An Overview on Adverse Drug Reactions (ADR) And Its Biomarkers

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Abstract: Adverse drug reactions (ADR) are a significant public health issue for both individuals and society. In developed nations, adverse drug reactions (ADRs) are among the top 10 leading causes of illness and death. ADRs are a public health issue though since they cause 5- 10% of hospitalizations and lengthen hospital stays . ADRs are between the fourth and sixth most common causes of death in some nations. Factors contributing to adverse drug reactions are age, sex, polypharmacy, pharmacogenetics, previous exposure etc. ADRs are classified into various categories depending upon their effect. Scales specifically designed for the identification of an ADR which includes Naranjo Scale Development,The WHO-UMC causality assessment system,Hartwig's Severity Assessment Scale. . Adverse drug reactions also represent a financial burden to both healthcare providers and the pharmaceutical industry. Thus, a number of stakeholders would benefit from development of new, robust biomarkers for the prediction, diagnosis, and prognostication of adverse drug reactions. There has been significant recent progress in identifying predictive genomic biomarkers with the potential to be used in clinical settings to reduce the burden of adverse drug reactions. These have included biomarkers that can be used to alter drug dose (for example, Thiopurine methyltransferase (TPMT) and azathioprine dose) and drug choice. The latter have in particular included human leukocyte antigen (HLA) biomarkers which identify susceptibility to immune-mediated injuries to major organs such as skin, liver, and bone marrow from a variety of drugs.

Keywords: Adverse drug reactions, prognostication, pharmacogenomics, biomarkers, human leukocyte antigen.

INTRODUCTION

Pharmacovigilance is a critical element of prescribing. However, it is not frequently used in Indian hospitals. Adverse medication reactions have been linked to several studies as a major factor in significant morbidity and death [1].The incidence of adverse drug reactions (ADR) varies with studies which show incidences ranging from as low as 0.15% to as high as 30% [1–3].Elderly and hospitalized patients are reported to be more susceptible to ADRs than the adult population (16.6% vs. 4.1%) [1].There are few Indian reports on ADR monitoring. This might be because ADR monitoring is still developing in this area. After decades of dormancy,

the demand for a productive pharmacovigilance programme arose, leading to the establishment of the National Pharmacovigilance Program in November 2004 [4].Under this initiative, two zonal, five regional, and 24 peripheral centres have been formed, with the Primary Drugs Standards Control Organization in New Delhi serving as the central co-ordinating organisation.This program's goals are to raise awareness of ADR monitoring among health professionals and to promote a culture of reporting.The purpose of hospital-based ADR monitoring and reporting programmes is to detect and measure the hazards related to drug consumption. This knowledge may help identify and reduce preventable ADRs while typically boosting prescribers' ability to deal with ADRs more effectively. National pharmacovigilance programmes are infrequently attended by pharmacists. [5].Adverse drug responses (ADR) are a significant public health issue for both individuals and society[6]. . The World Health Organisation's definition of an ADR is ''a response to a drug which is noxious, and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function'' [7].ADRs are described as "an considerably damaging or unpleasant reaction occurring from an intervention associated to the use of a pharmaceutical product; adverse effects commonly predict hazard from future administration and demand prevention, or particular therapy, or change of the dose regimen, or withdrawal of the product[8]."Along with the authorised use of a pharmaceutical product in standard doses, the term has been expanded to encompass responses resulting from mistake, abuse, or misuse as well as suspected reactions to drugs that are not licenced or that are being used as intended. In clinical practise, this move shouldn't impact how we handle ADRs despite the possibility that it could modify the reporting and surveillance practises used by manufacturers and drug regulators.[8]In developed nations, adverse drug reactions (ADRs) are among the top 10 leading causes of illness and death. ADRs exhibit different characteristics based on factors like genotype, age, sex, race, pathology, drug category, administration method, and drug-drug interactions. In order to maximise drug efficacy and safety in treating serious health issues like cancer, brain disorders, and cardiovascular disease and its associated disorders, pharmacogenomics (PGx) provides the doctor with useful cues[9].ADRs raise mortality rates, hospital admissions, lengths of hospital stays, healthcare costs, and withdrawal of drug from market[5]. ADRs are a public health issue though since they cause 5- 10% of hospitalizations and lengthen hospital stays . ADRs are between the fourth and sixth most common causes of death in some nations . Additionally, they have financial consequences; Segura and Maldonado [estimated that ADRs cost Colombia roughly USD 55 billion in 2010. If the drug's role is identified at each stage of the pharmaceutical process, it may be possible to prevent more than 30% of ADRs[10]. Drug reactions, drug allergies, and drug hypersensitivity are frequently used interchangeably. Regardless of the cause, medication responses include all unfavourable effects connected to drug administration. Hypersensitivity to drugs characterised as a patient's immune system's reaction to a pharmacological substance. The term "drug allergy" is limited to an IgE-mediated response[11].

Adverse Drug Reaction Terms and Definitions

Terms	Definitions
Adverse Drug Reaction (ADR)	• A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function (WHO)**a** • An appreciably harmful or unpleasant reaction, caused by an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product (Edwards)**b**
Adverse Drug Event (ADE)	• Any unexpected, unintended, undesired, or excessive response to a drug that requires discontinuing the drug (therapeutic or diagnostic), requires changing the drug therapy, requires modifying the dose (except for minor dosage adjustments), necessitates admission to a hospital, prolongs stay in a health care facility, necessitates supportive treatment, significantly complicates diagnosis, negatively affects prognosis, or results in temporary or permanent harm, disability, or death (ASHP)**c** • Harm directly caused by a drug at normal doses (Edwards)**b**
	• Any untoward occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relation to the treatment (WHO) **a**
Unexpected Adverse Reaction	• Injuries caused by medical interventions related to a drug • Adverse drug events may result from medication errors or from ADRs in which there was no error (Bates)**d**
Serious Adverse Effect	• An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug (Cobert)**e**
Signal	• Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening (Edwards)**b**
Medication Error	• Reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented (Edwards)**b** • Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer (NCC MERP)**f** • Errors in the process of ordering or delivering a medication, regardless of whether an injury occurred or the potential for injury was present (Bates)**d** • Inappropriate use of a drug that may or may not result in harm (Nebeker)**g**

(a) WHO: International Drug Monitoring: The Role of the Hospital. Technical Report Series No. 425. Geneva: WHO, 1969. (b) Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356:1255-9.(c)American Society of Health-System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. Am J Health Syst Pharm 1995;52:417-9. (d) Bates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. J Gen Intern Med 1995;10:199-205. (e) Cobert B. The theory and definitions of drug safety (Pharmacovigilance). In: Cobert's Manual of Drug Safety and Pharmacovigilance, 2nd ed. Sudbury, MA: Jones & Bartlett, 2012:4-5. (f) NCC MERP. About Medication Errors [homepage on the Internet]. Available at www.nccmerp.org/about-medication-errors. Accessed March 7, 2015. (g) Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med 2004;140:795-801.

There are immunologic and nonimmunologic etiologies for drug reactions (Table 1). The majority of adverse medication responses (between 75 and 80 percent) are brought on by predictable, nonimmunologic consequences. The other 20 to 25 percent of drug-related adverse events are caused by harmful outcomes that may or may not be immune mediated.IgE-mediated drug allergies fall under the category of immune-mediated responses, which make up 5 to 10% of all adverse drug reactions and actual drug hypersensitivity[11].

