
the drug information Pharmavista 61 which is adapted from the German ABDA-Database 62 for the Swiss market and is used in all community pharmacies and also by some physicians. This database is also available online as a subscription-only service.

Simply knowing that two drugs may interact does not provide enough information for the health care provider. It is also important to have information on measures that can be taken to reduce the likelihood of an adverse outcome. Therefore, drug interaction monographs have to contain information about the potential adverse effect, the rating of severity of the potential adverse event, the mechanism of the interaction, and suggestions for the clinical management including dose-adjustment, sequential dosing time, alternative therapies, monitoring or patient related risk factors. Bergk et al. revealed that German practitioners wish more informative support on drug interactions, especially concerning management. In particular, information about non interacting alternative therapies was thought to be lacking.

2.2.5 Drug Interaction Classification Systems

It is often difficult to distinguish clinically important from unimportant drug interactions. It has become unrealistic to expect individual practitioners to read all of the relevant data and determine on their own which drug interactions are the most clinically important. Accordingly, most books and software evaluating drug interactions use classification systems to help the health care provider with this process. In the database Pharmavista potential drug interactions are classified into ‘severe’ (life-threat / intoxication / permanent harm), ‘moderate’ (frequent therapeutic problems / combination can be administered but close monitore-
ing required), ‘minor’ (increased or decreased drug effect / only specific subgroups affected), ‘negligible’ (Usually induces no or limited clinical effects / generally no modification of therapy required) and ‘external specifications’ (only assumed or described in particular cases/ clinical consequences unclear). Studies using the Pharmaceutical Specialities in Sweden (FASS) classification divided major drug interactions into those that could be managed by dose adjustment (category C) and combinations that should be avoided (category D)\textsuperscript{51, 62}. However, category- D still includes drug combinations that can be therapeutically useful and safely administered under certain circumstances\textsuperscript{88}. Apart from dosage, there are further factors modulating the risk arising from drug interactions: Some are only relevant in predisposed persons; others are blunted if the interacting pair is combined with further co-medication (e.g., potassium substitution in patients receiving digoxin and a potassium-sparing diuretic), and yet others only occur when the combination is administered strict concurrently and can be avoided by temporally separated administration interval of sufficient length (e.g., aluminium or magnesium antacids combined with ciprofloxacin)\textsuperscript{88}. Earlier studies reported frequencies of drug interactions and classified them according to their potential severity (e.g., major, moderate, minor). Bergk et al\textsuperscript{88} used the classification of adverse effects by Edwards and Aronson\textsuperscript{10} (Table 2.2) which incorporates grading of the clinical relevance together with management options to estimate the risk arising from drug interactions. They developed an algorithm to differentiate between drug combinations that require specific management efforts and those that should be avoided by all means.
Table 2.2: Classification of adverse effects induced by drug interactions modified after Edwards’ and Aronson’s classification of adverse drug reactions by Bergk et al.

<table>
<thead>
<tr>
<th>Type of drug interaction</th>
<th>Characteristics</th>
<th>Management options*</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Augmented (doserelated)</td>
<td>Related to pharmacologic action of drugs Extent: Gradual or dose dependent change mostly indicated by a clinical surrogate Management possible Mechanism: Pharmakokinetic or pharmacodynamic additive effect of both drug on same target system</td>
<td>Any or all of the following: Reduce dose, substitute or compensate by third compound, or change route of administration or separate</td>
<td>cimetidine + theophylline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acarbose + glibenclamide digoxin +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>potassium-sparing diuretics calcium +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>digoxin</td>
</tr>
</tbody>
</table>
### Table 2.2 – Continued from previous page

