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INDIA – A NEW CONTRIBUTOR TO THE PHARMACOVIGILANCE MOVEMENT

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ABSTRACT: Every drug has two facets and the sinister side is becoming more apparent every day, sometimes resulting in product recalls by regulatory agencies due to serious adverse effects. Monitoring of unwanted side effects of allopathic drugs administered alone, and in combination with other drugs or dietary products causing drug-drug and drug-herbal/food interactions were lacking earlier, but information is now being unearthed in India. The aim of pharmacovigilance programmes is to bring this treasure trove of knowledge under one umbrella for consumers and all other stakeholders. Such programmes are meant to create awareness among physicians and surgeons for the better treatment of patients by advocating safe use of drugs, and at the same time collect risk/benefit data and collaborate globally to form a strong post-market surveillance network. Hopefully, the seeds of such programmes sown today will blossom into powerful and efficient tools and lead to meaningful outcomes in the future. Presently, pharmacovigilance in India is in its nascent stage. After two unsuccessful attempts, the third Indian venture to construct a pharmacovigilance network has taken root and is expected to bear fruit. The overall objectives of this review are: to ensure the safe use of medicines in diverse and sensitive patient populations; to improve patient care through judicial use of drugs and plant-derived remedies; to improve public health and safety by the assessment of risks and benefits of medicaments; and to promote education and clinical training of health professionals in the management of risks/benefits associated with existing and new medicines.

INTRODUCTION: Drugs are multi-faceted and their benefit to risk ratio is often the most important criteria evaluated before marketing. A low safety profile is one of the major reasons for clinical failure of a drug candidate [1].

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Quite often; safety testing during the clinical stage does not guarantee a risk-free pass to any marketed drug. Recent drug withdrawals like rosiglitazone (increases cardiovascular disorder risk) [2], sibutramine (increases cardiovascular disorder risk) [3], rimonabant (increases psychiatric disorder risk) [4] and tegaserod (increases cardiovascular disorder risk) [5] bear testimony to this statement.

These drug-induced serious risks were identified by continuous post-market surveillance, a process called 'pharmacovigilance'.

The World Health Organisation (WHO) defines pharmacovigilance as, 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem' [6]. The term was first used in the early 1970's almost exclusively by the French, until the 1990's when its usage became widespread [7].

The forerunner of pharmacovigilance could be seen in the 18th century, when an increasing number of publications made man aware of the dangers of medicines and therapeutic procedures [8]. In 1906, with the establishment of the Food and Drug Administration (FDA), a turning point had been reached [8].

The most pivotal event in the history of pharmacovigilance occurred in 1961 when 'thalidomide', a drug used to prevent morning sickness during pregnancy was found to cause 'phocomelia', a limb abnormality disorder in the children of mothers who had used thalidomide [9]. In response to the thalidomide tragedy, the WHO set up an International Drug Monitoring Programme in Geneva in 1968, which was shifted to Uppsala, Sweden in 1978. This centre is now known as the Uppsala Monitoring Centre (UMC). One hundred and thirty four member countries report to UMC through their National Pharmacovigilance Centres [6, 8].

PHARMACOVIGILANCE IN INDIA:

Need for pharmacovigilance in India: India has a population of around 1.2 billion [8]. Such a large population along with vast differences in the genetic makeup of the people obviously will result in major contrasts in drug responses. Thus, the developed market Adverse Drug Reaction (ADR) information that pharmaceutical companies and regulatory authorities in India relied on were not very useful. Also, many Indian companies have been engaging in Research and Development (R&D) to develop new drugs and better dosage forms. Clinical trials are also being conducted in India on a huge scale. The lag time between drugs manufactured elsewhere and their availability in India is also decreasing. But India-specific ADR information was absent.

All these factors were considered to make an India-specific pharmacovigilance programme the need of the hour [10-12].

Pharmacovigilance programmes in India: India's unsuccessful trysts with pharmacovigilance occurred in 1986 and 1997. Lack of ADR monitoring systems, lack of information dissemination among healthcare professionals and lack of government funding were the major reasons for failure. The National Pharmacovigilance Programme was established in January 2005 with sponsorship from the WHO and World Bank funding [8, 10, 11].

Recognising its earlier mistakes and pitfalls, a lot more thought was put in while formulating the framework of the subsequent new pharmaco-vigilance programme. In July 2010, the Central Drugs Standard Control Organisation (CDSCO), New Delhi, under the control of Ministry of Health & Family Welfare, Government of India, started the Pharmacovigilance Programme of India (PvPI) [8, 10, 11, 13]. The National Co-ordination Centre for monitoring ADRs was set up at All India Institute of Medical Sciences (AIIMS), New Delhi, in 2010 and later shifted to the Indian Pharmacopoeia Commission, Ghaziabad in 2011[13]. The objectives of PvPI are [13]:

- Formation of a nation-wide system for patient safety reporting.
- Identify and analyse ADRs of reported cases.
- Evaluate benefit-risk ratio of existing medications.
- Generation of evidence based safety information.
- Supporting other regulatory agencies.
- Communication of information to all healthcare professionals and consumers.
- Creation of a pharmacovigilance centre that meets global standards.

- Provide training and consultancy to other centres across the globe.

