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Eco pharmacovigilance: A Concern for environmental Safety

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Abstract
Pharmacovigilance is well known that the World Health Organization (WHO) launched the initiative to report any negative drug reactions.Theterm"pharmacovigilance"referstothescienceandpracticesinvolvedinidentifying,evaluating, comprehending, and averting drug side effects or other potential issues related todrugs. Eco pharmacovigilance (EPV) can be characterized as the process of identifying, assessing,determining the cause and effect of pharmaceuticals in the environment, as well as preventingtheirnegativeeffects.
Ecopharmacovigilance is the study of all drug-related side effects on humans and other animalsas well as toxic reactions in the ecosystem. The use of drugs is growing daily in the veterinary and human populations. One report states that antimicrobials are used in 100,000 tonnes world wide.Monitoring the side effects of pharmaceuticals is the goal of both PV and EPV. PV is done on patients, whileEPVis done in the environment. It is far more difficult to prevent a pharmaceutical residue from human usage in the environment, which is an inevitable result of patient drug use. It can be addressed by efficient sewage treatment, which could stop serious environmental degradation. One of the major global challenges is that any observed ecological trends or negative environmental effects will initially be linked to a specific one. The antiviral medication oseltamivir, sometimes known as Tamiflu, has also been shown instudies to havelittle chance of harming the environmentdespite being widely used due to thebirdflupandemic.

Key Words:
Pharmacovigilance , Eco pharmacovigilance , Drug Regulations, Environment, Pharmaceutical.
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INTRODUTION

Pharmacovigilance:

Pharmacovigilance, or drug safety, is the term for the pharmacological science that deals with the identification, evaluation, comprehension, and avoidance of unfavourable effects, especially those that are short- and long-term side effects of medications. PV plays a significant and essential role in clinical research. A major global problem that can be linked to a lack of time and report forms is the underreporting of adverse drug reactions (ADRs). It is well known that the World Health Organization (WHO) launched theinitiative to report any negative drug reactions [1].
Theterm"pharmacovigilance"referstothescienceandpracticesinvolvedinidentifying,evaluating, comprehending, and averting drug side effects or other potential issues related todrugs. It is essential to the operation of public health initiatives, clinical practice, and drug regulation systems. In order to promote safe and appropriate drug use, pharmacovigilance works in three ways:

(a) Encouraging the discovery of previously undiscovered adverse drug reactions (ADRs), interactions, and frequency increases.

(b) Identifying risk factors for the emergence of ADRs;and

(c) Quantifying aspects of benefit/risk analysis and disseminating information to enhance drug prescribing and regulation [2].

Ecopharmacovigilance:

Concern over EPV research has recently grown due to the rising incidence of pharmaceutical contamination. The pharmaceutical industry and multinational corporations have realized over the last thirty years that pharmaceutical drugs have a negative environmental impacton the world[3].

Recent years have seen an increase in concerns about the possible environmental impact of pharmaceuticals(PIE), leading to the requirement that all new drugs undergo a thoroughEnvironmental Risk Assessment (ERA) before being released into the market. After a product islaunched, there isn't a formal framework or mechanism in place to review the ERA or keep an eye out for any potential negative environmental effects. This article's goals are to evaluate some of the difficulties and opportunities that may arise when attempting to put EVP procedures into practice, as well as to investigate what EPV might actually email. A few of the difficulties associated with EPV are addressed in our approach to creating Environmental Risk Management Plans, or ERPs[4].

Ecopharmacovigilance is the study of all drug-related side effects on humans and other animals as well as toxic reactions in the ecosystem. The use of drugs is growing daily in the veterinary and human populations. One report state that antimicrobials are used in 100,000 tonnes worldwide. Each year, over thirty prescriptions of the non-steroidalanti-inflammatory drug(NSAID) class are taken. When asked how they get rid of prescription leftovers, almost all households said they either flushed them down the drainordumped them in the trash [3].

The study of the effects of pharmaceuticals disposed of in the environment is known as ecopharmacovigilance or EPV for short. As "the science and activities relating to the detection, assessment understanding and prevention of adverse effects or any other possible drug related problems," pharmacovigilance is defined by the World Health Organization (WHO). Ecopharmacovigilance(EPV) can be characterized as the process of identifying, assessing, determining the cause and effect of pharmaceuticals in the environment, as well as preventing their negative effects[5].

AstraZeneca has created a framework to capture environmental risks for all stages of the productlife cycle, from early development to launch. The data encompasses aspects such as the active pharmaceutical ingredient's (API)physico-chemistry,pharmacokinetics,humanmetabolism,preclinicaltoxicology,andenvironmental information when accessible [6].