<table>
<thead>
<tr>
<th>Type of drug interaction</th>
<th>Characteristics</th>
<th>Management options*</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B: Bizarre (not doserelated)</strong></td>
<td>Not related to pharmacologic action of drugs and any or all of the following: Extent: Nongradual or doseindependent change, mostly no clinical surrogate indicating the extent Management impossible Mechanism: Unknown or pharmacodynamic with a nongradual or doseindependent or sudden effect.</td>
<td>Avoid</td>
<td>sotalol + tricyclic antidepressant (QT prolongation) paroxetine + St. John’s wort (serotonin syndrome) allopurinol + captopril (hypersensitivity reactions)</td>
</tr>
<tr>
<td><strong>C: Chronic (dose- and timerelated)</strong></td>
<td>Dependent on cumulative dose or continuous long-term use</td>
<td>Avoid long-term use</td>
<td>acetaminophen + carbamazepine (induced hepatotoxicity) L-Asparaginase + epipodophyllotoxin (treatment-related leukaemia)</td>
</tr>
<tr>
<td>Type of drug interaction</td>
<td>Characteristics</td>
<td>Management options*</td>
<td>Examples</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>D: Delayed (time-related)</td>
<td>Usually dose-related Occurs or becomes apparent sometime after use of combination</td>
<td>Avoid</td>
<td>acetaminophen + carbamazepine (induced hepatotoxicity) L-Asparaginase + epipodophyllotoxin (treatment-related leukaemia)</td>
</tr>
<tr>
<td>E: End of use (withdrawal)</td>
<td>Occurs after withdrawal of one drug because of adaptive effects after longterm exposure</td>
<td>Withdraw slowly</td>
<td>Beta-blocker + clonidine</td>
</tr>
<tr>
<td>F: Failure (failure of therapy)</td>
<td>Reduced pharmacologic action of one or both drugs Extent: Gradual or dose dependent change mostly indicated by a clinical surrogate</td>
<td>Either increase dose or change route of administration or separate or both</td>
<td>alprazolam + St. John’s wort carbamazepine + theophylline levothyroxine + iron</td>
</tr>
</tbody>
</table>
* Different possibilities of how drug interactions can be managed; but not every option applies to all examples.
Figure 2.3: Management-oriented algorithm according to 4 decision layers for systematic evaluation of drug interactions by Bergk et al. The type of drug interaction is classified according to Edward and Aronson as exemplified in Table 2.2.
Hansten and Horn\textsuperscript{59} used a similar management-oriented approach to innovate a new drug interaction classification system. They applied this classification into their drug interaction compendium ‘Drug Interactions: Analysis and Management’\textsuperscript{49} and the booklet ‘The top 100 Drug Interactions - A Guide to Patient Management’\textsuperscript{89}. The so called ‘Operational Classification for drug interactions’ (ORCA) (Table 2.3) was developed by the Drug Interaction Foundation with input from an international group of physicians. They perceived the deficiencies of the drug interaction classification systems used in the United States and Europe and aimed to improve the clinical utility of classification systems. This classification enables health care providers to decide ultimately on a course of action (or inaction) for each potential drug interaction giving them information on management options that can reduce patient risk\textsuperscript{59}. 
Table 2.3: Operational Classification of Drug Interactions (ORCA) innovated by Hansten and Horn

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Characterisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Avoid Combination</td>
<td>Risk of combination outweighs benefit</td>
</tr>
<tr>
<td>2</td>
<td>Usually avoid combination</td>
<td>Use only under special circumstances</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Interactions for which there are preferably alternatives for one or both drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Interactions to avoid unless the benefit is judged to outweigh the increased risk</td>
</tr>
<tr>
<td>3</td>
<td>Minimise Risk</td>
<td>Assess risk and take one or more of the following actions if needed:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider alternatives: Alternatives may be available that are less likely to interact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Circumvent: Take action to minimise the interaction (without avoiding combina-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Monitor: Early detection can minimise the risk of an adverse outcome.</td>
</tr>
<tr>
<td>4</td>
<td>No Special Precautions</td>
<td>Risk of adverse outcome appears small</td>
</tr>
<tr>
<td>5</td>
<td>Ignore</td>
<td>Evidence suggests that the drugs do not interact</td>
</tr>
</tbody>
</table>
2.2.6 Computerised drug interaction screening systems

One of the responsibilities of pharmacists is to prevent patients from unsafe or noneffective drug regimens. In particular they should avoid the dispensing of interacting combinations of drugs that may cause hazardous adverse effects. In Switzerland and in other countries, every community pharmacy is obliged to use a computerised screening system for this task. Computerised drug interaction screening software analyses prescriptions prospectively for potential drug interactions. There is good evidence that electronic decision support by drug interaction surveillance software in the prescription fulfilment process can reduce the number of potentially hazardous drug interactions. Halkin et al. revealed that drug interaction surveillance software in community pharmacies and physician offices can reduce up to 67.5% dispensing of prescriptions with severe interactions. Malone et al. reported that 20% and 46% of prescription drug claims with 25 clinically important potential drug interactions were reversed when pharmacies were alerted. On the other hand, available systems have been shown to have significant deficiencies.