TABLE 1: Immunologic and Nonimmunologic Drug Reactions

TYPE	EXAMPLE
Immunologic Type I reaction (IgE-mediated) Type II reaction (cytotoxic) Type III reaction (immune complex) Type IV reaction (delayed, cell-mediated) Specific T-cell activation Fas/Fas ligand-induced apoptosis Other	 Anaphylaxis from Beta-lactam antibiotic Hemolytic anemia from penicillin Serum sickness from anti-thymocyte globulin Contact dermatitis from topical antihistamine Morbilliform rash from sulfonamides Stevens-Johnson syndrome Toxic epidermal necrolysis Drug-induced, lupus-like syndrome Anticonvulsant hypersensitivity syndrome
Nonimmunologic **Predictable** Pharmacologic side effect Secondary pharmacologic side effect Drug toxicity Drug-drug interactions Drug overdose **Unpredictable** Pseudoallergic Idiosyncratic Intolerance	**Example** Dry mouth from antihistamines Thrush while taking antibiotics Hepatotoxicity from methotrexate Seizure from theophylline while taking erythromycin Seizure from excessive lidocaine (Xylocaine) Anaphylactoid reaction after radiocontrast media Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy Tinnitus after a single, small dose of aspirin

TABLE 2 Gell and Coombs Classification of Drug Hypersensitivity Reaction

Immune reaction	Mechanism	Clinical manifestations	Timing of reactions
Type I (IgE-mediated)	Drug-IgE complex binding to mast cells with release of histamine, inflammatory mediators	Urticaria, angioedema, bronchospasm pruritus, vomiting, diarrhea, anaphylaxis	Minutes to hours after drug exposure
Type II (cytotoxic)	Specific IgG or IgM antibodies directed at drug-hapten coated cells	Hemolytic anemia, neutropenia thrombocytopenia	Variable
Type III (immune complex)	Tissue deposition of drug-antibody complexes with complement activation and inflammation	Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis	1 to 3 weeks after drug exposure
Type IV (delayed, cell-mediated)	MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release	Allergic contact dermatitis, maculopapular drug rash*	2 to 7 days after cutaneous drug exposure

EPIDEMIOLOGY

Research indicates that between 5% and 10% of patients may experience an ADR at admission, during admission, or upon discharge, despite a variety of prophylactic measures. The prevalence of ADRs has remained mostly stable throughout time[3]. According to estimations, adverse drug reactions (ADRs) account for 3-6% of hospital admissions, the 4-6th greatest cause of mortality, and a $136 billion yearly cost in the United States (US)[12].According to estimates, ADRs account for about 5% of all hospital admissions, 5% of hospitalised patients will encounter an ADR during their hospital stay, and ADRs result in 197,000 deaths per year across the Europe [13].Prescriptions for elderly patients might be difficult. The risk of adverse drug events is frequently increased by multimorbidity and polypharmacy, with reports of an ADR incidence in community-dwelling elderly adults as high as 78% , incidence in a care home population of 1.89 per 100 resident-months , and causing 5.8% to 23.6% of older adults to be admitted to the hospital[14]. The median incidence rate of adverse drug reactions among Indian hospitals is high (12.9%), according to a recent systematic study[15].

Factors contributing to adverse drug reactions:

Age

Children and the elderly are particularly vulnerable to ADRs due to physiological variations between them. ADR risk is increased by variations in the cardiovascular, hepatic, and renal systems [16].

Polypharmacy

This raises the possibility of a medication interaction-related ADR. The underlying condition may have an impact on pharmacodynamics, and polypharmacy can potentially change pharmacokinetics [17, 18].

Sex

NMBs and latex are two medicines that are more frequently associated with anaphylaxis in females. An ADR is approximately twice as likely to affect women. This may be caused by variations in pharmacokinetics based on body mass, hepatic clearance, and hormones. [19].

SMOKING

Smokers are more likely to experience anaphylaxis to antibiotics, which may be brought on by sensitization brought on by repeated antibiotic treatments for respiratory infections [20].

Atopy

Patients with an atopy history are more likely to develop a latex allergy and have anaphylaxis to contrast media.Additionally, they are more prevalent in people who have fruit allergies, particularly those to banana, chestnut, and avocado. [21]

Previous exposure

Patients with spina bifida and medical personnel who undergo several surgeries are more likely to develop a latex allergy. Workers who come into contact with latex on the job are also affected by this.[20,21]. Healthcare professionals may be predisposed genetically in addition to prior exposure, unlike high-risk patients where environmental sensitization from a young age is the main reason.[22]

Pharmacogenetics:

Many medicines used in the perioperative phase differ in their pharmacokinetics and efficacy, including the varying reactions to routinely used anaesthetic agents like propofol, fentanyl, and ondansetron. Disparities in pharmacogenetic diversity may help explain these differences**.** [23–25].Suxamethonium apnoea, malignant hyperthermia, acute porphyria, and adverse drug reactions (ADRs) caused by polymorphisms in the cytochrome P450 system are only a few examples of genetic predispositions that are particularly relevant in anaesthesia **(Table 3)** With the price of gene sequencing projected to decrease, it might be possible to identify those at risk for adverse drug reactions (ADRs) due to pharmacogenetics in advance. Nevertheless, despite the fact that this would enable individually tailored perioperative treatment, it creates logistical, ethical, and budgetary issues.[26]

Table 3:- Genetic variations with relevance to anaesthesia

Genetic variation	Effect	Related drugs
Plasma pseudocholinesterase	Deficient enzyme activity, prolonged drug effect (suxamethonium apnoea)	Suxamethonium, mivacurium
Defective coding for ryanodine receptor	Malignant hyperthermia	Inhalational anaesthetics Suxamethonium
CYP2D6 gene	Poor, intermediate, extensive or ultrarapid metabolisers	Diazepam Codeine Tramadol Ondansetron, b-blockers
Porphobilinogen deaminase deficiency	Acute intermittent porphyria	Barbiturates, Clonidine Cephalosporins ,Benzodiazepines ,Phenytoin

CLASSIFICATION

The classic types A and B of the modern pharmacological categorization of adverse drug responses differentiated between dose-related and non-dose-related events. They were then given the labels "Augmented" and "Bizarre" for mnemonic reasons. 10 Later, two more response types—delayed reactions and reactions that were affected by both dosage and time, or types C and D—were introduced[27].

The last grouping can be divided into two parts: withdrawal effects and time-related responses. Unexpected therapeutic failure has lately been suggested as the sixth type. [Table 1] illustrates this classification with instances of adverse medication responses in each group and therapeutic advice[17].

Adverse drug reactions SCALES

Naranjo Scale Development

Before 1981, the Kramer algorithm was a complex decision-making process with six axes used to evaluate the chance that a medicine delivered resulted in an undesirable clinical outcome (and was therefore an ADR).

In order to more effectively "monitor ADRs and...to [conduct] post marketing drug monitoring," as well as to increase inter-rater reliability, Naranjo et al. recommended a much simpler probability scale.

Based on the responses to 10 questions, this scale would allow categorical classification of ADRs as "definite," "probably," "possible," or "doubtful." First, Naranjo et al. defined ADR as "any unpleasant, unanticipated, and undesirable consequence of a medicine after dosages used in humans for prevention, diagnosis, or therapy" (according to the World Health Organization definition). Therapeutic failures, deliberate and unintentional poisoning, and drug misuse are not included in this description. Then, 63 ADRs reported in the peer-reviewed literature were evaluated by six investigators (two doctors and four pharmacists), who totaled six investigators. They came up with ten questions, assigned "yes," "no," or "do not know" responses to each, and utilised an empirical weighted scoring method to determine the results. A "yes" response to a query resulted in a score of 1, +1, or +2. A

"no" response resulted in a score of 1, 0, +1, or +2. Don't Know scored a score of 0 for the response. The 10 questions' combined scores, which varied from -4 to +13, were interpreted to represent the intensity of the causal association,
or more specifically, the likelihood that a medicine had caused an ADR and that the complication was not a symptom of the condition. A sum greater than nine was empirically defined as "definitely" having caused the ADR; a sum of five to eight "probably" caused the ADR; a sum of one to four "possibly" caused the ADR; and a score less than one indicated association with drug was "doubtful"[28].