So far, PvPI has been a roaring success, but some problems like less information exchange between the concerned authorities, lack of training for healthcare professionals and poor reporting by the population still linger [10].

A few suggestions which could overcome these problems are [10]:

- Compulsory pharmacovigilance reporting by hospitals and pharmaceutical industries.
- Proper risk/benefit information exchange between the concerned authorities.
- Creation of a single adverse event reporting form to be used by all parties concerned.
- Continuous education and clinical training of healthcare professionals and pharmacy students.
- Joining hands with the Information Technology (IT) sector to build a country wide strong risk/benefit data base of drugs for the pharmacovigilance system.

This review discusses some of the issues and concerns which need to be tackled in pharmacovigilance, namely: antibiotic resistance, clinical implications of drug-herbal/food interactions, dosage adjustment in paediatric and geriatric patients, prescribing to pregnant and lactating women, contamination of herbal and *Ayurvedic* products, buying of drugs via internet, as well as pharmacovigilance of vaccines and genetically modified products.

ANTIBIOTICS – AN OLD ALLY OR A NEW FOE: When Alexander Fleming accidentally discovered penicillin in 1928; little did he know that he had started a revolution in drug discovery [14, 15]. Antibiotics were the rage in the latter half of the 20th century. Thanks to the penicillin discovery, subsequently many new bactericidal molecules were isolated from natural sources and even synthesised *in vivo* [16]. This helped to cure many life-threatening diseases and even led to the belief that humans would be impervious to infectious diseases.

Advent of Antimicrobial Resistance: The period from 1940-1980 could be called as "the golden age of antibiotics". Oxazolidinones was the only new class that joined the approved antibiotic list in the 1990's [17]. On the other hand, resistance mechanisms have been evolving for millions of years [18, 19]. Introduction of antibiotics escalated the selection of resistant species and strains based on Darwin's principle [17, 20] and once acquired, resistance is lost at a very slow pace [21]. In 1944, penicillin resistant strains of *Staphylococcus aureus* were isolated, nearly 2-years after the antibiotic's therapeutic introduction [20]. This has extended to other antibiotics, with resistance observed soon after their first clinical use. Nowadays, multi-drug-resistant organisms (MDROs) have raised their head, e.g. MDR tuberculosis [22]. These resistant superbugs represent a severe challenge unless a swift counter is used.

Factors implicated for antimicrobial resistance include [16, 23-26]:

- Excessive and indiscriminate use of antibiotics in humans and animals.
- Usage when not indicated (e.g. viral infections).
- Sub-therapeutic dosage or inadequate treatment duration.
- Use as growth promoters in agriculture and subsequent food preparations.
- Nosocomial infections.
- Population mobility.
- Reluctance of manufacturers to invest in antibiotic research due to marketing problems.
- Rigid drug approval regulations.

Mechanisms of antimicrobial resistance: Resistance can be of intrinsic, acquired or adaptive type [20].

Intrinsic Antimicrobial Resistance: This occurs due to the inherent properties of the microbe. They include:

- Semipermeable outer membrane with low permeability – e.g. Gram-negative pathogens *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [20].

Acquired antimicrobial resistance: This occurs when an originally susceptible microbe becomes resistant due to incorporation of new genetic material (plasmids, integrons, transposons and naked DNA etc. by vertical or horizontal transfer) or mutations (single or multi step) [20, 27].

- Drug inactivating enzymes – e.g. β-lactamases produced by staphylococci, gonococci etc. which hydrolyse the β-lactam ring of the molecule [16, 17, 20, 27].

- Drug efflux pumps – e.g. Tetracycline resistance in Gram-negative bacteria [28] and fluoroquinolone resistance in *Streptococcus suis* [29].

- Drug target modification – e.g. altered penicillin binding proteins in certain Penicillin-resistant pneumococcal strains [27].

- Altered metabolic pathways – e.g. some sulfonamide resistant bacteria utilise preformed folic acid instead of synthesising it from p-amino benzoic acid (PABA) taken from the medium [27].

- Decreasing drug entry through porins – e.g. OprD porin involved in *Pseudomonas aeruginosa* resistance to carbapenems and OmpC porin involved in *Salmonella enteric* resistance to cephalosporins [20].

- Reduced target expression – e.g. decreased expression of Topoisomerase IV is implicated for low-level fluoroquinolone resistance in *Staphylococcus aureus* [30].

Adaptive antimicrobial resistance: where, there is a temporary rise in the resistibility of the microbe in response to the drug, due to altered gene/protein expression, as a result of exposure to stress, nutrient medium, growth or sub-inhibitory levels of the antibiotic e.g. *Moraxella catarrhalis* decreases M35 porin expression in response to aminopenicillin exposure. This type of resistance reverts when the inducing condition is removed [20].

The human fight back: Around halfway through the 20th century, antibiotics had proven to be an irreplaceable weapon against infectious agents, but as the years went by, this weapon turned out to be a thorn in the flesh. Currently, antimicrobial resistance has reached a peak, but concerted efforts can bring victory again. These efforts are:

- Providing economic incentives to pharmaceutical and food industries to accelerate new antibiotics research [26].

- Review regulatory aspects of antibiotic approval [26].