Hazlet et al. showed that the performance (sensitivity, specificity, positive and negative predictive value) of most tested drug interaction screening programs was suboptimal.

Barrons evaluated these factors for PDA software products for drug interactions and found greater than 90% ability to detect important and to ignore unimportant interactions for 4 of 9 software products, whereas 2 of them were evaluated to be more comprehensive and easier to use than the others. Vonbach et al. compared four drug interaction screening programs and found for Phar-
Table 2.4: Factors to evaluate the performance of drug interaction screening programs adapted by Hazlet et al.\(^{63}\)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Ability of the software program to correctly identify those drug interaction pairs that were defined as clinically important (number of true positives / [number of true positives + number of false negatives])</td>
</tr>
<tr>
<td>Specificity</td>
<td>Ability of the software to ignore drug interaction pairs that were not defined as clinically important (number of true negatives / [number of true negatives + number of false positives])</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>Probability that when a warning was issued by the computer, it was for a DDI defined as clinically important (number of true positives / [number of true positives + number of false positives])</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>Probability that the absence of a computer alert reflected the determination that no clinically important drug interaction existed (number of true negatives / [number of true negatives + number of false negatives])</td>
</tr>
</tbody>
</table>

Mavista\(^{61}\) the highest sensitivity with an acceptable positive predictive value and specificity. Furthermore, they evaluated the drug interaction monographs of Pharmavista positively as comprehensive due to very useful descriptions regarding the effect, mechanism, clinical management, discussion of evidence negatively because the literature is not clearly referenced. German general practitioners were unsatisfied with the contents of drug interaction information sources\(^{88}\). In particular they missed information about the mechanism of a drug interaction and the management guidelines including the advice for dose adjustment and about alternative therapies. Hansten\(^{80}\) complains that management guidelines in the current drug interaction information sources are often inadequate. He recommends inclusion of information on measures that can be taken to reduce the likelihood of an adverse outcome\(^{85} \textit{ et al.}\).
2.2.7 Computerised drug interaction alerts

Too many alerts complicate the medication surveillance because the identification of relevant signals becomes more difficult. Thus, knowing that most of the time the patient will not suffer from an adverse outcome, health care providers ignore most drug interaction alerts provided in ambulatory care. Several recent studies have focussed on computerised drug interaction alerts and how health care providers perceive them. Weingart et al. revealed that general practitioners overrode 89% of level 1 (severe) and 96% of level 2 (moderate) drug interaction alerts. Chui and Rupp and Murphy et al. found comparable results for community pharmacists’ responses to drug interaction alerts. In these studies override was defined as the absence of any intervention by the health care provider. Reasons given for overriding alerts are:

- The patient was no longer taking the interacting medication
- The interaction was not clinically significant
- The patient was stable on the combination
- The benefit of the treatment outweighed the risk of the interaction

In a questionnaire survey by Magnus et al. 22% of general practitioners admitted that they frequently override drug interaction alerts without properly checking them. Abarca et al. examined community pharmacists attitudes towards computerised drug interaction alerts; despite a large proportion of clinically unimportant alerts, community pharmacy managers did not believe these alerts were meaningless or a waste of time. However, they were not completely confident that their computer systems provided them with meaningful drug interaction alerts.
2.2.8 Drug Interaction Classification

According to the mechanism of action, the drug interactions are classified as:

Pharmacokinetic Interactions

1. Alteration of GI absorption

   Interactions that involve a change in the absorption of a drug from the GI tract may develop through different mechanisms and be of varying clinical importance.

   (a) Alteration of pH

   (b) Complexation and Adsorption

2. Stimulation of metabolism

   Drug metabolism occurs primarily in the liver and most commonly involves oxidation, reduction, hydrolysis and conjugation reactions. Quantitatively, the most important hepatic enzymes are the cytochrome P-450 enzymes which have been divided into families and subfamilies on the basis of the similarity of their amino acid sequences.

