

General Review of Ecopharmacovigilance (EPV)

Dr. S. Sreeremya

Faculty of Pharmacology

Department of Pharmacology

Crescent College of Nursing, Palakkad, Kerala, India

Email ID: *sreeremyasasi@gmail.com*

ABSTRACT

As there is a paradigm shift in the area of pharmacology, pharmaceutical industry is booming year on year. The cases of pharmaceutical pollutants landing the environment is also increasing in alarming rate. So, the stream of ecopharmacovigilance (EPV) is a department working inside the pharmaceutical industry, to check the pollutants released and direct the pharam industry towards sustainability.

KEYWORDS: *ecopharmacovigilance (EPV), department, pollutants, pharmaceutical industry, sustainability*

INTRODUCTION

The Burden of Improper Disposal of Pharmaceutical Waste

Over time, little attention has been paid to the environmental impact of pharmaceuticals and the effluents released by pharmaceutical industry. Until recently, very few studies and analysis have estimated the burden of the pharmaceutical products on the environment; these studies are limited to a few countries. The methods availed were often non-standardised, making comparisons difficult. Drug usage in both humans and animals is ever aggrandizing.

One study projects that the global consumption of the veterinary antimicrobials will be more than 100,000 tons by 2030. Earlier reviews, mostly from high-income countries, demonstrated the presence of the pharmaceuticals in water bodies. However, one of the most extensive studies and further research estimates the presence of medications in 1052 rivers across 105 countries showed that the most contaminated rivers were in the low-middle-income countries of the sub-Saharan Africa, South Asia, and South America (Tudor TL

et al.,2022).

Ecopharmacovigilance (EPV)

Ecopharmacovigilance (EPV) is a new area of interest in the current healthcare systems. Presently, very little focus or debate is made on this stream of science in our country. Contrary to PV no stringent regulation are made in this topic. Ecopharmacovigilance (EPV) is the science rakished to understanding, detection and the assessment activities for prevention of adverse effects or other problems due to the existence of the pharmaceuticals in the environment. As India became the pharmacy of the world making stellar growth over the years, more discussions and analysis are needed in this area as it is the need of the hour (Trueman P et al.,2022).

Pharmaceutical pollutions has become a serious concern to our eco system, affecting the small animal species to even human beings who stand in the top of the food chain. According to WHO, the unscientific disposal of expired, leftover, substandard, spurious and the adulterated medicines is one of the most significant causes for antimicrobial resistance among the animals and human beings. Other issues reported include declining population of vultures, the feminization of male fishes, sterility in frogs were also reported. A large percentage of the medicines synthesized are not consumed by the patients and get expired. For example, data from the European nation, named Germany showed approximately 10% of medicines sold in the country were disposed of in household waste.

The Unused medicines can be stored by many individuals for later use when needed, especially for the minor ailments (Tiseo K et al., 2020). This behavior may not always be appropriate and depends on the specific type of medicines, duration of use and instructions from the provider. Stored in households can be helpful in case of emergencies and reduce the physician visits and are thus considered as cost-effective and convenient.

There are many reasons for medicines not being completely availed such as patient's recovery from a disease, greater number of medicines bought as compared to the need, the death of the patient, fear of the medicine's adverse effects, poor patient compliance, and forgetfulness. These unused medicines are specifically stored in homes and may ultimately pave to wastage of medicines. There is a high probability that these unused medicines may be

discarded in a specifically inappropriate manner that can harm the environment. Long-term exposure to various types of the medicines in the environment can cause toxic effects to the water system and can also even affect aquatic animals, plants and microorganisms (Dr. Amiya et al.,2021). Physiochemical analysis of water is the main source by which the properties of water can be identified (S.Sreeremya, 2018a).

Many methods can be implemented to get accurate result (S. Sreeremya, 2018b). Use several living organisms also help in waste water treatment (Dr. S. Sreeremya, 2020a). The biodegradable efficiency of various pharmaceutical components has to be checked and assessed (Dr. S. Sreeremya, 2020b) prior to leap into the stage of commoditisation (Dr.S.Sreeremya,2024a). The history of pharmacology is the initial step which has opened the doors of other sub streams in pharmacology like Eco-pharmacovigilance (Dr. S. Sreeremya, 202b).

NEED FOR EPV IN DEVELOPING COUNTRIES INCLUDING INDIA

Though it is impossible to precisely eliminate pharmaceutical entry into environment through human and the animal excretion, it is possible to reduce the entry through hospital wastes, improper disposal of unused drugs and the wastes emerging from manufacturing industries. Considering the established facts of the detrimental effects caused by pharmaceuticals entering the environment, there is a need for setting up of a strong law and rules concerning eco-pharmacovigilance (Evren Şavlı1 et al., 2019). In recent years, an approach termed the eco-directed sustainable prescribing (EDSP), which was proposed to specifically prevent the adverse effects of APIs in the environment resulting from the medical prescriptions, has been well-accepted as an indispensable part during the EPV implementation.