- Vigilance programme – building local, national and international level surveillance networks to facilitate information exchange about new strains of resistant organisms as well as treatment regimens [25, 26]. Strict monitoring of antibiotic prescribing with treatment guidelines along with consumer and professional education is also required [17].

- Faster identification of the causative organism by culturing stool swabs, and respiratory samples [22].

- Forming libraries of microbial genotypes by utilisation of high-throughput technologies, which will enable identification of specific gene targets [22, 31]. Such specific targets will enable better treatment regimens and prevent needless use of broad spectrum antibiotics.

- Development of new antibiotics from unconventional sources. e.g. antimicrobial action of alkaloids from *Tribulus terrestris* L. against Gram positive and negative bacteria [32] and broad spectrum action of *Anacardium occidentale* and *Carica papaya* [33].

Microbes have been present and have survived since time immemorial, and antimicrobial resistance is never going to stop. The only respite we can take solace in is slowing its progress.

DRUG INTERACTIONS AND THEIR CLINICAL IMPLICATIONS: A drug-drug, drug-herbal or drug-food interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or some environmental chemical agent. The interactive effects may be additive, synergistic or antagonistic in nature, resulting in the alteration of actions of one or more drugs [34]. Drug interactions are often described in information sheets or reference texts like pharmacopoeias. If drug interactions reduce the therapeutic efficacy or increase adverse effects or toxicity, they are termed as clinically significant [35]. Based on the interacting agent, drug interactions can be divided into drug-drug, drug-herb and drug-food interactions, while based on the mechanism of interactions, they can be categorised into pharmacokinetic-interactions affecting the absorption, distribution, metabolism, and elimination of a drug, or pharmacodynamic-interactions causing synergistic or antagonistic effects.

Drug-drug interactions: An individual suffering from multiple diseases requires multiple medications, i.e., polypharmacy. The combination is selected in such a manner that the drugs complement each other, for instance combination of anti-tubercular drugs to prevent resistance [36]. But sometimes, adverse interactions may occur. Sloan has shown that the interactive potential for 2, 5, 8 or more drugs used together is 5-6%, 50% and almost 100%, respectively [37]. **Table 1** enlists some of the major drug-drug interactions reported in the literature.

TABLE 1: DRUG-DRUG INTERACTIONS

Drug	Interacting Agent	Mechanism	Category of drug interaction
Cisapride	Clarithromycin, flucanazole, nefazodone, ritonavir, amiodarone, verapamil	Cisapride is metabolised by CYP3A4. These drugs inhibit CYP3A4 and increase plasma concentration of cisapride.	Pharmacokinetic[38]
Celecoxib	Fluconazole	Celecoxib is metabolised by CYP2C9. Fluconazole inhibits CYP2C9 and increases plasma concentration of celecoxib.	Pharmacokinetic[39]
Amitriptyline	Celecoxib	Amitriptyline is metabolised by CYP2D6. Celecoxib inhibits CYP2D6 and increases plasma concentration of amitriptyline.	Pharmacokinetic[39]
Warfarin	Aspirin	Aspirin has anti-platelet effects with gastric mucosal damage and causes a hyperthrombinemic response to warfarin. This increases the risk of bleeding.	Pharmacodynamic[40]
Fluoroquinolones	Divalent and trivalent cation containing compounds. E.g. Sucralfate	Divalent and trivalent cations form insoluble complexes in the gut with fluoroquinolones, which reduces fluoroquinolone absorption by 65-70%.	Pharmacokinetic[40]
Digoxin	Propantheline	Propantheline reduces gastric motility and increases absorption of slow dissolving digoxin by 30%.	Pharmacokinetic[37]
Digoxin	Verapamil	P-glycoprotein is a drug transport protein that eliminates digoxin. Verapamil inhibits p-gp and enhances digoxin bioavailability.	Pharmacokinetic[41]
Sildenafil	Nitrates	Sildenafil and nitrates both enhance nitric oxide effects. Co-administration can result in potentiation of nitrate hypotensive effects.	Pharmacodynamic[40]
Salbutamol	Propranolol	Propranolol is a non-selective β-blocker, while salbutamol is a β_2 agonist. Co-administration results in antagonism of salbutamol's action by propranolol.	Pharmacodynamic[34]
Fluoxetine	Non-selective MAO inhibitors	Fluoxetine is a SSRI. SSRIs and MAOIs both result in high concentrations of serotonin. Concomitant use of these drugs results in serotonin syndrome.	Pharmacodynamic[40]

Drug-herb interactions: Any form of a plant or plant product that comprises a single herb or combinations of herbs believed to have complimentary effects can be an herbal drug. Although herbal remedies are considered to be safe because they are natural, they have the potential to cause various adverse effects and may also interact with other conventional drugs. These herbs may contain a single biologically active chemical constituent or multiple constituents that interact with the allopathic drugs to produce an adverse effect [42].

Herbal remedies have been used in India and many other countries for over thousands of years. Recently, the use of herbal and dietary substances has increased manifold in the United States. National telephone surveys documented an increase in the percentage of people using herbal remedies from 2.5% in 1990 to 18.8% in 2002. Approximately 16% of patients combine herbal medicines with prescription medications unknowingly [43]. Since herbal remedy usage is at an all-time high, clinicians and surgeons must inquire about the use such health remedies before prescribing allopathic drugs. Especially, patients treated for cardiovascular diseases, pregnant and nursing mothers, cancer patients should be informed about the potential for benefit and harm caused by polypharmacy. **Table 2** summarizes some drug-herbal interactions reported in the literature.

