

# Accentuating the Role of Pharmacovigilance and Ecopharmacovigilance in Context to Man and Ecology - A Review

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**Abstract:** *A pharmaceutical drug is a drug used to diagnose, cure, treat, or prevent disease. World is witnessing the increased production of pharmaceutical drug to meet the demand of ailing and sick population. Pharmaceutical drugs are dynamic in the biotic system and nature and may sometime induce adverse reaction, which may threaten not only the targeted species but also non targeted species of both terrestrial and aquatic forms. Pharmacovigilance plays a pivotal, prominent and stupendous role in ensuring the drug safety through identification, quantification and documentation of drug-related inconvenience; helping the diminution of drug-related ailment and delivering secured healthcare systems. Pharmacovigilance works on the facts, information and understanding, feature and mechanism of drug linked injury. World Health Organisation emphasized Pharmacovigilance as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'. Pharmacovigilance holds the task of imparting information to clients, practitioners and controller on the safety and handling of drug related issues, fabricating programmes for effective use of drugs and measures, gathering and considering information from patients and clinical experts. Environmental pharmacology or Eco-pharmacology is a relatively new and emerging specialty of pharmacology dealing with the adverse effect of these drugs on the environment and its components.*

**Keywords:** Pharmacovigilance, ecopharmacovigilance, adverse effect and pharmaceutical drugs

## 1. Introduction

World is witnessing the manufacture of innovative drug encapsulated with the greater efficiency and superiority capable of addressing wide range of health related ailment, which intern depend upon rigorous clinical research and trials pertaining to drug usage, reactions and safety. Pharmaceuticals are the potent group of chemical substances and are designed to bear biological effects at low concentrations (1). Bio transformed pharmaceutical products may persist in the environment and may actively accumulate in the food chain (1) and (2). Long-term presence of antidepressants and other pharmaceuticals have been traced in rivers and lakes (3). Excreted or discarded pharmaceutical product enters the urban wastewaters and finally goes into wastewater treatment plants. Some of the pharmaceutical products may show relative resistance to degradation (4) and mixed or sequestered into the biosolids (5), (6), (7), (8), (9) and (10). Municipal biosolids when applied to agricultural land, the contaminants present in it may percolate down to ground water. Previously, pharmaceuticals have been detected in fields that had been irrigated with treated wastewater (11). Veterinary pharmaceuticals can be transported into runoff from land receiving animal manures (12), (13) and (14). Biosolids that are applied to agricultural fields have the potential to be transported in surface runoff and may enter the food chain. Thus, tracking the drug movement and associated toxicity in the ecosystem holds the paramount importance. Pharmacovigilance is 'The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem' (15). Pharmacovigilance plays a

significant and vital role in conducting clinical research for ensuring the drug safety not only during the production phase but also during post marketing phase (16) and (17). Reliable pharmacovigilance is critical to construct trustworthy information ensuring the safety of wide spectrum of medicines and for the fabrication of appropriate guidelines for safe use and handling of drugs. Pharmacovigilance helps in the identification of possible short term and long term effect of drug use (18). Pharmacovigilance works to reduce the adverse drug reactions by identifying understanding the mode of reaction and mechanism of drug. Adverse drug reaction can be quoted as "A response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function (19) and (20). Pharmacovigilance also deals with polypharmacy, iatrogenesis, paradoxical reaction (21). Pharmacovigilance is known to India since 1998 (22). Presently scope and range of the pharmacovigilance has become widened with the inclusion of herbal medicines, traditional and complementary medicine, blood products, biological, medical devices and vaccines. Ecopharmacovigilance is the new and emerging science in pharmacovigilance, deals with the adverse effect of pharmaceutical products on environmental entities. India can become a hub for clinical research trials and activities due to its ever increasing population, high enrolment rate and low cost (22), (23), (24) and (25). Adverse effect of pharmaceutical drugs on the environment and non targeted biological entities is relatively less studied, The world has witnessed the stunning decline in the vulture population across the Indian subcontinent due to

adverse drug reaction (diclofenac) on the non intended species and may probably take several years to restore the vulture population to its original level. Who knows? how many species of such avian and animals are being suffered, unnoticed by the human being, craving the need for an efficient and well network of ecopharmacovigilance to be developed in the line of pharmacovigilance to assess the impact of various pharmaceuticals on the environment and its components.