Ecopharmacovigilance, as a kind of pharmacovigilance for the environmental, aims to specifically monitor the adverse effects of pharmaceuticals both on the environment and on the humans through indirect non-therapeutic exposure.

Conclusion: India is struggling to mainly balance economic development and environmental protection. EPV provides useful reference for the disposal of the environmental issues allied with pharmaceuticals in the environment in a timely way. Compared to the west, EPV in india is in infancy. Nations have to build some perfect laws and regulation system on EPV,

defining the evaluation index for the EPV, continuing the clinical rational medication, and the pharmaceutical take back programs popularizing the concept of the EPV and strengthening the policy-guided and scientific researches of EPV in pharmaceutical firms and academia. The Medical Expert Systems have reached good performance, as "MYCIN, for diagnosing of the bacterial infections"(Vidhi Gautam, et al.,2018).

INTEGRATION OF CONCEPTS

Pharmacovigilance comprises a whole range of the routine activities and an expanding scope of unique activities beyond the regular reporting of the Adverse Drug Reactions. As described in the EMA Good Pharmacovigilance Practices guide-lines, rules imposed, additional pharmacovigilance activities have been recommended to typically identify delayed safety concerns. Some regulatory agencies such as the EMA¹³ require the manufacturer to conduct a risk analysis that estimates the concentrations that will be found in the environment in order to gain the market approval. Low concentrations (defined by USFDA as less than one part per billion) are assumed to pose only the acceptable risks (but still a risk!). Researchers know that pharmaceuticals' environmental impacts are often so slow and inconspicuous that they go unnoticed until it is very late. The Eco-pharmacovigilance could very well be proposed as an additional risk minimisation activity.

Some authors and researchers have proposed targeted implementation focusing on the monitoring of the occurrence of the high-priority pharmaceuticals in environmental samples, the management of primary emission sources, the legislation and research on high-priority pharmaceutical pollutants, as well as the targeted educational strategies for the specific vital populations. These proposals, in turn, can mainly influence the health of these animals and eventually humans (Jun Wang et al.,2020).

Environmental effects

- **Disruption of Ecosystems:** The Pharmaceuticals can disrupt the delicate balance of aquatic ecosystems. The Trace amounts can affect wildlife in various ways, impacting there
- **Reproduction:** Hormones and the other medications can interfere with fish and amphibian reproduction.
- **Behaviour:** The Antidepressants and other drugs can alter animal behaviour, making

them more susceptible to predators. Development: Certain drugs can precisely cause developmental problems in aquatic organisms (Avinash D et al.,2013).

Antimicrobial resistance

The widespread use of major antibiotics in humans and animals contributes to the rise of antibiotic-resistant bacteria in the environment. These "superbugs" become much more difficult to treat, posing a threat to both human and animal health. The Examples of Contamination: A 2022 study revealed that the pharmaceutical pollution threatens "environmental and/or the human health in more than a quarter of the studied locations" across various rivers worldwide.

Addressing the Issue: The Safer Disposal Practices: Proper disposal programs for unused medications are essential to mainly minimize environmental contamination. Eco-friendly Drug Development: The pharmaceutical industry is much exploring ways to many design drugs that biodegrade more readily, reducing their environmental impact.

The Improved Wastewater Treatment: Upgrading wastewater treatment facilities to remove pharmaceuticals more effectively is crucial. The Regulation and Monitoring: Stricter regulations on the pharmaceutical manufacturing and disposal, along with ongoing monitoring of environmental levels, are necessary. The Regulatory frameworks play a critical role in specifically establishing and maintaining a robust eco-pharmacovigilance system.

Here's how they contribute: The Role of the Regulatory Frameworks

1. Standardization and Data Collection

The Regulatory frameworks define clear guidelines for conducting environmental risk assessments (ERA) of the pharmaceuticals before they reach the market. These guidelines establish standardized methods for testing bio-potential environmental impacts, facilitating the data collection and comparison.

The Risk Management and Mitigation: Frameworks can mainly mandate specific actions based on the identified risks. This could include. The Restrictions on the use of certain drugs in specific contexts (e.g., limitations on the veterinary antibiotics). Requirements for safer disposal practices (e.g., take-back programs for the unused medications). Development plans

for more environmentally friendly alternatives.

Improved Monitoring and Reporting: The Regulations can require pharmaceutical companies and healthcare providers to report suspected environmental impacts associated with drug use. This data is crucial for mainly identifying emerging problems and informing future risk assessments and policy changes (Bikash Medhi et al.,2012).