Table 2: Drug-herb interactions

Drug	Interacting agent	Mechanism	Category of drug interaction
Captopril	Allicin	Allicin is reported to inhibit angiotensin I converting enzyme (ACE) and it reduces blood pressure by synergistic interaction with captopril.	Pharmacodynamic[44]
Calcium channel blockers (CCBs)	DC-2,DC-3 Coumarin glycosides isolated from carrot	DC-2 and DC-3 are thought to act by blocking calcium channels. Concomitant use with CCBs can cause loss of contractility.	Pharmacodynamic[45]
ACE inhibitors	Phenolic rich soybean extract	Phenolic rich soybean extracts inhibit ACE significantly. Synergistic effect with ACEIs is possible.	Pharmacodynamic[46]
Thiazide and loop diuretics	Glycyrrhizin	Hyper-mineralocorticoidism is caused by glycyrrhizin. Hypokalemia is one of its characteristics. Thiazide and loop diuretics also deplete potassium ions. Co-administration of liquorice and these drugs can cause hypokalemia.	Pharmacodynamic[47]
CYP3A4 substrates	Tomato juice	Tomato juice contains one or more mechanism-based and competitive CYP3A4 inhibitor(s). This may result in decreased metabolism and longer half-life of the drug along with an increased effect.	Pharmacokinetic[48]
α-Adrenergic blockers	Saponins and alkaloids present in radish	Saponins and alkaloids present in radish are α-agonists. Co-administration with α-blockers could result in an antagonistic action and therapeutic failure.	Pharmacodynamic[49]
HIV Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	St. John's wort (SJW) extract containing hyperforin	SJW induces CYP3A4 via activation of a nuclear steroid/pregnane and xenobiotic receptor (SXR/PXR). CYP3A4 induction results in high metabolism of NNRTIs and causes therapeutic failure.	Pharmacokinetic[50]
Talinolol	*Gingko biloba* extract	Repeated ingestion of *Gingko biloba* extract increased talinolol bioavailability. It is thought that the extract influences P-gp and other drug transporters.	Pharmacokinetic[42]
Imatinib	Ginseng	Ginseng inhibits CYP3A4 which is involved in metabolism of imatinib. Enzyme inhibition causes decrease in imatinib metabolism and results in imatinib-associated hepatotoxicity.	Pharmacokinetic[51]
Nifedipine	Ginger	Ginger and nifedipine act synergistically to cause platelet aggregation.	Pharmacodynamic[52]

Drug-food interactions: Drug usage without prior food ingestion may be harmful is what has been generally advised to children and these words are lived by them forever. This notion holds true, but sometimes prescriptions are handed out by physicians with specific instructions regarding drug administration. Awareness about drug-food interactions is the reason for such specific instructions.

Food can either directly interact with the drug or indirectly result in physiological changes which affect the drug therapy. Direct interactions include chelation by polyvalent metal ions or inhibition of absorption through the mucosa by acting as a barrier. Indirect effects include changes in gastric pH which could affect drug absorption or stability and efficacy of transport proteins. Meal volume or fatty meal also affects drug absorption and bioavailability. Large solid meals delay gastric emptying and could degrade acid-labile drugs, whereas larger transit times allow the drug to efficiently dissolve and get absorbed through the lipid bilayer membrane of the gastrointestinal tract [53, 54]. **Table 3** enlists some drug-food interactions.

TABLE 3: DRUG-FOOD INTERACTIONS

Drug	Interacting agent	Mechanism	Category
MAO Inhibitors	Tyramine rich foods	MAO Inhibitors decrease the degradation of catecholamines and increase their concentration. Tyramine is a precursor for synthesis of catecholamines. Concurrent ingestion of the two results in excessive catecholamine presence. Catecholamines increase the heat rate and constrict blood vessels resulting in a hypertensive crisis. This is called 'Cheese reaction'.	Pharmacodynamic[37]
Warfarin	Vitamin K rich foods	Warfarin is an anticoagulant while Vitamin K is useful in the process of clotting. Therapeutic failure occurs if they are ingested together.	Pharmacodynamic[37]
Amitriptyline	2 week high protein/low carbohydrate diet, broccoli, cauliflower, Brussels sprouts, cabbage, charcoal broiled meat	All these foodstuffs induce CYP1A enzyme. Amitriptyline is a CYP1A substrate and ingestion of these foods with the drug could metabolise the drug quickly without any therapeutic effect.	Pharmacokinetic[55,56]
1,4- Dihydropyridine calcium antagonists	Grapefruit juice (GJ)	These drugs are metabolised by CYP3A4. GJ is a potent CYP3A4 inhibitor and could increase the bioavailability of these drugs.	Pharmacokinetic[57]
Tetracycline	Dietary cations	Certain antibiotics chelate with cations like calcium which reduces drug absorption.	Pharmacokinetic[54,58]
Ibuprofen	Coca-Cola	Ibuprofen has a pKa of 5.3. The pH of Coca-Cola is around 2.5. Ibuprofen remains largely unionised in acidic pH and thus is absorbed more from the stomach on administration with Coca-Cola.	Pharmacokinetic[59]
H_2 antagonists	Food	These drugs are preferably to be taken before food. If they are administered later, the acid already secreted in the stomach will cause therapeutic failure.	Pharmacodynamic[54]
Sedatives	Alcohol	Both of them are responsible for depressant-like action. Concomitant usage can result in severe psychological impairment.	Pharmacodynamic[58]
Mercaptopurine(MP)	Substances containing xanthine oxidase (XO)	XO inactivates MP. Cow's milk contains high levels of XO. Administration of cow's milk and MP could result in significant bioavailability reduction.	Pharmacokinetic[60]