The European Union's Water Framework Directive (WFD), which periodically assesses eachwater course in the EU27 to ascertain its ecological status, includes provisions for tracking the effects of pharmaceuticals. If any of the watercourses comply with good ecological status, more research is conducted to ascertain the cause of non-compliance. Since the cause of the non-compliance is known, corrective action are determined by methodical planning. In 2013, the nation began implementing the Pharmacovigilance Program of India after considering the situation there. To ensure the success of this program, many more regulations and strict laws are required. Therefore, it appears very unlikely that ecopharmacovigilance will be introduced be in India anytime soon[5].

Eco pharmacovigilance is the scientific study and application of methods for identifying, evaluating, comprehending, and averting negative consequences or other issues arising from theuse of pharmaceuticals in the environment.

Therefore, the following headings can be used to discuss the science of ecopharmacovigilance:

- Consequence of pharmaceutical pollution to the environment.
- Drug laws and ecopharmacovigilance.
- Strategies for lowering the quantity of drugs dischargedinto the atmosphere.

Environmental pharmaceuticals[7].

Velo proposed the term "ecopharmacovigilance" first. To characterize this recently developedfield, several other articles have suggested the terms ecopharmacology, environmentalpharmacology, pharmaco environmentology, pharmacovigilance, and ecopharmacostewardship. Although the term EPV and some of its approaches are introduced in these articles, their coverage of sustainable pharmacy encompasses much more ground, including green drug design,greenchemistryinprocessdevelopment,minimizingmanufacturingemissions,betterprescribing practices, and the handling of unused medications. Furthermore, a large number ofthe EPV strategies that have been supported up to this point have been primarily preventive innature andh aveassumed that the presence of pharmaceuticals in the environment will unavoidably have a negative impact without takingrisk or likelihood of impact into account[8].

It is still very early in the science, and its exact meaning is not entirely clear. EPV uses non-therapeutic environmental exposure to track the negative effects of pharmaceuticals on humans. It is the result of a compromise between the need for environmental protection and a highly industrialized society dependent on chemicals. To improve scientific understanding of pharmaceuticals in the environment, more research on specific biological monitoring of different species, measurement, prediction, and identification of potential effects of pharmaceutical pollutants are needed due to the complexity of pharmaceutical environmental exposure and the unique biochemical effects of drugs. A basic understanding of pharmaceuticals in the environment and environmental risk assessment is required. A new regulatory requirement before the launchofanydrugis the Environmental Risk Assessment(ERA)[9].

Comparison of Pharmacovigilance and Ecopharmacovigilance:

Monitoring the side effects of pharmaceuticals is the goal of both PV and EPV. PV is done onpatients, while EPV is done in the environment and may potentially be done on humans through indirect non-therapeutic exposure. Clinical trials provide a clear definition of drug exposure in humans by monitoring plasma levels and recording dosages, which can occasionally be linked to adverse drug reactions (ADRs).

Throughout the PV process, medications that are prescribed to patients are tracked, and adverse drug reactions are recognized, addressed, and clarified as needed. The doctor-patient relationship, which is crucial for identifying adverse drug reactions in patients, is not comparable to the routine monitoring of species in the environment, unless there is a specific reason for it[10].

Table1:Differences between EPV and PV:[9]

Ecopharmacovigilance	**Pharmacovigilance**
All animals in all environmental niches might be a trisk of exposure. Indirect contact with people is included in this.	Prescription medication exposure is limited to atargetpopulation (humanorveterinary) and Identifiable individuals.
The plasmalevels of some fish are being Tracked for scientific research, but there is no regular monitoring in place.	Regular monitoringcouldbeimplementedand exposedpopulationsareunderconstantsupervisio n.
Environmental concentrations can be measured or predicted, but the dose is unknown. In the absence of sophisticated biological monitoring work, actual exposure Levels are unknown.	Thedrug regimendefinesandestablishesthedose.Levelsofexposur ecanbequantified.
It is not feasible to directly identify harmful environmental effects by talking to the relevant species. Assessing the effects on the Environment requires human intervention.	Youcantalktothepatientdirectlyaboutmostissuesandgett heirclarification.
Not bound by any regulations.	Quiteregulated.
It is challenging to narrow down the cause of negative environmental effects whentheyare observed.	ADRs may or may not be simple to link to aspecificmedication or patient subset.

Ecopharmacovigilance: Need of the hour

Evaluation of pharmaceuticals:

Pharmaceuticals in water have been examined using a significant amount of water extracted sincethe 1970s, when chemical analysis of pharmaceutical goods started. These tests made use of the Gas Chromatography/ Mass Spectrometry (GC/MS) technique. This approach is in appropriate because of its low sensitivity because the data collected at this time was usually in the parts perbillion(ppb)levels,butfrequentlyinthehigherrange. In an article, the World Health Organization (WHO) detailed an analysis method that is frequently employed by scientists worldwide to examine the medications.