MAJOR CONSEQUENCES

The Exposure of both humans and animals to drugs in the environment can impact them directly or indirectly, with the microbial resistance being a primary concern. Prolonged exposure to low doses of the antimicrobials through sources like drinking water has the potential to induce resistance. Certain high-risk populations, such as the children, pregnant women, the elderly, and individuals with renal or the hepatic insufficiencies, may face a higher risk due to altered pharmacokinetics, where even the minor doses can prove toxic. In addition, some drugs even in very small doses may mainly exhibit synergistic actions.

Moreover, the possibility of a Type B (bizarre) adverse reactions and the Nocebo effect cannot be ruled out at subtherapeutic concentrations in the environment.



Figure: 1

The vulture population in the Indian subcontinent has been quite significantly declining due to indirect exposure to diclofenac (Fig-1). The Diclofenac was used indiscriminately for treating livestock. The vulture population is drastically reduced as a result of the kidney failure following their consumption of animal carcasses that contain the diclofenac residues. The Residual diclofenac is the result of indiscriminate use of this medicine in animal

husbandry. Governments and the nongovernmental organizations have taken action to protect these vital scavengers, paving to assignment of endangered status of these birds. In India, ban on diclofenac for veterinary use has been mainly implemented. The presence of minute amounts of sex steroids from the oral contraceptive pills in surface water has induced sterility in frogs. Their number is decreasing. This contaminant is also mainly resulting in the feminization of male fishes (Cuklev et al.,2011).

In veterinary practice, ivermectin is availed as an antihelminthic. When expelled through feces, it adversely affects organisms like the dung beetles. Some researchers have sought to establish a link between the concerning the decrease in sperm count in humans over the past five decades and inadvertent exposure to various drugs in the environmental terrain. Not only the drugs but also the excipients and additives availed in formulations may pose environmental threats (Cuthbert et al.,2005).

EDSP

Eco-directed sustainable prescribing (EDSP) is a ecofriendly method of lowering the environmental impact of active pharmaceutical ingredients (APIs). The EDSP is certainly one of the most pivotal steps in the eco-pharmacovigilance (EPV) program. In some of the recent polls, majority of the physicians felt that there is a much higher percentage of Apisin the environment. They were concerned about the bio-potential environmental impact and ecological concerns linked with API residues, and they backed the effectiveness and the necessity of EDSP under the eco-pharmacovigilance with the hopes of reducing API exposure in the environment. The Physicians expressed an interest to get involved in EDSP practices in the future (Dr Niroop Revannasiddaiah et al.,2015).



Figure: 2

IMPACT OF ANTIBIOTICS

Antibiotics, which are a significant part of contemporary medicine for both humans and animals, are designed to have desirable or the helpful effects on disease infections caused by pathogens. Antibiotics, like the other pharmaceutical chemicals (Fig-2), are tiny organic polar molecules that are generally ionizable and must be mainly removed by metabolism or biotransformation. Urine, feces, or a combination of both mostly excretes these chemicals and their precise metabolites. Domestic home, urban, hospital, the industrial wastewater, aquaculture, and extensive medicated livestock production are the main biosources of antibiotic contamination. They may enter natural surface-ground water in measurable but the very minute concentrations since present sewage treatment systems are unable to effectively remove them.

Apart from the other contaminants, antibiotics can disrupt the micro ecosystem by increasing the diversity of the resistance. Ibuprofen, diclofenac, naproxen, the acetaminophen, and ketoprofen were the top five most common non-steroidal anti-inflammatory drugs (NSAIDs) present in the environment, that paved the way to the decrease in vulture population as per a study. Observation from the adverse environmental impact of pharmaceutical compounds.

1. Groundwater in the Toansa village of Punjab, India has been observed to be contaminated up to a depth of approx. 100 feet.
2. Diclofenac sodium caused vultures to die in the Indian subcontinent.
3. The Male fishes were feminized by ethinyl estradiol.
4. Spawning in shellfishes by Fluoxetine.
5. Frogs were killed by the contraceptive tablets.
6. Aggression caused in Lobsters due to the anti-depressants.

Pharmaceuticals are certainly prevalent environmental contaminants that can be mainly released into the environment through a variety of methods, including patient excretion through the sewer system and manufacturer or hospital releases into waste waters. The study of the antibiotic resistance in the environment is currently very significant to the researchers. The aggrandizing sensitivity/resolution of chemical and analytical methods, such as ultra-high-performance liquid chromatography/the quadrupole time-of-flight mass spectrometry (UHPLC-QqTOF-MS) and the long adsorption time detections of substances in passive samplers, has enabled the detection of the antibiotics in water (Tulp, et al., 2004).

CONCLUSION

Towards sustainability is the focus of EPV. The usage of various drugs like diclofenac by human being in the life time, those human dead bodies consumed by vultures, these vultures when dead were assessed, they were died by kidney failure due to the percentage of diclofenac in vultures body. The pharma pollutants are distracting the web chain of the environment. So, EPV has a major role to play to focus on sustainability.

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