The Naranjo Scale in overdose patients

- Poisoning is notably left out of the Naranjo Scale's definition of an ADR.
- Despite this, the Naranjo Scale has been used on overdose patients more frequently.
- Attempt to establish if a treatment intervention was the cause of an adverse occurrence.
- This application falsely assumes that an adverse event in a patient who has been poisoned might constitute an ADR. We could not locate a definition of ADR that includes poisoning.[28]

Table4 : Naranjo ADR probability scale—items and score

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

Question	Yes	No	Don't know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspect drug was administered?	+2	-1	0
3. Did the AR improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the AR reappear when drug was re-administered?	+2	-1	0
5. Are there alternate causes [other than the drug] that could solely have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. 0 Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased.	+1	0	0
9.Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by objective evidence	+1	0	0

Scoring for Naranjo algorithm: >9 = definite ADR; 5–8 = probable ADR; 1–4 = possible ADR; 0 = doubtful ADR.

The WHO-UMC causality assessment system

The majority of case reports in pharmacovigilance include alleged adverse medication responses, which is a problem in and of itself. Adverse responses are seldom drug-specific, diagnostic testing are frequently lacking, and a repeat challenge is infrequently morally acceptable. In reality, very few adverse responses are either "certain" or "unlikely"; instead, most are either "possible" or "probable" in nature. Many approaches for an organised and unified assessment of causation have been created in an effort to address this issue. However, it hasn't been demonstrated that any of these algorithms can generate an accurate and trustworthy quantitative evaluation of relationship likelihood. However, causality assessment has developed into a widespread, standard technique in pharmacovigilance.

The WHO-UMC system was created in collaboration with the National Centers taking part in the Programme for International Drug Monitoring and is intended to be a useful tool for evaluating case reports. In essence, a composite assessment is made, taking into account both the quality of the observation's documentation and the clinical-pharmacological components of the case history. Other factors like prior information and statistical chance play a less significant role in the system since pharmacovigilance is mainly concerned with the detection of unknown and unexpected adverse responses. It is acknowledged that the definitions' semantics are crucial, and that therefore, individual assessments may vary. Other algorithms are either very complicated or too specialised for widespread usage. This approach provides direction for the broad justifications that ought to be made when choosing one category over another[29](see table 5).

Table 5: WHO–UMC causality categories

Causality term	**Assessment criteria (all points should be reasonably complied)**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacologic phenomenon)

	• Rechallenge satisfactory, if necessary
Probable/ likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically • reasonable Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

The use of the WHO-UMC system

To illustrate how the system functions, we advise contrasting the definitions of "Probable" and "Certain" first. The fourth criteria in the category "Certain," "Event decisive pharmacologically or phenomenologically," which refers to an exact and objective event, is the first. M edical condition or a recognised pharmacological phenomena (such as "grey baby syndrome," chloramphenicol, or anaphylaxis that occurs right after taking a medication that has already been administered). This indicates that any other incident is instantly disqualified and is never eligible for the designation "Certain" (even in the case of a positive rechallenge observation). Unless the evidence in the report is already persuasive without a re-exposure, rechallenge information with a satisfying result is required for "Certain" (i.e., what occurred when the medication was initially discontinued and then restarted). On the other hand, there is no need for a second challenge for "Probable." The time between the beginning of the drug and the onset of the event must be "plausible" for it to be considered "Certain." This means that there must be a convincing argument, supported in sufficient detail, for the hypothesis that the drug is causally involved, either pharmacologically or pathologically. The temporal connection for "Probable" should be "reasonable"; this is a more equivocal phrase that encompasses anything that is not absurd. Additionally, the phrasing for the second criterion, "alternative reasons," is different in "Probable." For "Certain," the occurrence of the incident cannot be attributed to any known illness the patient has or any other medications they may be taking. On the other hand, if the occurrence is marked as "Probable," it is "unlikely" to have been caused by some other factor. In addition, there are variations in the dechallenge situations—that is, what transpired after halting. In a "Certain" case report, the sequence of events provides a strong basis for blaming the suspected substance in pharmacological or pathological terms, but in a "Probable" instance, it is enough if it is "clinically reasonable" (i.e. not unreasonable). First, the timing of the link seems uncertain (given the information available at the time), and/or another explanation is more likely. When there is insufficient information to make an accurate judgement, the phrase "Unclassified / Conditional" is acceptable.There is a need for more data, and such data are being sought for or are currently being examined. The judgement is finally "Unclassifiable" when the information in a report is lacking or inconsistent and cannot be completed or validated. Due to the fact that "Possible" and "Probable" are by far the most frequent categories in case reports, the typical method for utilising the system is to select one of these categories (based on the assessor's perception) and check to see if the different criteria match the case report's content. should the report.When the evidence is more convincing, one can go up one category (for example, from "Possible" to "Probable"), but when it is less convincing, one should try a category down. The next neighbouring phrase is attempted to determine whether that classification is accurate or whether it once again doesn't seem to match. By evaluating the actor drug, which affects the kinetics or dynamics of the other medication (which has typically been taken over a longer period of time), in the medical context of the patient, the WHO-UMC approach may be used to identify drug-drug interactions[29].

Table 6: Hartwig's Severity Assessment Scale

Level 1	An ADR occurred but required no change in treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)

Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay (LOS)
Level 4	Any level 3 ADR which increases length of stay by at least 1 day . OR The ADR was the reason for the admission
Level 5	Any level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7	The adverse reaction either directly or indirectly led to the death of the patient

Mild= level 1 and 2, moderate= level 3 and 4, severe= 5, 6 and 7. [30]

Adverse drug reaction (ADR) monitoring involves following steps :-

1. Identifying adverse drug reaction (ADR).
2. Assessing causality between drug and suspected reaction by using various algorithms.
3. Documentation of ADR in patient's medical records
4. Reporting serious ADRs to pharmacovigilance centres /ADR regulating authorities.[30]

Mechanism by which ADR Occurs :-

ADRs can be categorised as either pharmacological reactions that enhance the drug's established pharmacological effects or idiosyncratic reactions that are unpredictable. The majority of medication responses are pharmacological in nature, frequently dose-related, and brought on by either the primary or secondary pharmacological properties of the drug. Predisposing factors for these ADRs include dosage, pharmaceutical variation in drug formulation, anomalies in pharmacokinetics or pharmacodynamics, and medication-drug interactions. secondary pharmacological properties of the medication. Dose, pharmacological variation in drug formulation, pharmacokinetic or pharmacodynamic anomalies, and medication-drug interactions are among the factors that predispose to these ADRs. Pharmacological adverse drug reactions (ADRs) take place when drug concentration in plasma or tissue exceeds the "therapeutic window" or when there is enhanced sensitivity to the medication (even in amounts thought to be typical for the general population). Idiosyncratic adverse drug reactions (ADRs) are less frequent, frequently significant, not dosage dependant, and do not exhibit a clear dose-effect connection for either toxicity or response severity. Many organ systems may be affected by the harmful effects. either alone or in combination. Although the exact mechanism of these effects is unknown, theories include receptor abnormalities, abnormality of a biological system that the medication unmasks, immunological response, drug-drug interactions, or being multifactorial[31].