DRUG DOSAGE ADJUSTMENT IN PAEDIATRIC AND GERIATRIC PATIENTS: Paediatric and geriatric patients represent two extremes of the human-age spectrum which are often ignored for dose adjustment. Almost all the time, clinical trials for new drugs enrol healthy volunteers or patients who are 18-50 years-old. This fallacy or pitfall leaves prescribers in a lurch when circumstances call for paediatric or geriatric dosing. Extrapolation/interpolation and empirical scaling or just hunches are often the guiding beacons for prescribers. Such practices are nothing short of treading on thin ice since miscalculations of drug doses could lead to serious consequences.

Paediatric dosage prescribing strategy: The term 'paediatric' covers several age groups. A useful stratification is the one proposed by the World Health Organisation (WHO): 1) preterm newborn infants; 2) term newborn infants (0-28 days); 3) infants and toddlers (>28 days-23 months); 4) children (2-11 years); and 5) adolescents (12-16/18 years) [61]. The variation in pharmacokinetic and pharmacodynamic parameters within the paediatric groups is overwhelming. For example, there are differences in gastric pH of neonates (6-8) and infants (1-4) [62]. Hence, bioavailability of acid labile drugs like penicillin could be increased in neonates. Such differences make prescribing an arduous task for physicians. The other factors which hamper production of paediatric formulations are [61, 63]:

- Undefined paediatric dosage requirements and lack of scientific evidence.
- Preparing multiple dose options to cater to the wide range of paediatrics.
- Low sale volume of drugs in comparison to adult medications. Thus, the manufacturers do not have a heavy return on their investment, and hence it is not considered a priority.
- Kids prefer liquid dosage forms but preparing a stable liquid formulation is cumbersome.
- Organoleptic properties of some drugs are difficult to mask in liquid dosage forms.
- Lack of placebo-controlled, double blind clinical trials done in children due to ethical and legal implications.

Due to such tribulations, over 60% of paediatric patients in hospitals and 90% of those in intensive care units receive unlicensed or off-label drugs [64]. Sometimes, such use is necessary, e.g., treatment of *Pseudomonas aeruginosa* pulmonary super infections in children with cystic fibrosis [65].

Paediatricians adjust doses for children by normalising adult dose using body weight (mg/kg), deciding the dose based on age or normalisation of adult dose based on surface area [66]. These methods do not take into account the pharmacokinetic changes that occur as the child grows. Physiologically based pharmacokinetic modelling (PBPK) and allometric scaling (AS) provide a more accurate picture of the dose required [66-68]. System specific PBPK models represent the human physiology by utilising mathematical equations and physiological parameters and considering physiological blood flow, organ volume and blood-organ partitioning. AS on the other hand, is a scaling approach which allows prediction of volume of distribution and clearance based on a power function whose exponent is derived using physiologically linked theoretical grounds [68]. The predictions made by computer based modelling software depend on the quality of the software, the data and the rationale of the data [68].

In order to enhance the acceptability of such models, an exchange of ideas between paediatricians and clinical pharmacologists is required [66]. Such process will increase the value of modelling systems and help in accurate prescribing of drugs in different aged children.

Geriatric dosage prescribing strategy: Geriatric patients with a thin and frail stature constitute a sizeable percentage of the population worldwide. Advances in medicine and technology have further increased the average lifespan of a person. But as the lifespan increases, so do the corresponding problems. An elderly patient often suffers from a host of illnesses for which polypharmacy is sought. Coupled with the major pharmacokinetic and pharmacodynamic changes, adverse iatrogenic reactions are just waiting to occur.

The major reasons for extreme vigilance while prescribing to elderly patients are [69]:

- The elderly have an increased prevalence of diseases.
- Multiple medications are often prescribed to treat co-morbid conditions.
- Under- and over-prescribing is common in elderly and frail patients.
- Altered drug responses occur in elderly patients due to gastrointestinal, hepatic, and renal changes.
- Non-compliance by the geriatric patient.

The pharmacokinetic changes occur in the absorption rate (delayed gastric emptying, less acid secretion), first pass metabolism (reduced level of hepatic metabolizing enzymes), drug distribution (increased body fat content, reduced water content, decreased serum albumin), and decreased renal and hepatic clearance. Pharmacodynamic changes occur due to altered receptor sensitivity (decreased α_2, β and cholinergic function, increase in benzodiazepine and warfarin sensitivity) and altered homeostasis (decreased orthostatic circulation, postural control, cognitive function, thermoregulation and visceral muscle control) [69, 70].