3. Inhibition of metabolism

   A number of situations have been reported in which one drug has inhibited the metabolism of another, usually resulting in a prolonged and intensified activity of the latter.

4. Alteration of excretion

   Although some therapeutic agents are eliminated via other mechanisms, most drugs and their metabolites are excreted via the kidneys. The most important clinical implications of altering renal excretion involve the use
of drugs that are excreted in their unchanged form or in the form of active metabolites.

(a) Alteration of Urinary pH
(b) Alteration of Active Transport

Pharmacodynamic Interactions

1. Drug having opposing pharmacological effects: Interactions resulting from the use of two drugs with opposing effects should be among the easiest to detect.

2. Drug having similar pharmacological effects: An excessive response attributable to the concurrent use of drugs having similar actions.

3. Alteration of electrolyte concentrations: Several important drug interactions occur as a result of the ability of certain therapeutic agents to alter the concentration of electrolytes.

4. Interaction at receptor sites

5. Reducing the risk of drug interaction: The reduction of the risk of drug interactions is a challenge that embraces a number of considerations.

2.2.9 Factors contributing to the occurrence of Drug Interaction

2.2.9.1 Multiple Pharmacological Effects

Most drugs used in current therapy have the capacity to influence many physiological systems. Therefore, there is an increased possibility that two drugs
concomitantly administered will affect some of the same systems. When considering the potential for interactions between drugs there often is a tendency only to be concerned with the primary effect of the drugs involved and to overlook the secondary activities they possess.

2.2.9.2 Multiple Prescribers

It is necessary for some individuals to see more than one physician, and it is very common for a patient to be seeing one or more specialists in addition to a family physician. Some individuals also are seeing other health professionals (e.g., dentists, podiatrists) who may prescribe medication.

2.2.9.3 Use of Nonprescription Drugs

Many reports of drug interactions have involved the concurrent use of a prescription drug with nonprescription drug. When a physician questions patients about medications they have been taking, the patients often neglect to mention the non-prescription medications that they have purchased. Interactions also may result from the concurrent use of two or more products available without a prescription.

2.2.9.4 Patient non-compliance

For a variety of reasons many patients do not take medication in the manner intended by the prescriber. Some have not received adequate instruction from the prescriber and pharmacist as to how and when to take their medication. In other situations particularly involving patients who are taking several medica-
tions, confusion about the instructions may develop even though the patient may have understood them initially.

### 2.2.9.5 Drug Abuse

The tendencies of some individuals to abuse or deliberately misuse drugs also may lead to an increased incidence of drug interactions. Many drug interactions that occur are undetected or unreported.

In most cases the clinical situation is too complex to allow recognition of an unexpected event in a patient’s course as related to his or her drug therapy.

With few exceptions, the intensity of action of drugs in the therapeutic setting cannot be quantitated accurately. Even when a deficient, excessive, or abnormal response to one or both drugs is recognized clearly during concomitant administration, it is attributed usually to factors other than drug interaction.

The index of suspicious for most clinicians concerning drug interactions is quite low, and many practicing physicians are hardly aware of the phenomenon. Practicing physicians tend to doubt their observations concerning drug interactions unless the same interaction has been reported previously. Physicians frequently fail to report drug interactions even when they have unequivocally recognized them.

Drug interactions are common causes of treatment failure and adverse reactions. Patients who have a number of chronic disorders, patients who take many med-
ICations or patients who have impaired renal function are at increased risk for these problems. Special attention must be given to drugs that require blood level monitoring, since these agents have a narrow margin of safety.

2.2.9.6 Significance of the Problems

The estimated incidence of clinical drug-drug interactions range from 3 to 5 % in patients taking a few medications but increases to 20% in patients receiving 10 to 20 drugs. The effect of these interactions can range from clinically insignificant alterations in blood drug levels to life-threatening reactions, including death.

2.2.9.7 Resources for Information on Drug Interactions

Printed manuals are available that provide detailed information on the significance of specific drug interaction, their time course and their management. Regularly updated specialty texts include Drug Interaction Analysis, Management and Drug Interaction Fact.