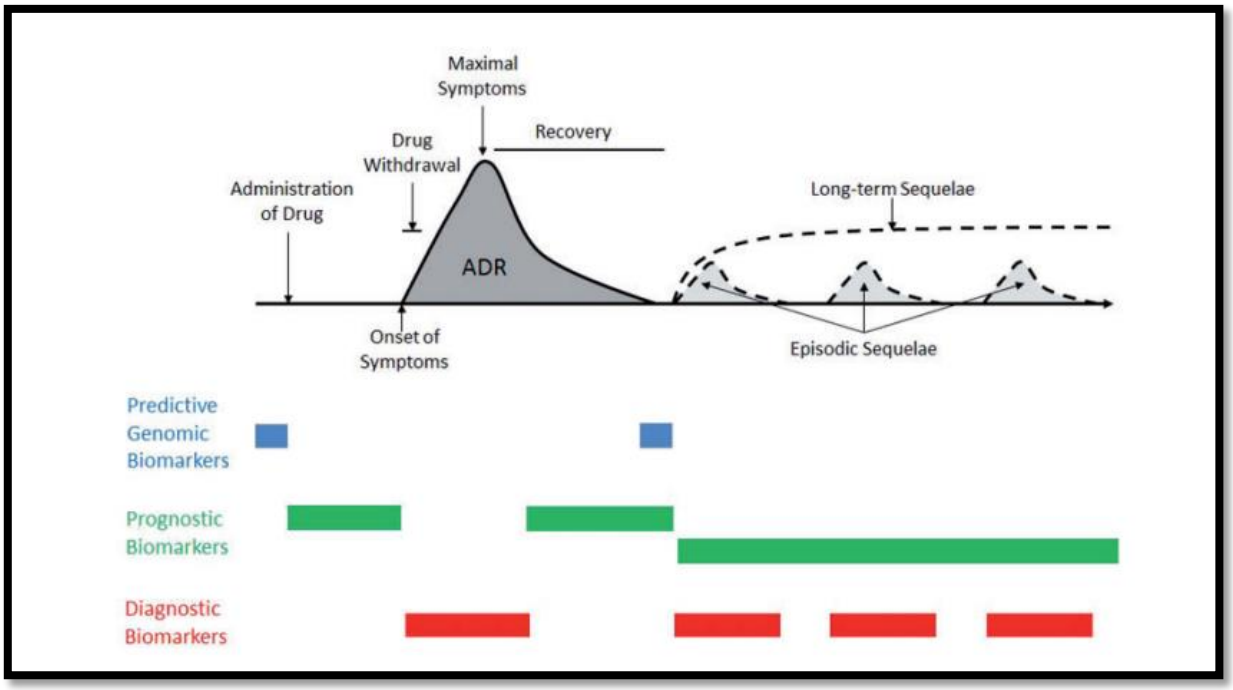
Biomarkers:-

The body's organ systems are susceptible to ADRs, which can range in severity from mild reactions (such as a skin rash or a mild elevation in liver enzymes) that go away when the causal drug is stopped to severe, life-threatening reactions like skin blistering reactions (such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)) and fulminant liver failure[32].

System	ADR	Causal drug	Indication	Associated genetic variant
Skin	Hypersensitivity (SJS/TEN/DRESS/ maculopapular exanthem)	Carbamazepine Phenytoin Allopurinol Nevirapine Abacavir	Epilepsy Gout HIV HIV	HLA-B*15:02 (Han Chinese) HLA-A*31:01 (Caucasian/Japanese) HLA-B*15:02 (Han Chinese) HLA-B*58:01 HLA-C*04:01 HLA-B*35:05 (Thai) HLA-DRB1*01:01 HLA-B*57:01
Gastrointestinal	Hepatotoxicity Pancreatitis	Flucloxacillin Co-amoxiclav Nevirapine Minocycline Lapatinib Azathioprine	Gram +ve bacterial infection Bacterial infection HIV Bacterial infection Breast cancer Rheumatoid arthritis, Crohn's disease	HLA-B*57:01 HLA-A*02:01, DRB1*15:01-DQB1*06:02 HLA-DRB1:01:01 HLA-B*35:02 HLA-DQA1*02:01/HLA-DRB1*07:01 HLA-DRB1, HLA-DQB1
Renal	Nephrotoxicity	5-aminosalicylic acid	Inflammatory bowel disease	HLA-DRB1*03:01
Hematological	Agranulocytosis	Clozapine	Schizophrenia	HLA-B/HLA-DQB1

		Sulfasalazine Antithyroid drugs	Inflammatory joint/ bowel disease Hyperthyroidism	HLA-B*08:01, HLA-A*31:01 HLA-B*27:05 (Caucasian) HLA-B*38:02, HLA-DRB1*08:03 (Han Chinese) DRB1*08032 (Japanese)
Musculoskeletal	Necrotizing autoimmune myopathy	Statins	Hypercholesterolemia	HLA-DRB1*11:01

The invention of biomarkers for identifying people prone to ADRs before starting medication may be advantageous from the viewpoints of patients and healthcare providers. Biomarkers may also have a predictive role in predicting the likelihood of postreaction recovery as well as the possible emergence of severe sequelae (for example, ocular postreaction problems in SJS/TEN survivors) (Figure 1)



Schematic of a typical delayed onset idiosyncratic ADR and indicative points at which theoretical predictive, prognostic, and diagnostic biomarkers could be used for informing patient treatment decisions and care pathways. (A color version of this figure is available in the online journal.) ADR: adverse drug reaction

Immune-related adverse events (irAEs) that could have serious or even fatal consequences. Patient survival could only be increased by enhancing effectiveness and minimising toxicity to the greatest extent available. Cardiotoxicity, neurotoxicity, and interstitial pneumonia are the most common fatal toxicities and can each occur in up to 45% of patients.

Potential biomarkers associated with irAEs

All organs may have irAEs, and the target organs and ICIs may each have a different kind of irAEs. The following list of putative biomarkers has been identified based on the available data to predict irAEs.

Nonspecific biomarkers

It might be challenging to make quick clinical conclusions in situations with nonspecific symptoms like fever, coughing, and weariness since complicated screening imaging diagnostic or haematological examination take time and require careful differential diagnosis. Therefore, it is crucial to create biomarkers that are simple to detect in order to recognise non-specific irAEs.