A concept of combining pharmacovigilance and environmental pharmacovigilance is intended to focus attention on envisaging the impact of pharmaceutical drugs on environment and non targeted species. This science is also known as pharmacoenvironmentology or ecopharmacology.

Following the effective pharmacovigilance of the drug on the intended target species, subsequent role of ecopharmacovigilance begins to assess the effect of these drugs on environmental components and biodiversity. Thus, understanding the science of pharmacovigilance and ecopharmacovigilance, its aim, importance in upholding and sustaining healthy society, biodiversity, illuminating awareness regarding the safe drug usage and its effect on the environment, present trends and future prospects ought be ornately discussed.

Pharmacovigilance and environmental integrity are intimately allied to each other. There are two major dimensions to their interrelationship, one is addressing the ecological effect on the non targeted species and second is to address the ecological exposure. The study and monitoring of adverse drug reactions indeed provide valuable information pertaining to effect of drug pertaining to environment, biology and biodiversity.

## 2. Role of Pharma Covigilance in Context to Man

The efficient pharmacovigilance has greater potentiality to reduce or minimize the entry of drugs in to the environment. Sighting the importance, detailed feature of pharmacovigilance has been elaborately discussed as follows.

## 3. Aims of pharmacovigilance

Pharmacovigilance stands and works on definite and basic aims, are as follows

- Caring the patients and clients regarding safe use of medicines (26).
- Preventing possible harm to the patients, monitoring the effectiveness and adversities associated with drug during manufacturing and post manufacturing phases.
- To keep the record of severe or extreme adversity of drug usage.
- Betterment of public health and safety by rendering safe drug.
- Evaluating positive, negative, efficacy and risk associated with the medicine.

- Bridging the effective communication between the pharmacovigilance and public by educating them, with respect to role and importance of pharmacovigilance(17).

## 4. Task of pharmacovigilance

Safety monitoring in the clinical trials by gathering crucial information pertaining to drug adversities and considering the clinical examination report of the patients is regarded as the fundamental task of the pharmacovigilance(27). Safety assurance pertaining to new drug through pharmacovigilance takes into account wide range of aspects, including performance aspects of clinical trials, safety aspects of medicines *viz.*, complementary, traditional and biological medicine. Timely identification and drafting the report on the adverse drug reaction and ensuring the patients and client about the drug safety and handling of the drug holds paramount importance in this regard (27) and (28).

## 5. Adverse Drug Reaction

An adverse drug reaction (ADR) can be defined as harm associated with the use of given medications at a normal dose (19) and (20). Deafness and kidney failure associated with gentamicin (an antibiotic), bleeding of the intestine associated with aspirin therapy, dementia associated with heart bypass surgery, depression or hepatic injury associated with interferon, glaucoma associated with corticosteroid based eye drops, hair loss and anemia associated with cancer chemotherapy, headache associated with spinal anesthesia, hypertension associated with ephedrine, liver damage from paracetamol, stroke or heart attack associated with sildenafil (Viagra) when used with nitroglycerine, insomnia caused by some stimulants, irreversible peripheral neuropathy associated with the use of fluoroquinolone medications (29), (30) and (31), spontaneous tendon rupture associated with fluoroquinolone drugs (32) are the some of the instances of adverse drug reactions.

## 6. Polypharmacy

Conditions which involves, using multiple medications by a patient is called polypharmacy and sometimes end with the adverse drug reaction and reactions arising from the drug-drug interaction, resulting in the unexpected by product of the active ingredient. Act of polypharmacy can be profoundly noticed in the elders, aged psychiatric patients, those who are guided by several physicians and pharmacies (33) and (34) and patients with low educational background (35) are more prone to polypharmacy.

## 7. Iatrogenesis

Is the unintended and unpleasant health complications caused by administration of particular medicine while undergoing treatment. The act of iatrogenesis may be caused by chance, medical blunder, disregard and through the interactions of prescribed drug by the physician. Death toll ranging from 120,000 to 225,000 per year has been reported in United States due to iatrogenesis (36). In psychology point of view, iatrogenesis can occur due to misdiagnosis (37). Different conditions of the patients attributed as

iatrogenic comprises of fibromyalgia (38), posttraumatic stress disorder (39), dissociative identity disorder (37), bipolar disorder (40), somatoform disorder and substance abuse, antisocial youths (41), and chronic fatigue syndrome (42) and (43). The main factors leading to problems were inadequate patient evaluation, lack of monitoring and follow up and failure to perform necessary tests (44).