The suitability of various methodologies for the sorts of pharmaceuticals under evaluation is discussed in the study. For instance,GC-MS/MS analysis works better for volatiletargetcompounds while LC-MS/MS analysis works better for assessing polar molecules that are very soluble in water [4].

The effects of antibiotics:

The majority of these substances and their metabolites are expelled by the urine, the face, or a mixof the two. Antibiotic pollution primarily originates from domestichomes,cities, hospitals, industrial effluent, aquaculture, and large-scale medicated livestock production. Due totheinefficiency of current sewage treatment systems, they may find their way into naturally occurring surface-ground waterin detectable but extremely low amounts.

Modern medicine uses antibiotics extensively for both human and animal use. These drugs areintended to treat infections caused by microorganisms and to have positive or beneficial effects ondisease. Much like other pharmaceutical compounds, antibiotics are small, polar, organic molecules that are usually ionizable and need to be eliminated by metabolism or biotransformation[11].

Eco-focused sustainable prescription:

One way to reduce the environmental impact of active pharmaceutical ingredients (APIs) is through eco-directed sustainable prescribing (EDSP). One of the most crucialphasesinthe ecopharmacovigilance (EPV) programme is undoubtedly EDSP. According to themajority of physicians inseveral recentsurveys, the percentage of APIs in the environmentishigher.

They supported the usefulness and requirementof EDSP under ecopharmacovigilance in thehopes of lowering API exposure in the environmentbecause they were concerned about thepossibleeffectsontheenvironmentandecological issues related to API residues.Doctorsindicateda desire toparticipateinEDSPproceduresinthefuture[3].

Riskmitigation:

The best way to reduce the risks that pharmaceuticalactiveingredients (APIs) pose to the environmentis toemployamixofstrategies:

1. Advanced waste water treatment is being introduced,alongwith advanced sewagetreatmentsystems.
2. Pharmaceutical waste management regulations and guidelines should be improved, andthere should be incentives linked to the product that encourage the development of "green"medicines.
3. Increasing stakeholders' awareness, i. e. regulatory agencies, patients, physicians, nurses,andpharmacists.
4. Pharmaceutical-returnprograms.

India'sadvancementinecopharmacovigilance:

Given India's enormous pharmaceutical industry, ecopharmacovigilance is absolutely essential.Cooperative research projects involving the public, private, and academic sectors are necessary.Further research is necessary in order to improve our scientific understanding of how medicationsaffecttheenvironmentandtobetterassesse nvironmentalrisk.

EcopharmacovigilanceisarelativelynewconceptinIndia. Theinformationaboutpharmaceuticals found in the environment is not sufficiently supported by the data. Despite itsefforts, the Indian government has not been able to identify pharmaceuticals as pollutants despitestudying the levels of heavy metals and minerals in the environment. India is one of the biggesthubs for the production of bulk drugs worldwide, home to numerous pharmaceutical companiesand manufacturing facilities. As a result, the environment, drinking water, and the ground become unprecedentedly contaminated with drugs.

Table2: MedicinesfoundintheIndianenvironment[12].

Aspirin	NSAIDs
Cetirizine	Antihistamine
Trimethoprim	Folicacidsynthesisinhibitor,Antibiotic
Metoprolol	Beta-adrenoreceptorantagonist
Enalapril	Angiotensin-convertingenzymeinhibitor
Levocetirizine	Antihistamine
Ofloxacin	Antibiotic,fluoroquinolone
Ciprofloxacin	Antibiotic,fluoroquinolone
Enrofloxacin	Antibiotic,fluoroquinolone
Lomefloxacin	Antibiotic,fluoroquinolone
Norfloxacin	Antibiotic,fluoroquinolone
Terbinafine	Antimycotic
Citalopram	Selectiveserotoninreuptakeinhibitor

Pharmaceutical InEnvironment(PIE):

Environmentalpharmaceuticalsaretypicallyderivedfro mpharmaceuticalsexcretedfromhumans and animals, as well as from manufacturing effluent discharge and the discarding ofunneeded medication. Guidelines for patient take-back programs and disposal procedures can successfully manage the disposal of left over medications.

It is far more difficult to prevent a pharmaceutical residue from human usage in the environment, which is an inevitableresult of patient drug use.Itcan

beaddressedby efficientsewagetreatment, which could stop serious environmental degradation[13].

The amount of pharmaceuticals found in the environment has increased recently, ranging fromng/Ltolow mg/L insurface waters, and affecting many different therapeuticclasses.In a study on pharmaceutical disposal methods, the majority of the homes contacted either threwaway the contents in the trash can or rinsing them under the faucet. A household stockpile ofunused medications may result in unintentional or intentional wrongful ingestions, as indicatedbythefactthatover7%ofrespondents failed to discardthem.
In the United States alone, non-steroidalanti-inflammatorymedicine(NSAID)dosagesexceeding30billionaretakeneachyear.