The known nonspecific biomarkers of irAEs

- **CRP, IL-6**
- **Blood cell count**
- **Cytokines**
- **TMB**
- **sCLTA-4**

Organ-specific biomarkers

- Gastrointestinal irAEs
- CD177 and CEACAM1
- Endocrine disorder
- Immune-related pneumonia
- Anti-GNAL and anti-ITM2B in Hypophysitis
- Dermatologic toxicity

Genomic biomarkers:-

Pharmacodynamic/pharmacokinetic-related genetic biomarkers

For a variety of medications where pharmacokinetic genetic variation can play a significant role in predicting the likelihood of an ADR, clinical implementation recommendations are available. These include (but are not limited to) TPMT and bone marrow toxicity caused by azathioprine/mercaptopurine[33][34]. respiratory depression caused by codeine (morphine) and CYP2D6[35] and myotoxicity brought on by simvastatin and SLCO1B1. An intriguing new study has revealed a non-synonymous variant in the prostaglandin transporter-encoding SLCO2A1 gene is linked to thiazide-induced hyponatremia[36] . The CYP2C9*2 and CYP2C9*3 polymorphisms in the geneencoding P4502C9, which is responsible for the metabolism of the active S enantiomer of warfarin, are a key determinant of daily dose requirement in patients. Additionally, the amount of warfarin that must be taken is closely correlated with a polymorphism in the promoter region (c.1639A > G) that lowers the hepatic production of vitamin K epoxide reductase (VKORC1), the drug's target. In fact, over half of the variance in daily dosage need is due to genetic polymorphisms in the CYP2C9 and VKORC1 genes[37] Examples of tests which have been demonstrated to be cost-effective include HLA-B*57:01 for abacavir hypersensitivity,44 HLA-B*15:02 and HLA-A*31:01 for carbamazepine hypersensitivity, and TPMT for azathioprine[38].Flucloxacillin, a commonly used antibiotic for Gram-positive bacterial infections, has the potential to cause hepatotoxicity, which has a high correlation with the HLA-B*57:01 allelotype. 9 However, the prevalence of flucloxacillin-induced liver damage is around 8.5 instances per 100,000 people48, and it has been calculated that a total of 13,513 people would need to be tested in order to avoid one case of hepatotoxicity.[39][40]

Immunogenetic biomarkers

There is an immunological pathogenesis for many type B (idiosyncratic) ADRs, such as SJS/TEN and drug-induced liver damage (DILI). This is in line with the reports of extremely significant genetic connections between certain HLA genetic loci within the major histocompatibility complex area on chromosome 6 and such responses. Preprescription genotyping is actually advised by the majority of regulatory bodies, including the FDA, for two of these connections (HLA-B*57:01 and abacavir hypersensitivity and HLA-B*15:02 and carbamazepine-induced SJS/TEN in select SE Asian populations). The incidence of these responses has been decreased in areas where the genetic test has been routinely used, therefore this has clinical significance.[41][42].In addition, the severity of ADRs linked to gene-drug combinations was divided into two main categories: severe (death-threatening or fatal) ADRs, and common (common). Drugs linked to severe ADRs by pharmacogenetic testing included allopurinol, which caused SJS/TEN/drug reaction with eosinophilia and systemic symptoms (DRESS), abacavir, which caused hypersensitivity, carbamazepine, which caused SJS/TEN/hypersensitivity, azathioprine, which caused severe bone marrow toxicity, irinotecan, which caused severe neutropenia, and flu The other two were drug-associated common ADRs and pharmacogenetic testing. With the exception of the research determining Factor V Leiden screening before to receiving oestrogen coupled with oral contraceptives, the majority of the genetic information involving gene-drug pairings was published by the CPIC guideline and drug labels were authorised by the US FDA.[43-45]

The most prevalent causes were "non-genetic treatments" and "nondrug-related ADRs".

Therapeutic area-gene and ADRs				Clinical guideline	FDA approved labelling	Number of studies by region		
Drug	**Gene**	**ADRs**	**Severity of ADRs**			**Asians**	**Europeans/ USA**	**Total**
Cardiovascular disease (24)								
Warfarin	*CYP2C9 and VKORC1*	bleeding	NS	CPIC, DPWG, CPNDS	√	2	12	**14**
Clopidogrel	*CYP2C19*	major cardiac/adverse CV events	NS	CPIC,DPWG	√	1	8	**9**
Statins	Pharmacogenetics test	myopathy	NS	CPIC, DPWG	√	–	1	**1**
Gout (8)								
Allopurinol	*HLA-B*58:01*	SJS/TEN, DRESS	S	CPIC	√	6	2	**8**
HIV infection (8)								
Abacavir	*HLA-B*57:01*	Hypersensitivity	S	CPIC, DPWG	√	1	6	**7**
Efavirenz	*CYP2B6*	CNS toxicity	NS	CPIC,DPWG	√	–	1	**1**
Autoimmune disease (8)								
Azathioprine	*TPMT*	severe bone marrow toxicity	S	CPIC, DPWG	√	1	7	**8**
Epilepsy/neuropathic pain (6)								
Carbamazepine	*HLA-B*15:02*	SJS/TEN	S	CPIC, CPNDS	√	5	–	**5**
Carbamazepine	*HLA-A*31:01*	SJS/TEN, Hypersensitivity	S	CPIC, CPNDS	√	–	1	**1**
Cancer (3)								
Irinotecan	*UGT1A1*	severe neutropenia	S	DPWG	√	–	2	**2**
Fluoropyrimidines	*DPYD*	severe hematologic, GI toxicity	S	CPIC, DPWG	√	–	1	**1**
Major depressive disorder (1)								
Nortriptyline	*CYP2D6*	anticholinergic symptoms	NS	CPIC, DPWG	√	–	1	**1**
Hormone replacement therapy (1)								
Estrogen combined in oral contraceptives	Factor V Leiden	venous thromboembolic disease	NS	DPWG	–	–	1	**1**

*****Number of studies classified by therapeutics, area, gene, and ADR, by region.**

CBA: cost-benefit analysis, CEA: cost-effectiveness, CMA: cost-minimization analysis, CUA: cost-utility analysis, CPIC: the Clinical Pharmacogenetics Implementation Consortium, CPNDS: the Canadian Pharmacogenomics Network for Drug Safety, DPWG: the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group, DRESS: drug reaction

with eosinophilia and symptomatic symptoms, FDA: the United States Food and Drug Administration, NS: Non-Severe ADRs, S: Severe ADRs, SJS: Stevens-Johnson syndrome, TEN: toxic epidermal necrolysis

There is a great deal of interest in the idea that the development of genetic testing to identify everyone at risk of adverse events before to prescription can result in the retention of valuable pharmaceuticals. Genetic susceptibility is an essential component of major adverse drug responses.

There are now 2 types:- - abacavir hyper sensitivity and HLA-B*57:01 and carbamazepine toxicity and HLA-B*15:02 - that have been translated to the clinic.[46].

Drug prescription should take into consideration ethnic variances. Numerous statistics show how ethnic differences affect medicine effectiveness and safety, particularly in Asian, African, Jewish, and Arab populations.[47]Drug exposure and treatment results are influenced by the function and expression of CYP enzymes, which are extremely diverse. Many transcription factors (TFs) in the liver regulate the expression of CYP enzymes, and master regulators of the expression of different CYP enzymes exhibit racial variances.[48][49].In 2.29 million Americans, the three most prevalent CYP2C19 alleles (*2, *3, and *17) were found to be present in frequencies and multiethnic distributions of 15.2%, 0.3%, and 20.4%, respectively, with significant ethnic variation. Diplotypes CYP2C19*1/*17 (26%) and CYP2C19*1/*2 (19.4%) are the most prevalent; CYP2C19*2/*17 (6.0%), CYP2C19*17/*17 (4.4%), and CYP2C19*2/*2 (2.5%) are the least prevalent. 15% of patients get one or more high-PGx-risk CYP2C19 drugs, such as proton pump inhibitors for ulcers, selective serotonin reuptake inhibitors for depression, clopidogrel for blood thinning, and voriconazole for fungal infections. CYP3A4 participates in the metabolism of several xenobiotic substances. [50]. Four major categories were identified in the first genetic anthropological research of 56 Arab people throughout the Middle East and North Africa: I Levantine Arabs (Palestinians, Jordanians, Lebanese, Syrians), Iraqi and Egyptians, related to Western Mediterraneans; (ii) Sudanese and Comorians, in clusters with Sub-Saharans; (iii) Sudanese and Comorians, in clusters with Sub-Saharans; and (iv) the second Arabian Peninsula cluster, which includes Omanis, Emiratis, and Bahrain The Kurdish and Berber minority are native and genetically related to the host population and nearby communities. Similar to other Asian groups, the CYP2C9*2 allele was undetectable in the Vietnamese Kinh population, a significant ethnic group in Vietnam. The predominant allelic variation in the Kinh population is CYP2C9*3.[51]