Online drug interaction programs are also available, although their accuracy ranges from only 18 to 89 percent. In addition, the Physicians’ Desk Reference is now available on CD-ROM, along with a drug interaction program. This program is updated yearly.
2.3 Organized Spontaneous ADR Reporting

2.3.1 Introduction

Ever since the beginning of time, humanity has been surrounded by different hazards. As times have passed, these hazards have changed. The risk of being attacked and killed while hunting for mammoths in our modern society is extremely small. On the other hand, the risk of being injured or killed in a traffic accident is quite high in some parts of the world. The word “risk” is probably derived from the Greek word “rhiza, the hazard of sailing too near the cliffs”.

The idea of risk and risk management was well understood by the ancient Greeks, who together with the Romans, identified many common hazards and also worked out potentially effective ways of minimizing their capacity to cause harm. Since man first began to practice medicine, it has been known that all kinds of treatment procedures, surgical as well as non-surgical can lead to injury or unwanted effects.

Today, it is well known that adverse drug reactions (ADRs) constitute a major problem in society and in drug therapy, as a health care problem and as an economic burden. They are a common cause of hospitalization, especially among the elderly. In several studies, it has been shown that the frequency of patients being admitted to hospital due to direct effect of an ADR can be estimated to be 5 - 10%. In some studies however, the frequency was estimated to be as high as 20% of all cases admitted to a department of internal medicine or to a geriatric clinic. However, the pattern of drugs used has changed considerably since the first of this series of studies was conducted.
In addition to the distress of the patients actually suffering from one or several ADRs, the cost of ADRs has been estimated to be as high as £0.5 billion each year in UK, due to prolongation of hospital visits\textsuperscript{[107]}. The definition of an adverse drug reaction most commonly used and accepted is every undesirable or harmful effect caused by a drug used in a normal dosage for prophylaxis, diagnosis or therapy.

In his ethical rules, initially Ethics of Virtue, Hippocrates (460 - 370 BC) stated: “Primum est non nocere” (most important is not to harm). According to these ethical rules in the endeavour to cure, comfort and relieve, doctors should always give priority to the principle primum est non nocere. This principle has been generally and internationally accepted. For e.g, in the Geneva convention and in the ethical rules of the Swedish Society of Medicine. In old Babylonia, Hammurabi, stated in a law from the year 2200 BC that a physician who injured or caused the death of a patient should loose one of his own hands. However, this law did not apply to female patients or slaves as they were considered to be less worth.

2.3.2 The Birth of Organized Spontaneous ADR Reporting

Until the development of modern and effective drugs, the most important risk associated with drug treatment was an insufficient effect. In January 1848 a simple operation on a young girl was performed and a newly introduced agent, chloroform, was used for general anaesthesia. Unfortunately the girl died dur-
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ing the operation, possibly due to an episode of ventricular fibrillation. As a result of a general concern among the public and the profession about general anaesthesia, a commission inviting physicians in Britain and its colonies to report deaths related to anaesthesia was set up by the Lancet. The findings of this commission were later published. This was certainly one of the forerunners to the system of spontaneous reporting of ADRs \[108,109\]. At the beginning of the 20th century, there was a growing commitment from governments, national authorities and the scientific community to provide safe and effective drugs for a growing population. However, during the first half of the 20th century, very little effort, time and money was spent on the study of unwanted effects of drug. In the United States, as a political response to epidemics of severe ADRs a political pressure for a regulatory alteration developed during the first half of this century. In the autumn of 1937, one hundred and seven people died of acute renal failure after using sulphanilamide. However, neither sulphanilamide nor efficacy was to blame for this tragic event. Instead it was due to the solvent that had been used in the preparation of the so called elixir, diethylene glycol. The toxic effect of this solvent had been well established already six years prior to this event. As a result of this, the Food, Drug and Cosmetic Act was ratified in 1938. In the beginning of 1950s a series of cases of aplastic anemia, associated with the use of chloramphenicol demonstrated the necessity for surveillance of drugs also after their approval. Chloramphenicol had passed the testing before approval but due to the small number of exposed patients, the occurrence of this rare event was too small to be detected \[110\].