Physical limitations could result in non-compliance. Vision impairment results in failure to read the label or follow the dosage regimen, reduced strength and flexibility hampers bottle opening [71], and decrease in memory hampers remembrance of dosing intervals.

Therapeutic compliance can be achieved in numerous ways. Larger font labels, easy to dispense packaging systems and telephone reminders could go a long way in increasing compliance [71]. Since the geriatric patients are often looked after by multiple physicians and caretakers, development of an Electronic Medical Record (EMR) inventory, that is, creation of a database where all the medications prescribed to a patient are entered is the need of the day. This will prevent unnecessary or inappropriate prescribing and thwart the threat of drug-drug interactions [72].

It is imperative that needless polypharmacy be stopped, since the drug-drug interaction potential in geriatrics is 42.5-52.4% and this leads to almost 2.8% of all elderly patient hospitalisations [73]. Another need of the hour is "Intelligent polypharmacy". The prescriber should be knowledgeable enough to know that multiple medications are only needed when they target the disease by various pathways. Greater risk of side effects than benefits should be prevented while prescribing [74]. Good communication and record sharing of prescribed drugs among the attending physicians, nurses, and pharmacists should be encouraged.

Paediatric and geriatric patients will always be treated separately from the 'working age population'. Prescribing for them is a challenging and tedious task. What's required is comprehensive knowledge of pharmacology as well as pathophysiology of co-morbid conditions affecting the metabolic disposition of drugs and adjustment of dosage, as deemed necessary.

DRUG PRESCRIBING DURING PREGNANCY AND LACTATION: Pregnancy and lactation are the most awaited and wonderful events of a mother's life. It is during this stage when the embryo, foetus or the new born can be exposed to the mother's intake of prescription or non-prescription medications. Some pregnant women may suffer from chronic conditions, which may escalate during pregnancy or the post-partum period. Some mothers may develop complications at the time of delivery. Hence, drug administration might become necessary and justified [75]. On account of the thalidomide disaster, it is now known that a number of drugs have teratogenic potential and should be avoided during pregnancy [9]. It was the thalidomide tragedy of 1961-62 that led to the establishment of modern regulatory mechanisms of marketed drugs.

Classification of drugs prescribed in pregnancy: The US Food & Drug Administration (FDA) has evaluated the potential of drugs which are capable of causing birth defects if used in pregnancy, and has divided such drugs into five classes[75, 76]:

- Category A - Adequate and well-controlled studies have failed to demonstrate a risk to the

foetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

- Category B - Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women or animal reproduction studies have shown an adverse effect, but well-controlled studies in pregnant women have failed to show any foetal risk.

- Category C - Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks or no study has been conducted on animals and humans.

- Category D - Adverse reaction data from marketing or investigational experience or studies in humans have shown positive evidence of human foetal risk, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

- Category X - Studies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

This classification system has been shown to be limited in its use. Difficulties in translating pre-clinical results to the clinical scenario and lack of clinical trials in pregnant women are some of the reasons for limiting the classification's usefulness.

Hence, post-marketing surveillance remains a valuable tool for collecting safety and risk information of drugs used during pregnancy. Unfortunately, reporting is scarce and inaccurate due to some congenital or behavioural abnormalities being detected late in life [75].

In spite of such drawbacks, the post-marketing system is followed globally.

Pregnancy stages affecting drug action: Maternal exposure timing, drug dose, placental drug transfer, pharmacokinetic changes in the mother and pharmacodynamic effects of the drug all contribute to foetal action of the drug [76, 77].

Congenital abnormalities mostly occur if exposure to the teratogen occurs during the first trimester or the period of organogenesis, i.e., between the 18th day and 10th week of gestation 78. The drug dose should be minimised as much as possible to avoid embryo-foetal toxicity, and ideally it should be administered before pregnancy or when pregnancy is diagnosed [77].

Lipophilic, unionised, low molecular weight drugs cross the placenta easily [76]. Weakly basic drugs often are trapped in foetal circulation due to its acidic pH compared to maternal plasma [77]. Pregnancy- induced pharmacokinetic changes occur due to an increase in volume of distribution which reduces plasma levels of fat soluble drugs [76], increase in renal drug elimination [79], and decrease in maternal gastric emptying time which delays drug onset [76].

Drugs contraindicated in pregnancy: Certain drugs are known teratogens and are to be avoided at all costs during pregnancy. Use of these drugs may result in foetal harm. Table 4 enlists examples of such drugs.

TABLE 4: DRUGS CONTRAINDICATED IN PREGNANCY

Drug	Comments
ACE Inhibitors	Usage in the II and III trimester may damage the kidney and deform the face, limbs and lungs[76]
Paroxetine	May cause adverse cardiovascular effects[80]
Warfarin	Associated with fetal haemorrhage, nasal hypoplasia, microcephaly and mental retardation among other effects[81]
Chloramphenicol	Grey baby syndrome[76]
Lithium	Associated with increased risk of congenital cardiac malformations[80]

Drug use in Lactation: Breast milk is the most nutritious food an infant can obtain. The WHO advocates exclusive breast feeding for the first 6 months of life. Unfortunately, breast feeding is on the decline, especially in Western countries. One of the reasons could be maternal drug therapy, which results in unnecessary avoidance of breast feeding [77]. Drugs cross over into breast milk mainly by passive diffusion [82], although drug transporters are also being implicated [77]. Highly lipophilic, low protein bound and weakly basic drugs transfer more easily into milk [77, 82]. The amount and extent of drug transfer into breast milk is often measured by milk to plasma (M/P) ratio [82]. It is said that drugs with high M/P ratios are unsafe for the nursing infant, whereas those with low M/P ratios are safe. This is not always true and therefore, this parameter should only be a tool to predict the dose ingested via milk [77]. **Table 5** enlists examples of some drugs which are to be used with caution while nursing.