HLA associations in drug-induced liver injury, hypersensitivity reactions and skin rash

It has been believed for over 30 years that HLA type is a predictor of risk for certain adverse drug reactions, and Including both DILI, including certain responses that do not clearly display hypersensitivity reaction characteristics, and hypersensitivity reactions affecting the skin, well-established and repeatable relationships have recently been identified.[52]

HLA and drug-induced liver injury

The incidence of this adverse medication response will normally be quite low, on the order of 1 in 10,000 patients treated, despite the fact that many different pharmaceuticals now in use can induce DILI.[52]

The anaesthetic halothane, which was widely used up until the 1980s and was also a significant contributor to idiosyncratic hepatitis at that time, was mentioned in the earliest publications relating HLA and genetic susceptibility to DILI.

A Japanese research showed a connection between the HLA class II serotype DR2.[53]

The class I serotype HLA-A11 was shown to be significantly correlated with DILI caused by tricyclic antidepressants and diclofenac, while the class II serotype HLA-DR6 was significantly correlated with DILI caused by chlorpromazine in a broader investigation of a variety of different medicines.[54]

Flucloxacillin responses are the source of the strongest HLA connection with DILI that has been documented to far. A GWA research revealed a very substantial connection (odds ratio 80) with the class I HLA allele B*57:01, which has previously been shown to be a major risk factorr for abacavir hypersensitivity events.[55]

HLA and hypersensitivity reactions affecting the skin

Early and delayed responses can be distinguished between adverse medication reactions that result in skin hypersensitivity. Early or immediate-type responses involve IgE and their underlying mechanism is well understood, though genetic risk factors. Skin reactions of the delayed-type hypersensitivity exhibit significant heterogeneity, ranging from extremely mild types in which the skin is the sole organ affected and drug withdrawal causes a quick improvement to drug-induced hypersensitivity syndrome (sometimes referred to as DRESS). Additionally, certain individuals may have an unusually severe skin rash that includes blistering, such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). There is a vast body of evidence that suggests T-cell responses to medications are a crucial stage in delayed immune-mediated reactions that impact the skin.[56]

Recent investigations have linked HLA to these responses, indicating a role for T-cell reactions in drug-induced skin rashes.Weak associations between TEN and SJS and HLA class I serotype B12 were discovered [57].

Carbamazepine-induced skin reactions

Prior to a candidate gene study that involved genotyping for HLA alleles and a variety of polymorphisms in cytochromes P450 in Taiwanese cases of carbamazepine-induced SJS, progress on HLA associations in relation to skin reactions was slower than that for liver reactions. However, this association between this adverse drug reaction and the class I allele B*15:02 was found to be very potent (Table 1) [58].

In a number of nations, B*15:02 genotyping is now advised in people of Han Chinese, Thai, Malaysian, Indonesian, Philippino, and south Indian ancestry before carbamazepine prescription. [59]

Abacavir hypersensitivity

A skin rash, as well as gastrointestinal and respiratory symptoms, are signs of a severe hypersensitivity reaction to the anti-HIV medication abacavir. Although the symptoms may initially be relatively moderate and controlled by drug withdrawal, a later re-exposure will cause more severe symptoms that might be deadly. Mallal and colleagues' early evidence of a link between abacavir hypersensitivity and a haplotype encompassing HLA-B*57:01, HLA-DR7, and HLA-DQ3 was made utilising a candidate gene method.[60]

Non-HLA genetic associations in adverse drug reactions

A variety of genetic risk factors, in addition to HLA, have been discovered for idiosyncratic adverse medication responses, albeit only a small number of them have received strong replication.

Although idiosyncratic adverse medication responses are frequently thought to be concentration-independent, certain adverse drug reactions are also made more susceptible by hereditary variables that influence drug concentration through their function in drug disposition.[61]

CYTOCHROMES P450 (CYPs)

The nomenclature "CYP" is followed by a number designating the gene family (for a gene to be in the same family, its amino acid sequence should be identical in over 40% of cases), a letter designating the subfamily (over 55% of identical amino acid sequence), and the gene number for cytochrome P450 (CYPs).Human genome sequence has revealed about 107 human P450 genes: 59 active and about 48 pseudogenes. [62]

The majority of hepatic enzymes involved in drug metabolism are polymorphic. When a variant allele occurs at least 1% of the time in the general population, a gene is regarded as polymorphic. . The first category contains many pseudogenes, or genes that code for chemical metabolism but have been inactivated as a result of environmental adaptation. With the exception of CYP1A1, CYP2E1, and CYP3A4, which are comparatively well-conserved, the bulk of the genes in CYP families 1 to 3 are also functionally polymorphic. This conservation may be caused by the fact that these enzymes contain some endogenous substrates in addition to the exogenous. [63]

Polymorphic phase I enzymes are responsible for the metabolism of around 59% of the medicines included in ADR research, and CYPs make up 86% of this group. Contrarily, ADR reports only cover 20% of medications that aren't polymorphic enzyme substrates.[55]

CYP1A1

CYP1A1 is mainly expressed in extrahepatic organs, especially in epithelial tissues. A relevant feature of this enzyme is its ability to catalyse the first step in the metabolism of polycyclic aromatic hydrocarbons (PAHs, also present in tobacco smoke), which may lead to a formation of electrophilic carcinogenic molecules. CYP1A1 also catalyses oxidation of several xenobiotic chemicals such as 7-ethoxyresorufi n, theophylline, caffeine, 7-ethoxycoumarin, and chlorzoxazone, and of endogenous chemicals such as 17β-estradiol and estrone[65].

The regulation and structure of CYP1A1 are impacted by polymorphism. The first step in regulation is the binding of the inducing agent (xenobiotic substrate to be metabolised) and intracellular arylhydrocarbon receptor (AhR). Humans have genetic variants in the AhR gene, and interindividual variations in the AhR phenotype have been noted.[66]

More than 11 alleles of CYP1A1 have been identifi ed, (41) of which CYP1A1*2B, *2C, *3, *4, *5, *6, *7, *8, *9, *11 show amino acid changes. However, it is unclear whether these amino acid changes alter catalitic activities in oxidation of xenobiotics, including PAHs.[67]

The m ajority of studies on CYP1A1 polymorphism-related cancer risk have examined how altered CYP1A1 interacts with other gene variations that impact the activation and detoxification of CYP1A1 substrates as well as with phase II enzyme deficiencies (most often GST).[68]

Another study found that carriers of CYP19 (TTTA)7(- 3bp) and CYP1A1 C6235T polymorphisms had a signifi cantly increased risk of ER-positive breast cancers, which could be a useful information in screening for chemoprevention with tamoxifen[69].

Other studies partly support that polymorphic variations in CYP1A1 (*2A, *2C, *4) may play a role in colorectal cancer(70-72).