In the middle of the 1950s, a drug containing the active substance thalidomide was initially introduced as an effective medication for influenza. The reason for using
the drug to treat influenza was that the febrile reaction to the intravenous intro-
duction of dead Escherichia coli bacteria in an unknown number of rabbits was
decreased to some unreported degree by an unreported dose of thalidomide. It
was later discovered that thalidomide also had a sedative effect in man. The drug
was approved on what would seem to be very weak scientific grounds. Thalido-
mide was marketed as a new, mild sedative with an amazing absence of acute
toxicity even at high doses and triumphantly conquered the market. The drug
was marketed in the western world as Neurosedyn, Distaval, Grippex or Kevadon.
During the years following the marketing of thalidomide the drug was prescribed
to thousands of people, including fertile women. In December 1961 a general
practitioner, McBride in Australia, reported in a short letter to the editor of the
Lancet that he had noted a number of cases of limb malformations among babies
and that a common denominator seemed to be the intake of thalidomide by their
mothers. At the same time, two similar reports were published by German
physicians describing the same kind of limb malformations. These three reports
were the start of the discovery of a worldwide drug disaster. Exactly how many
children who were born with some kind of malformation, especially those affecting
the limbs, is not known. Estimates of no less than 6000 malformed children, but
no more than 8000, have been discussed. In the wake of this public health disas-
ter, governments in many countries set up procedures for a systematic evaluation
and collection of adverse drug reactions. These systems are based on the spon-
taneous reporting of suspected adverse drug reactions by physicians and general
practitioners. At first, such systems were organized in Australia, Canada, former
Czechoslovakia, Ireland, the Netherlands, New Zealand and Sweden. A few
years later, ten countries agreed to collect all reports provided by their national
centres in a World Health Organization (WHO) drug monitoring project. Since
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1968, this database has been located in Uppsala, Sweden, and receives spontaneously reported ADRs from more than 70 countries on a regular basis. The database at the Uppsala Monitoring Centre (WHO-UMC) now contains more than 3.1 million. Thalidomide was withdrawn from the market in 1961 in many countries. However, a few years later thalidomide was reintroduced as a treatment for complications in connection with leprosy, erythema nodosum leprosy (ENL).

Even though a clear evidence of its efficacy was not established, the drug had soon become the drug of choice for the treatment of ENL reactions. Exemptions from license requirements were made by national drug authorities in order to obtain narrow supplies of thalidomide to be used under strictly controlled circumstances. The effectiveness of the drug in minimizing symptoms of ENL was mainly due to the antipyretic effect of the drug. The major permanent disabilities in leprosy however, were not affected by thalidomide to any major extent. In controlled clinical trials, performed in the 1970s it was shown that prednisolone is more effective in controlling neuritis associated with ENL. Thalidomide has been used on other indications such as treatment of cancer and HIV. Limited trials have been performed showing a certain efficacy of the drug. However, each individual condition must be evaluated, and the drug must be used under supervision and stringent restrictions. In addition to this, there must be a system for monitoring. Those in the medical community who support the use of thalidomide for other conditions should make their own case, and the use of the drug on other indications cannot be based on studies in leprosy.
2.3.3 Spontaneous ADR Reporting Today