TABLE 5: DRUGS TO BE USED WITH CAUTION DURING NURSING

Drug	Comments
Sulfonamides	Can cause kernicterus [81]
Phenothiazine sedatives	Can induce sleep apnea and can increase risk of sudden infant death syndrome (SIDS) [82]
Clozapine	Increases risk of agranulocytosis, sedation and cardiovascular instability [82]
Clofazimine	Causes skin discolouration [83]
Anticancer drugs	Causes anaemia, diarrhoea and immunosuppression[83]

Prescription management of Teratogens and drugs excreted into Breast Milk: The most commonly prescribed teratogens or developmental toxicants include statins, anxiolytics, anticonvulsants, and antibiotics [84]. This suggests that many physicians seem to have lesser awareness regarding teratogenic medications. It is high time that health professionals be educated regarding teratogens and counsels their patients accordingly. To avoid any unintended harm, proper therapeutic monitoring of both the mother and foetus should be done during early pregnancy [75, 80].

Due to ethical and legal reasons, clinical trials conducted in pregnant women and nursing mothers are minuscule. This often reduces the body of data available about drug-related embryo-foetal toxicity and any detrimental effects on nursing. The information available today is based on case reports and post-marketing surveillance. This knowledge is useful, but still raises red flags regarding the overall safety of drugs used during pregnancy and lactation.

Pharmacovigilance of Herbal and Ayurvedic Products: Therapeutic products containing substances which are natural in origin or derived from plants are called herbal products. These formulations are increasingly being used as anti-diabetics, hepatoprotectives, anti-arthritics, memory enhancers and adaptogens [85].

Ayurvedic remedies also emerged from the relation between nature and man [86]. Since these products are natural in origin, it is commonly believed that they are safe, which actually inculcates a false sense of security [85]. These products have varying compositions and chemical properties [87], which not only cause different degrees of efficacy, but also harmful effects when used over prolonged periods. As luck would have it, natural product use is on the rise throughout the globe, spawning a multi-million dollar industry. WHO estimates current medicinal plants' demand to be around US$ 14.0 billion a year and to be nearly US$ 5.0 trillion by the year 2050 [88]. In India alone, around 7,800 facilities are involved in manufacturing natural health products and traditional plant-based formulations [88]. Although they are involved in export of these products, the number of industries actively following Good Manufacturing Practices (GMP) is debatable.

Many dietary supplements, natural health products, and *Ayurvedic* remedies have been found laced with synthetic pharmaceuticals as well as adulterated with heavy metals, pesticides, and microbial agents. Adulteration is defined as mixing or substituting the original drug material with other spurious, inferior, defective, spoiled, useless or other parts of the same or different plant or harmful substances or drugs which do not conform to the official standards.

A substance shall be deemed to be adulterated if it consists, in whole or in part, of any filthy, putrid or decomposed substance [89].

Some reasons for adulteration are [90]:

- Confusion in vernacular names between indigenous systems of medicine and local dialects.
- Lack of information about the authentic plant.
- Sourcing the authentic plant is tedious.
- Resemblance in morphology and or aroma.
- Careless collection of plant materials.
- Poor quality control and lack of Good Manufacturing Practices (GMP).

As mentioned earlier, herbal products and some *Ayurvedic* remedies are reported to contain heavy metals (arsenic, lead, mercury) [91], pesticides, microbes[88] and synthetic drugs [85].

Such contaminants could result in serious adverse consequences. For example, the presence of 0.1-0.3 mg of betamethasone per capsule was detected in some herbal products after a few patients developed corticosteroid-like effects [85].

Arsenic poisoning can result in nausea, abdominal pain, vomiting, liver damage, anaemia, muscle cramps, heart abnormalities and reduced motor nerve function, whereas lead poisoning can cause swelling of the brain and paralysis, weight loss, insomnia and dizziness.

Memory loss, slowed sensory and motor nerve function, tremors, insomnia and reduced mental function could result from mercury poisoning [92-94].

Proper authentication of the plant material used is important in order to avoid contamination and adulteration. The general analytical methods that can be used are Microscopy, Spectroscopy, Chromatography, Chemometry, Immunoassays and DNA fingerprinting [87].

As the modern world is slowly going back in time by looking into past knowledge for solutions, herbal and *Ayurvedic* products are touted as the next big thing. They are, as is pointed out by the intellect and texts of yore, useful and highly efficacious. But it is up to the modern researcher to utilise this treasure in the right manner.

Unfortunately, the long-term safety of self-medication with several functional foods and dietary supplements, *Ayurvedic* remedies, including their interaction with allopathic drugs, remains to be evaluated by well designed, placebo-controlled studies. Further, India should apply the similar pharmacovigilance standards to *Ayurvedic* products as is done for monitoring the benefits and risks of synthetic pharmaceutical agents.