CYP1A2

Most CYP1A2 expression occurs in the liver. In the adult human liver, CYP1A2 protein makes up 10% to 15% of the total P450. Between people, expression levels vary by around 40 times. The metabolic activation of several aryl- and heterocyclic amines, including 2- aminoanthracene and 2-acetylaminofl uorene, is catalysed by CYP1A2. CYP1A2 is substantially slower than CYP1A1 and 1B1 at catalysing the activation of PAH-diols to reactive metabolites. Other xenobiotic substances that are oxidised by CYP1A2 include caffeine, acetaminophen, antipyrine, lidocaine, phenacetin, theophylline, and R-warfarin. More than 16 polymorphic alleles of CYP1A2 have been discovered[73].

Coffee drinkers who have the CYP1A2 gene variation C have been observed to have an increased risk of myocardial infarction with increasing coffee consumption[74].

CYP1B1

CYP1B1 is mostly expressed in the steroidogenic tissues of the uterine, breast, ovary, testis, prostate, and adrenal gland in the endoplasmatic reticulum of extrahepatic organs. Numerous other extrahepatic tissues, including as the lung, kidney, thymus, spleen, brain, heart, colon, and intestine, also express it. Numerous human malignancies, including those of the skin, brain, testis, and breast, have higher amounts[75-76].

CYP1B1 transforms oestrogen into 4-hydroxylated molecules that may cause human breast cancer. [77-78]

Another research provided some evidence in favor of polymorphism variation in CYP1A2 and CYP1B1 contributing to colorectal cancer susceptibility[79].

The activation of carcinogens at various organ targets, with complicated gene-environment interactions, appears to be a crucial function of CYP1B1 and Phase II enzymes[80].

About 20% of the hepatic CYP content is made up of CYP2C9, which is mostly expressed in the liver.About 15% of currently prescribed medications are metabolised by it, including some that have significant clinical significance, such as angiotensin-2 antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), oral anti-diabetics, anti-epileptics, oral anticoagulants, psychotropic medications, and alkylating anticancer drugs (see table 7)[81-82].

Table 7 Important drugs which are substrates of enzyme CYP2C9

DRUG GROUPS	DRUG

Angiotensin II receptor blockers	Losartan, irbesartan,valsartan
Antidiabetics	tolbutamide, glipizide
Anticoagulants	Warfarin
Anticonvulsants	Phenytoin
Antimicrobials	metronidazole, sulphamethoxazole
Non steroidal antiinflammatory drugs	celecoxib, diclofenac, ibuprofen, indomethacin, naproxen, tenoxicam
Psychotropic drugs	amitriptyline, fl uoxetine

In addition, CYP2C9 facilitates the 3-hydroxylation of Benzo[a]pyrene9(B[a]P) and the metabolic activation of numerous PAH-diols to active metabolites, but at much slower rates than CYP1 enzymes[83].CYP2C9 genetic polymorphisms involve more than 34 alleles.[73]Environmental variables can also affect interindividual variability in CYP2C9 enzyme activity, which is stimulated by classical CAR, PXR, and GR ligands through various components in the promoter region or blocked by oral contraceptives, in addition to genetic variations[84].

CYP2C19

The vast majority of CYP2C19 PMs are derived from two variations, *2 and *3. CYP2C19*4, *5, *6, *7, and *8 are some of the less prevalent variations linked to PM (poor metabolism) status[85].PM status is associated with two loss-of-function alleles. Having PM status is linked to a reduced response to clopidogrel. In comparison to patients with normal CYP2C19 function, patients with impaired CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel, a lessened antiplatelet response, and generally have greater rates of cardiovascular events after myocardial infarction[86].Healthcare professionals are warned in a boxed statement on the FDA label that "poor CYP2C19 metabolizers treated with appropriate dosages of clopidogrel exhibit greater cardiovascular event rates after acute coronary syndrome than individuals with normal CYP2C19 function."[87]

CYP2D6

Despite having a small amount of liver tissue (approximately 2%), CYP2D6 makes up an unexpectedly significant enzyme for drug metabolism. All phase I and II metabolising enzymes have polymorphisms, but its polymorphisms are the most crucial for drug metabolism. This enzyme metabolises around 25% of all medicines available on the market and has over 80 distinct allelic variations.[88]Antidepressants, neuroleptics, antiarrhythmics, analgesics, antiemetics, and anticancer medications are the most significant substrates of CYP2D6 (Table 8).[89-90].

Drug group	**Drugs**
Analgesics	A codeine, dextromethorphan, fentanyl, hydrocodon, meperidine, methadone, morphine, oxycodone, tramadol
Antiarrhythmics	amiodarone, aimaline, fl ecainide, lidocaine, mexiletin, propafenone
b-Adrenoceptor antagonists	b-Adrenoceptor antagonists alprenolol, bisoprolol, bufuralol, carvedilol, labetalol, metoprolol, pindolol, propranolol, timolol
Psychotropic drugs	amphetamine, amitriptyline, fl uoxetine, fl uvoxamine, haloperidol, imipramine, clomipramine, chlorpromazine, clozapine, maprotiline, paroxetine, risperidone, thioridazin, trazodone, venlafaxin, zuclopenthixo
Other	guanoxane, captopril, tamoxifen, trimethoprim

The enzyme also seems to be a key player in the metabolism of polymorphic drugs that result in adverse drug reactions.[91]

About 50% of clinically used medicines' pharmacokinetics are adversely affected by CYP2D6 polymorphism(table above). A common doses, the results can either be adverse pharmacological reactions or no drug response.[92-94]

Drug treatment effectiveness and cost may be impacted by CYP2D6 polymorphism. The treatment of between 30% and 50% of CYP2D6 drug substrates is thought to benefit from predictive CYP2D6 genotyping**.[95]**

The clearance of the antidepressants desipramine, fluvoxamine, mexiletine, mianserin, nortryptiline, and paroxetine as well as the clearance of the neuroleptics perphenazine and zuclopenthixol as well as the competitive muscarinic receptor antagonist tolterodine have all been successfully predicted by the CYP2D6 genotype.[96]

In situations when prodrugs that require CYP2D6 activation are utilised, the efficacy of medication therapy is decreased due to CYP2D6 enzyme deficiency. The analgesic impact of codeine and tramadol is observed in this. The processes of N-demethylation and 4-hydroxylation, which are catalysed by CYP2D6, convert tamoxifen into its active metabolite endoxifen. When treating PMs with CYP2D6, a less effective therapeutic impact has been noted, and predictive pheno/genotyping is indicated.[97]

CYP2D6 gene mutations can also change the substrate specificity.[98]

CYP2E1

Only one human gene at the CYP2E locus has been identified. The centrilobular area of the liver has the highest concentration of CYP2E1 expression. Because it plays significant endogenous roles, this enzyme has undergone a fair amount of conservation. Similar to other gluconeogenetic enzymes, CYP2E1 is endogenously regulated so that its expression is suppressed during normal nutrition and elevated during hunger and diabetes. Fatty acids and the gluconeogenetic precursors acetone and acetol appear to be its physiological substrates[80].