## 8. Paradoxical reaction

It is the condition involving opposite drug reactions induced by the drug during medication. For example, benzodiazepine in susceptible individual may induce anxiety, aggressiveness, convulsions, violent and even criminal behaviour (45).

## 9. Post marketing drug surveillances

It is the process of monitoring the safety of a pharmaceutical drug or device after it has been released in the market (27). Rosiglitazone was withdrawn in Europe in 2010 for inducing heart attack, similarly drotrecogin/alfa withdrawn by Lilly in 2011- prowess shock study, Rimonabant in 2012 was withdrawn for inducing depression and risk of suicidal tendencies, sibutramine was banned in 2012 for inducing heart related side effect (46). Previous records revealed several instances of adverse drug reactions and associated risk after the release of drug into the market (26).

## 10. Pharmacovigilance in India

Even though the clinical research and Pharmacovigilance raised its head in 1996 and 1998, respectively, the real initial boost in the field of clinical research began with the large scale clinical trials in 2005. Series of clinical trials with proper supervision and regulation were executed; efforts were made to develop new treatment therapy. The studies of the clinical trials are structured and supervised to evolve and ensure safety and efficacy of a new drug or therapy and are tested in an effort to develop new treatment formulations that will help those who are distressed with the targeted ailment. World saw India as the better destination for conducting global clinical trials (47). Indian clinical market characterized by the large availability of patient populations, an extensive array of disease, lower expenses of operation and a congenial financial and intellectual property environment. Clinical research and pharmaceutical industry have achieved tremendous escalation worldwide by innovating and launching new drugs in the market (48). All the clinical trials are organised and supervised as per the guidelines issued by ICH GCP and the respective country where the trial is being conducted (49). India achieved new dimension in the area of clinical trials in 1997 when it joined WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Three centres were designated for monitoring Adverse Drug Reaction

- National Pharmacovigilance Centre, Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi
- KEM Hospital, Mumbai and
- JLN Hospital, Aligarh Muslim University, Aligarh (50).

Pharmacovigilance centre was established in India in 2002. National Pharmacovigilance Programme for India was formulated which was sponsored by WHO and funded by World Bank (51), established in January 2005 to be supervised by National Pharmacovigilance Advisory Committee, based in the Central Drugs Standard Control Organization (CDSCO), New Delhi (52). Pharmacovigilance programme of India was initiated in 2009-10.

## 11. International Collaboration

Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden, emphasized its member nation to strictly follow the guideline and timely reporting of adverse drug reactions encountered in the patients. The main task of the Uppsala Monitoring Centre is assembling, considering and communicating information pertaining to significance, impairment, efficacy and peril of drugs usage based on pharmacovigilance programme being carried in the member countries (53). The Council for International Organizations of Medical Sciences (CIOMS), through its Working Groups, intended to issue the safety guidelines on the drug usage and drug related ailments. Report of the CIOMS is used as a reference for budding future drug regulatory strategy and events (54).

## 12. Confronting the present trend of Adverse Drug Reactions

India is being reported to encompass more than 6,000 licensed drug manufacturers and over 60,000 branded formulations and stand fourth in pharmaceuticals production in the world (55). India, a developing country with the ever increasing population and wide spectrum of disease in different age group, crave for an efficient pharmacovigilance system, with the credentials of protecting the ailing and distressed unhealthy section of society with the release of novel drugs, emphasizing the decisive role of pharmacovigilance.

Adverse drug reactions are regarded as one among the leading factor causing more number of deaths (56), (57), (50), (45) and (51). Majority adverse drug reactions are not recognized and documented by the physicians on admission of the patient and may result in bereavement of huge number of patients.

## 13. Future prospect towards enhancing the efficacy of pharmacovigilance

- Fabricating the stringent regulatory measures, emphasizing timely consideration and reporting the event of adverse drug reaction.
- Taking into account the public health with the greatest regard.
- Conducting drug safety surveillance programme, timely and efficiently.
- Conducting post marketing surveillance programme, proficiently.
- Pharmacovigilance should make use of innovative and latest technology in understanding the drug reaction.