Today, spontaneous reporting of adverse drug reactions serves one of the most important methods for monitoring the safety of drugs after the marketing of a new drug from both the regulatory and economic point of view. In Sweden, physicians, dentists and other health care professionals with a license to prescribe drugs (e.g. nurses) are legally required to report suspected ADRs to the regulatory authority. The present rules for reporting ADRs in Sweden state, that all side effects related to new drugs should be reported except for those labelled as common in the summary of product characteristics (SPC). For all other drugs, suspected deaths, reactions leading to short-term or prolonged hospitalization, new and unexpected reactions, ADRs that seem to increase in frequency and seriousness should be reported. Like other things in life, spontaneous reporting of ADRs has both strengths and weaknesses. The strengths of this reporting system is that it is inexpensive and simple, covers all drugs during the whole life cycle of the drug, covers the whole population, including subgroups such as children and the elderly, does not interfere with prescribing habits and can be used for follow-up studies of patients with severe ADRs in order to study mechanisms. One of the main aims of the spontaneous reporting of ADRs is to produce signals regarding new potential ADRs. In order to fulfill this function appropriately, one must be aware of the fact that a number of false signals will be produced and therefore each signal must be scrutinized and verified before it can be acted upon. However, a serious drawback of this system is that for all reactions reported, the percentage reported in different situations is hard to estimate. In one study conducted in the county of Jmtland, Sweden, the under-reported rate of thrombo-embolic disease treatment in connection with oral contraceptive was as high as 100% during the five years study. Other studies have confirmed an under-reported rate of this magnitude.\textsuperscript{113}
There are several reasons for not reporting adverse drug reactions. Among the important ones is the fact that the reaction is already well known and even if the reaction is fatal, many physicians abstain from reporting, e.g., a fatal cerebral haemorrhage due to anticoagulants. Other factors responsible for the high degree of under-reporting are lack of time, prioritization and other issues in one’s daily activities and forgetting to report. The under-reporting rate differs from country to country and also within regions of the country. The northern region in Sweden, which consists of the four northern most counties, has been considered from a historical perspective to have a high degree of reported ADRs. Nevertheless, we know that there is a high degree of under-reporting here too, in some cases as high as 100%, as mentioned above. As a result of the sometimes extensive under-reporting of suspected and also certain ADRs in most cases it is very difficult, if not impossible, to assess the quantitative risk of specific ADRs associated with the use of drugs based on data obtained only from the spontaneous reporting database.

2.3.4 Under-reporting of Adverse Drug Reactions

From the point of view of a regional Centre for Pharmacovigilance and the national authority, the most apparent disadvantage of the system for reporting ADRs has to be what has previously been referred to as “underreporting”. This expression alludes to the fact that a vast majority of the health care professionals with a well-defined responsibility to report suspected ADRs often do not do so. The issue of under-reporting of ADRs is a well-known problem. In a study conducted by Inman and co-workers in the middle of 1970s the authors identified
seven major reasons for why a suspected ADRs was not reported. These reasons were later referred to as “Inmans seven deadly sins”:

1. Complacency, encouraged by one-sided drug promotions and the belief that only safe drugs are allowed on the market

2. Fear of possible involvement in litigation or investigation of prescribing costs by Health Departments

3. Guilt of having administered the treatment which may have harmed a patient

4. Ambition to collect and publish a personal series of cases

5. Ignorance of the committee’s recruitment for reporting of ADRs

6. Difficulty concerning reporting mere suspicions

7. Indifference on the part of an individual doctor regarding his essential role as a clinical investigator who should be contributing to the general advancement of medical knowledge.

Rather similar findings have been presented later in other studies. However, in the work done by Belton and co-workers, only one of the “deadly sins” appeared to be confirmed. When Inman made his study on factors and attitudes towards the reporting of ADRs, the yellow card system in the UK had been operational for ten years. His study was primarily made as an evaluation of the yellow card scheme. He concluded in this letter to the editor that other factors also could contribute today. The particular “deadly sin” that was confirmed by Belton was that the heavy workload deterred doctors from reporting suspected ADRs.
However, under-reporting of ADRs has been and probably will continue to be, one of the main obstacles in the field of drug surveillance. One can assume that irrespective of any activities from the national authority, a 100% reporting rate will never be attained, not even of serious and fatal reactions. It is just a matter of trying to decrease the rate of under-reporting to a minimum. Of course the rate of what should be considered to be such a minimum depends on the type of reaction and the degree of seriousness of it. It does not seem reasonable to collect reports of ADRs recognised as being common for drugs that have been used for decades. Such reports do not give much new information, unless such reactions constitute a major problem in the health care organization. On the other hand, serious reactions that appear when an old drug is used could generate valuable information and perhaps lead to different treatment strategies. Lumley and co-workers studied general practitioners in order to assess the number of ADRs observed in general practice and to record how many of them were actually reported to the CSM via the yellow card system. During the study period ten serious ADRs were suspected and 27 associated with drugs that the CSM had requested special reporting on (black triangle). A total of 37 ADRs should have been reported to the CSM but only 5 yellow cards (13%) were sent in. However, only 6% of the total number of ADRs seen, were reported.