Additionally, many cytokines regulate how CYP2E1 is expressed. In primary culture of human hepatocytes, IL-1, IL-6, and TNF- reduce the amount of CYP2E1 similarly to CYP1A2, CYP2C, and CYP3A.[99]

The expression of the enzyme is induced by IL-4 in contrast. A wide variety of substrates can be used by CYP2E1. CYP2E1 can metabolise more than 70 distinct compounds of various structures. These substrates are often hydrophobic and tiny. They consist of alcohols, ketones, and aldehydes, aromatic chemicals, halogenated alkanes or alkenes, anaesthetics, medications, and premutagens such nitrosamines (found in cigarette smoke) and azo carcinogens.[100-103]

In general, CYP2E1 polymorphism and smoking or alcohol consumption have been linked to gene-environment interactions that increase the risk of colorectal neoplasia. A human carcinogen called vinyl chloride (VC) is known to be metabolised by CYP2E1 into reactive intermediates that can lead to oncogene and tumour suppressor gene mutations. These intermediates are then further metabolised by glutathione-S-transferases and acetaldehyde dehydrogenase (ALDH2) to nonmutagenic end products.[80]

CYP3A4/5

In the human liver, CYP3A4 makes up around 30% of all P450 enzymes, making it the most common. A variety of structurally diverse xenobiotics and 50% of all clinically used medications can be metabolised more easily by CYP3A enzymes.[104-105]Additionally, they play a significant part in the metabolism of steroid hormones like testosterone and oestrogen as well as endogenous substrates like retinoic and bile acids.[106-107]Additionally, CYP3A4 plays a critical role in the metabolism and activation of a variety of dietary and environmental substances, including pesticides, flavonoids, PAH-diols, mycotoxins, aflatoxins B1, G1, and sterigmatocystin. . CYP3A4 has a lower catalytic activity in PAH activation than enzymes from the CYP1 family. On chromosome 7q21-q22.1, there are four human CYP3A genes: CYP3A4, CYP3A5, CYP3A7, and CYP3A43.[80] Clinically significant CYP3A enzymes CYP3A4, CYP3A5, and CYP3A7 are primarily expressed in the liver and share comparable substrate specificities.During development, CYP3A4 and CYP3A7 exhibit opposing patterns of expression[108].Up to six months after birth, CYP3A7 is mostly expressed in the liver of foetuses, however it can also be detected in some adult livers and other tissues.[109]

The predominant cytochrome P450 isoform seen in adult liver is CYP3A4. Regardless of polymorphism, CYP3A5 content is consistent throughout the whole developing process. CYP3A7 is crucial for the metabolism of xenobiotics that enter the foetus from the mother's circulation as well as the metabolism of endogenous substrates like critical hormones and retinoic acid in the foetus. Therefore, interindividual changes in CYP3A7 expression could lead to interindividual variations in the embryotoxicity and teratogenicity of certain drugs.[110-111].

Certain medicines and chemicals have the ability to inhibit CYP3A4. These include azole antifungal medications like ketoconazole, macrolide antibiotics like troleandomycin, HIV protease inhibitors like saquinavir, antidepressants like fluoxetine, and furanocoumarin, the 6',7'-dihydroxybergamottin found in grapefruit juice**.[112-113]**

Numerous medications and dietary substances have a high ability to induce the CYP3A4 enzyme. Rifampicin, an anticonvulsant like carbamazepine, and glucocorticoids are examples of medications that cause**.[114]**

Rifampicin, phenytoin, or carbamazepine coadministration may cause the plasma AUCs of a range of CYP3A4 drug substrates to be reduced by less than half**.[115]**

The plasma levels of the substrate may increase by up to 20 times when a potent CYP3A4 inhibitor is used with a medication that depends on CYP3A4 for its metabolism, which might result in toxic effects and unfavourable drug interactions. Likewise, the substrate's plasma levels may only reach 5% to 10% of their initial concentration when combined with an inducer, which would result in therapeutic failure.[116]

CYP3A7 is a well-conserved gene, similar to CYP3A4, and so far one frameshift mutation (CYP3A7*3) and one coding polymorphism (CYP3A7*2) have been identified**.[117]**

In Caucasians, Asians, and Africans, the prevalence of the CYP3A7*2 allele is 8%, 28%, and 62%, respectively. However, it is still unknown how this polymorphism affects endogenous substrate metabolism and foetal drug clearance. About 10% of adult livers exhibit significant CYP3A7 protein expression, which accounts for 24% of the total CYP3A protein in these livers, according to CYP3A7-specific antibodies. Although CYP3A5 is widely distributed throughout tissue, it expresses at a significantly lower level than CYP3A4. Only 20% of persons have livers that express CYP3A5.African-Americans tend to express it more than Caucasians do**.[118-119]**

A mutation at the splice site is the most frequent cause of non-expression. Variant allele frequency reveals interethnic disparities, with the wild-type CYP3A5*1 allele being more prevalent in Africans than Caucasians and Asians [120].

Despite being less active, CYP3A5 has a similar substrate selectivity to CYP3A4. A similar regulatory mechanism controls the constitutive expression of the CYP3A4 and CYP3A5 genes.[121]

Immunosuppressive medications cyclosporine, tacrolimus, sirolimus, and everolimus are significant CYP3A5 substrates because they exhibit high interindividual variability in pharmacokinetic characteristics and a restricted therapeutic index**.[122]**

African-Americans were more likely than white men to have the CYP3A4 -G variation (*1B) in a study of a multiethnic sample. White men had a low prevalence of the CYP3A4*1B variant, which limited the results of analyses that were race-stratified. These analyses also found little correlation between the CYP3A4 variant and prostate cancer risk among white men. However, the aggressive prostate cancer in African-American men with the *1B/*1B genotype was substantially related with that genotype[123].The FDA has been proactive in a number of other ways, including the publication of the “Pharmacogenomics Guidance Document” [124].

Table 9 Important drugs which are substrates of enzyme CYP3A

Drug groups	Drugs
Analgesics	acetaminophen, alfentanil, codeine, dextromethorphan
Antiarrhythmics	dysopiramide, lidocaine, quinidine
Antimicrobials	doxycycline, erytromycin, clarithromycin, clindamycin, ketoconazole, miconazole, troleandomycin, HIV-protease inhibitors
Antihistamines	astemizole, loratadine, terfenadine
Anticonvulsant	carbamazepine, etosuximide
Antilipemics	atorvastatin, fluvastatin, lovastatin, simvastatin
Antitumour drugs	busulphan, cyclophosphamide, doxorubicin, paclitaxel, tamoxifen, vinblastine, vincristine
Ca channel blockers	amlodipine, felodipine, nifedipine, nimodipine, verapamil
Steroids	estradiol, cortisol, progesterone, prednisone, testosterone

Immunosuppressants	cyclosporin, sirolimus, tacrolimus
Cardiotonic glycoside	Digitoxin
Narcotics	methadone, cannabinoids, cocaine, fentanyl
Psychotropic drugs	amphetamines, fluoxetine, haloperidol, clomipramine, clonazepam, chlorpromazine, midazolam, risperidone, triazolam

Conclusion:-

India has more than half a million qualified doctors and 15,000 hospitals having bed strength of 6, 24,000. It is the fourth largest producer of pharmaceuticals in the world. It is emerging as important clinical trial hub in the world. Many new drugs are being introduced every year and so every health care professional must have knowledge about importance of ADR monitoring and pharmacovigilance. PGx accounts for 20–95% of drug response variability, with a significant role in the incidence and severity of ADRs. Differential PGx features in children, aged patients, and women deserve special attention for preventing ADRs; and caution should be taken when extrapolating data from clinical trials performed in Caucasians to other populations due to ethnic-related PGx differences. Novel data on the PGx of drugs for the treatment of cardiovascular disease and related disorders, cancer and CNS disorders are of help in the clinical setting for optimizing therapeutics and reducing ADRs. This will need to be aligned to studies of cost-effectiveness and inclusion in clinical guidelines, as well as education and training of new and existing healthcare professionals. This will need to be aligned to studies of cost-effectiveness and inclusion in clinical guidelines, as well as education and training of new and existing healthcare professionals.

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