- Introducing the stringent pharmacovigilance inspection measures.
- Conducting national and international discussions regarding the scientific status of Pharmacovigilance.
- Maintaining the standard data base of all the pharmaceutical companies including the drug produced by them.
- Edification and guiding medical apprentice, pharmacists and nurses in the area of pharmacovigilance.
- Adopting latest and innovative tools of information technology in disseminating the idea of drug safety and pharmacovigilance.
- Instituting the network of Pharmacovigilance and pharmacoepidemiologists.

#### **14. Ecopharmacovigilance and ecology**

Discharge of pharmaceuticals in to the environment has become the matter of great concern. There is an immense need of developing research for producing a target specific drug and preventing adverse effect of pharmaceuticals on the environment and non targeted species, through ecopharmacovigilance. Previously diverse spectra of pharmaceutical drug traces such as those of anti-inflammatory, antidepressant and synthetic hormones have been detected in the soil, sediments, sewage water, underground water etc (58), (59) and (60). Detailed account of adverse impact of discharge of pharmaceuticals drugs and the possible impact on environment, biology and biodiversity and the role of ecopharmacology have been elaborately discussed.

#### **15. Impact of pharmaceuticals on environment and biology**

The antidepressant fluoxetine (an active ingredient in Prozac), after being excreted by the medicated human being is sometimes partially metabolized and incompletely degraded in the sewage treatment process and makes the organism being exposed to the partially degraded chemical, when the same sewage water used for the domestic purpose (61), (62) and (63). It (fluoxetine) has bioconcentration factor (BCF) of over 1000 in freshwater mussels *Elliptio complanata*, consumed by many vertebrate predators (64). Pharmaceutical drugs traces present in the biosolids when applied to the agricultural fields, may also take entry into the plant or remain attached over the external surface of the leaves may substantially harm the herbivores (65), (66) and (67). Some of the cationic drug components present in the soil may bind to the negatively charged clay particles (61) and (62) and accumulate in benthic or terrestrial ecosystem (61). The non-steroidal anti-inflammatory drug (NSAID) diclofenac known to cause the harmful effect in raptors (58) and (68).

Wider study has been conducted on the adverse effect of pharmaceutical drug exposure on freshwater taxa (69), (70), (71), (72) and (73) compared to terrestrial (66), (74), (75) and (76) and marine (69) and (60) species. The processes such as metabolism, distribution and excretion should be considered while assessing effective pharmaceutical dose (blood plasma or tissue concentrations) (68) and

bioaccumulation potential (71). The sources, pathways and food webs in terrestrial and freshwater systems should be effectively studied to assess the level of exposure of wild species to pharmaceutical drugs (66). Exposure of pharmaceuticals and its uptake within marine and estuarine ecosystems is relatively understudied (66). Pharmaceutical drugs have the potential to move through food chain, for instance, diclofenac (an NSAID) and propranolol (a beta-blocker) have BCFs of 10-180 in blue mussels *Mytilus edulis* (77). Waste water treatment plants habitats emergent insects that attract large number of bats compared to riparian foraging habitats (75) exposing large number of bats, birds and insectivores (76) to human pharmaceuticals, derived from the sewage water. Presence of higher level residues of barbiturates in carrion of euthanized pets may exceed the lethal dose for a range of scavenger and induce secondary barbiturate poisoning (62). The scavenging mode of Asian vultures and their relative sensitivity towards some NSAIDs caused near extinction of three keystone species (58) and (68).

The whole world witnessed the adverse reaction of diclofenac drug on the wild vulture population, resulted in stunning decline in the Gyps vulture in Indian subcontinents. It (diclofenac) is a NSAID advocated for use in painful and inflammatory rheumatic and certain non-rheumatic conditions. It is available in a number of administration forms which can be given orally, rectally or intramuscularly (78). Symptoms encountered by the diclofenac intoxicated vultures include lethargy, perch sitting with ruffled feathers, closed eyes and inability to raise the head and neck (dropped head) (79). Within approximately 12 hours the bird enters a catatonic state and becomes highly dehydrated due to the kidney failure. Intoxication by diclofenacin vultures causes necrosis leading to reduced excretion of uric acid, renal failure and visceral gout, and death within a few days after exposure (80) and (81).

Antidepressants and other psychoactive drugs bear adverse effect on living components of aquatic ecosystem (82). Such compounds are heavily prescribed and known to slowly degrade in the environment (59). Carbamazepine, which is used to treat epilepsy and bipolar disorder, is extensively present in sewage contaminated ecosystems (84) and (71). Behavioural modification in predators and prey is noticed after being exposed to psychoactive medication, may potentially harm aquatic food chains and ecosystems (82).