In a study conducted in Spain by Alvarez-Requejo and co-workers, ADRs collected during a short intensive study were compared with primary case reports to a regional centre in Spain. The intensive study was undertaken by 146 randomly selected GPs. The regional centre received reports concerning the whole regional population (2.5 million) and the under-reporting coefficient was estimated as the ratio between the number of ADRs observed by the doctors and the number of
reactions identified through the spontaneously reported cases\textsuperscript{119}.

The main finding in this study was that the under-reporting rate was substantial, although not homogeneous for different reactions. The under-reporting seemed to be positively selective as it mainly involved less severe and well-understood effects. These results underline the value of spontaneous reporting as a method for signal detection. However, the commonly held consideration that spontaneous reporting of ADRs is the best method for recognizing new and rare ADRs has been the subject of considerable criticism\textsuperscript{120}. The main weak points have been the absence of a known denominator of the number of people exposed to a drug and the existence of a significant amount of under-reporting. Under-reporting reduces the sensitivity due to an underestimation of the frequency and thereby the impact of the problem. It also makes the system vulnerable to selective reporting, which may introduce a serious bias.

2.3.5 The Future of Spontaneous Reporting of ADRs

In the future field of drug safety and drug surveillance, spontaneous reporting of ADRs will probably remain one of the more important methods. Different kinds of computerization including systems for individually based prescription, data will serve as a complement to this to optimise the rational use of drugs. One could also envisage computerized programmes for patients case records in which automatic detection of ADRs and also automatic reporting by an on-line function to the national drug authority are included. When a suspected ADR is mentioned or discussed in the patients record, a report will be sent by coded electronic mail or in some other way.
However, in such a system or scheme, questions about patient integrity and the possible risk of transferring classified information about individual patients, medical history and drug use without adequate security has to be solved. One can never accept the possibility that information about an individual patient can be obtained by unauthorized persons. Securing future systems for the reporting of ADRs in this way, making it impossible for people outside the system to access the information has to be one of the more vital and important issues to deal with. Today there are large number of different computerized systems within the Swedish medical organization. For e.g., only in the county of Stockholm, there are more than 20 different systems for computerizing patients records in operation. The abundance of different programs, some of them initiated as “home-made” ones, has made it difficult to develop a computer program that is compatible with all of them. The introduction and development of some kind of web-based reporting also in Sweden, would most certainly be a great achievement within the field of drug surveillance. This should not be affected by the particular programs used in the different counties or hospitals. Most of these computerized systems used in the health care system today are not equipped with any functional module for reporting ADRs. A possibility to report through the world wide web already exists in some parts of Europe and also between manufacturers and national drug authorities. Local projects within the health care system, in order to test different computerized system which would enable reporting of suspected ADRs, are also in progress at Sweden. Necessary steps and efforts in order to realise plans for a web-based reporting from the health care system in Sweden has a high priority. However, this work should be organised in such a way that all important aspects are considered and that all parties involved can
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coopcrate in order to obtain the best possible system.

However, in spite of all advanced technology, the decision to report a suspected ADR still remains at the discrimination of the individual reporter. The successful decentralized system operating in Sweden since 1992 has established spontaneous reporting of ADRs as a natural element in the health care system\cite{122}. Increasing the information to and training of all health care personnel who have to make decisions in their daily and routine work about drug therapy and decide whether specific symptoms might be related to drug therapy will pose as one of the most important challenges for the future. To keep awareness, existence of ADRs alive and to interest all groups of personnel in rational drug use, this kind of information and training must be given on a regular basis. It is of common knowledge that the results of any information given will fade away and that most of the information given will be forgotten after 6 to 12 months. It would therefore be desirable that information about ADR and reporting of ADRs could be given to all interested health care personnel at least once a year. Furthermore, it is also desirable that the existing collaboration between regional centres, the MPA and local drug committees in the above matters should be continued and broadened in many respects.

Spontaneous reporting of ADRs will probably remain one of the most important elements in the surveillance of drug safety. However the responsibility of reporting ADRs should be shared by all groups of health care personnel, specially well trained nurses who are in direct contact with the patients.