Health risks associated with internet purchase of drugs: The internet is rife with all kinds of information. Understandably, the medicinal arena is also covered in depth. The internet has also made purchasing with a click possible. This has resulted in mushrooming of neighbourhood pharmacies moving to the domain of the World Wide Web and made trips to the store avoidable [95].

The anonymity and cheap prices offered by online vendors are enticing consumers and driving them online searching for bargains[96]. This practice is highly dangerous and could lead to fatalities. Indeed, the National Association of Boards of Pharmacy, (US-NABP), reported that 96% of online drug sellers are fraudulent and violate safe practices [97] with death also being on the cards. In 2009, a traditional Chinese anti-diabetic medicine was found to contain 6-fold higher than normal glibenclamide dose, which resulted in the death of two people and hospitalisation of nine [98].

Sometimes, the active ingredient was found to be missing in the internet bought drug (e.g., Avastin, US, 2012) [98]. Such saddening events have prompted regulatory agencies to warn against buying prescriptions over the web [97]. However, a few legitimate e-pharmacies are present. These are often registered with an official association, e.g., Royal Pharmaceutical Society in Britain [95]. Unfortunately, the regulation of e-pharmacies in India has not started as yet.

Neither any official guidelines nor any laws governing such websites have been formulated in India.

While the convenience offered by online pharmacies is high, a careful thought must be put to the safety aspect of such medicines. Internet pharmacies are burgeoning in India each day, with many of them claiming that their websites have reliable information about each drug and sell only with prescriptions. Such claims should always be taken with a pinch of salt.

PHARMACOVIGILANCE OF VACCINES: Vaccines are undeniably one of the greatest human inventions. Thanks to Edward Jenner who propounded the theory of vaccinations, humanity has made dreaded diseases like smallpox and polio, a thing of the past. While it's true that vaccinations have made disease control a possibility, many children from low-middle income countries do not receive all the WHO recommended vaccinations [99].

Since population mobility is increasing, it has become important to monitor the spread of diseases and their carriers. Such pharmacovigilance systems are on the rise, especially in low and middle income countries (LMIC). To further increase the penetration of such systems, WHO developed the Global Vaccine Safety Blueprint in 2011 [100]. The aim of this program is getting systems in LMIC up and running, providing enhanced capabilities for special situations and setting up a global integrated network[100].

When Dr. Albert Sabin formulated the live-attenuated oral poliovirus vaccine (OPV), trials were conducted on monkeys. Such procedures have been replaced by newer, more efficient methods utilising transgenic mice and concepts of molecular biology[101]. These faster procedures are the need of the hour for LMIC, where endemic diseases thrive due to lack of specific vaccines.

Vaccine manufacturers tend to focus on high income countries because of commercial gain [99, 102], since LMIC require affordable vaccines which present a challenge to manufacturers. To counter such practices, low cost vaccine manufacturers like Serum Institute of India Ltd. are involved in technology transfers and then mass production [102].

Vaccine production is required globally, but the financial resources and proper manufacturing facilities are available with a few. Therefore, increasing partnership between countries is required. Proper networking and exchange of ideas and products can help to solve a universal problem.

PHARMACOVIGILANCE OF GENETICALLY ENGINEERED PRODUCTS: Genetically engineered pharmaceuticals include recombinant human insulin, human growth hormone, calcitonin, parathyroid, glucagon, interferons and somatropin [103]. These products are of high molecular weight and immense complexity due to the multitude of proteins involved and their interactions [104]. It is important to monitor each production step and characterize the obtained product, as slight parameter tweaks can affect the final product's nature [105].

Since these products often use living organisms, disease transmission is a possibility. Hence, post-marketing surveillance of genetically engineered pharmaceuticals is an absolute requirement. US-FDA has made it mandatory for sponsors to report any serious and unexpected adverse effects within 15 calendar days [106]. EU and Indian guidelines require the sponsor to submit a Risk Management Plan that includes pharmacovigilance and adverse event reporting [104, 107].

Genetically engineered therapies are fast becoming widespread and efficacious. The time may soon come when the demand overshadows the supply. To spur the growth of such products, maintaining the post-market safety records is a prime concern, and therefore, pharmacovigilance programmes must include monitoring of adverse event signals of the new therapeutic agents licensed for marketing in India.

CONCLUSION: Pharmacovigilance in India is still in its infancy. To address the needs of the diverse and large Indian population as well as pandemic problems faced in the country, a well-designed pharmacovigilance programme at par with those of international drug regulatory bodies was required. In spite of several failures, strong efforts in recent years have ensured that the Indian pharmacovigilance programme is up and running.

Health professionals are gradually accepting the programmes and gaining adequate knowledge which will help them in the safe prescribing of drugs and monitoring the drug-induced adverse effects in hospitalised and ambulatory patients. As time passes, gathering of made-in-India pharmacovigilance data might become a top priority in the management of risks and benefits of drugs prescribed by Indian physicians and surgeons. Such pharmacovigilance information will be highly useful for the Indian drug regulators in making evidence based scientific decisions about drug acceptance or withdrawal from the market.

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