#### **16. Pharmaceutical Drug and Agricultural Ecosystem**

Over 4000 pharmaceutical drug of both medical and veterinary health care including growth promoting substances (2) consequently reaches the sewage system and environment through the excretion of medicated animal (59). Some of the non degraded pharmaceutical products may get sequestered in to the biosolids, which consequently applied to farm lands (59). Of the 5- 7 million tonnes of biosolids annually produced in the USA an about 60 % of biosolids are applied to the farm land (85) and (86). In the dry areas with profound water scarcity the aqueous sewage is being used to irrigate the crop (87). The dung and urine derived out of medicated live stock when used as the

fertilizers for the agricultural crop, may adversely affect the soil environment (88). In India and many parts of the world cow dung and animal manures are used as fertilizer and are incorporated in to the soil (Fig1) and (Fig 2).



**Figure 1:** Animal manure heaped on farm land for agricultural use



**Figure 2:** Spreading and incorporation of animal manure in the agricultural field

In urban areas, treated sewage water is used to water the lawns; gardens and golf ground, make the organisms being exposed to the pharmaceutical products (66), (88) and (89). The anticonvulsant drug carbamazepine is known to persist in soil environment unchanged for at least 40 days and be taken up into crop plants, accumulating particularly into leaves (62).

## 17. Role of ecopharmacology

Ecopharmacology has the decisive role to play at this juncture in the matter concerning the assessment of adverse effect of pharmaceutical drug on the environment and biology and to prevent the further sacrifice of non targeted species.

## 18. Activities under the ecopharmacovigilance

- Assessing the environmental data pertaining to the pharmaceutical product.
- Assessing the adverse effect of pharmaceutical product on the environment.
- Tracking the possible mode or route of drug exposure into the environment.
- Accurately identifying the risk.
- Drug risk assessment throughout the drugs life cycle.

- Identification and reporting the vulnerable and susceptible group to prevent further exposure from pharmaceutical drug in an adverse way.

## 19. Prioritizing the ecopharmacology

It is bit obligatory to assess the potentiality of an active pharmaceutical ingredient (API) to arrive at its protein target i.e. an enzyme or receptor, including information on adsorption, distribution, metabolism and excretion of drug. Thus there is a need to understand howwell the molecule's active site (ligand) binds and interacts with the target (90).

Environmental regulation of pharmaceuticals has been given paramount importance in China (91), Europe (92) and (93), North America (94), Canada (95), and Japan (96). Despite of strict regulations have been installed for the environmental risk assessment and approval of pharmaceuticals, there is a bequest of untested products prevailing in use globally. There has been an insufficient data and report available in the developed and developing countries regarding environmental monitoring and regulation regarding presence of active pharmaceutical ingredient in the sewage water and sewage sludge (97). The budding evidence regarding the persistence of steroids in the environment and their potentiality to bring on biological effects at low concentrations in a wide range of taxa, including humans has significantly attracted the all legal, ethical and scientific environmental intellectuals across the globe (98).

Pharmaceuticals can break down into numerous metabolites within patients and transform into different byproducts in the environment, but their risks stays poorly understood. Many non targeted species get exposed to pharmaceuticals through multiple routes and with the complex mixture of compound, make the researchers to recognize the path of exposure quite challenging (99). Current facts concerning effect of pharmaceuticals in the environment and animal ecology, is based on research in Europe and North America (100). Factors, such as climate, culture, ecology and also existing regulatory frameworks of the respective country determine the effective supervision and excellent execution of ecopharmacovigilance that means that the risks prevailing in Asia and other developing countries may oblige different research approach and management solutions in addressing the menace effectively (100).

## 20. Conclusion

All the creatures existing on the earth has the legal, moral and ethical rights to exist, survive and reproduce as man does. Activity of human being has already deteriorated natural ecological balance and threatened survival of many wild species to death. Threat posed by the pharmaceutical drug to the environment and biodiversity is even though old perception but research in the field of ecopharmacovigilance is less exploited compared to pharmacovigilance. Ecopharmacovigilance ought to be addressed with different dimensions and technology to render the delivery of truly safe drug not only to human being but also environment and non targeted species.

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