Thevariouspathwaysbywhichdrugscouldentertheenvironmenthavebeenthoroughlyexamined[14].

Theseinclude:

- **Manufacturingunitsandhospitals:**
  Drug manufacturing facilities and hospitals are major sources of drug pollution. However, ifemissions are not adequately managed and controlled, localized elevated drug concentrationsmaydevelopclose tohospitalandmanufacturingsite discharges[15].

- **Excretion of pharmaceutical ingredients from patients:**
  Eithertheparentchemicaloritsmetabolitesareeliminatedbythepatientafterusingpharmaceuticals.Whenadministeredorally,amedicationcaneitherbecompletelyorpartially absorbed from the gastrointestinal tract in humans or animals. It is obvious that fecesand unabsorbed medication will enter the environment. Medication administered parenterally or orally to humans or animals may be metabolized to varying degrees and expelled into the environment (including exhaled air) as either the parent medication or its metabolites, or as acombination of the two. They enter food chains and concentrate as they go up into largerpredators after being released into thee cosystem[16].

Dischargesfromdrugformulations:
Significantamountsof medicinearealsoleftin theenvironmentby drugresidualsfromformulationssuchas transdermalpatches.
Ithasbeenobservedthatafterbeingremovedfromtheskin, transdermalpatchescontainingfentanylmaintain28-84%oftheloadedsubstance[17].

- **Animalcarcass:**
  Somedrugscanbeextremelytoxictoanimalsthatscavenge, especiallywhenfoundinhighconcentrationsinanimalcarcasses[18].

- **Leftovermedicines:**
  Theimproperdisposalofleftoverdrugs,whichencompassanyprescriptionsnolongerprescribedfortheirintendeduse, isaleadingcontributortoenvironmentalcontamination.A number of variables contribute to the build-up of leftover pharmaceuticals, but two main onesare the dispensing of allegedly unnecessarily large quantities (such 90-day supplies) and patientnon-compliance, which refers to failing to take prescriptions as prescribed [15].

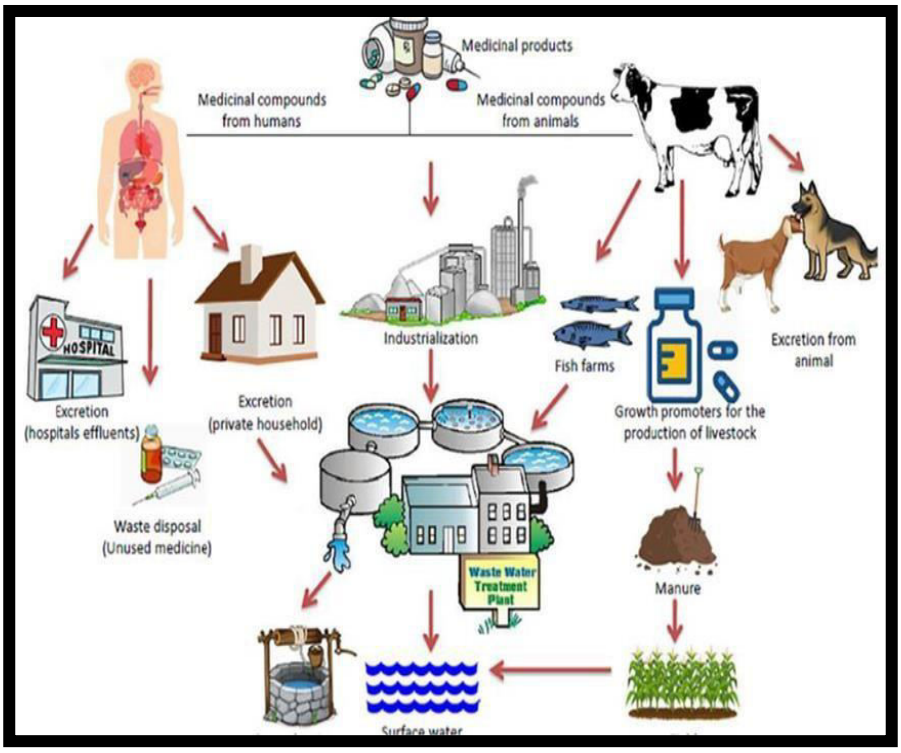

Fig.1: Pharmaceutical Exposure Routes in the Environment. (19)

Sources and routes of pharmaceuticals to the environment:

Pharmaceuticals are commonly found in drinking water, and their continual leakage into the atmosphere and potential for other side effects have alarmed the public effects on ecotoxicology. Out of the four thousand medications employed in the medical field, fewer than three hundred were already detected in water systems. This is because the quantities that are typically presentinaquatic settings, which range fromng/Ltoμg/L,need the employment of costly and responsive equipment.

When drugs are administered to people or animals, any amount of the drug and its metabolites will be expelled through the urineandbreath[19].

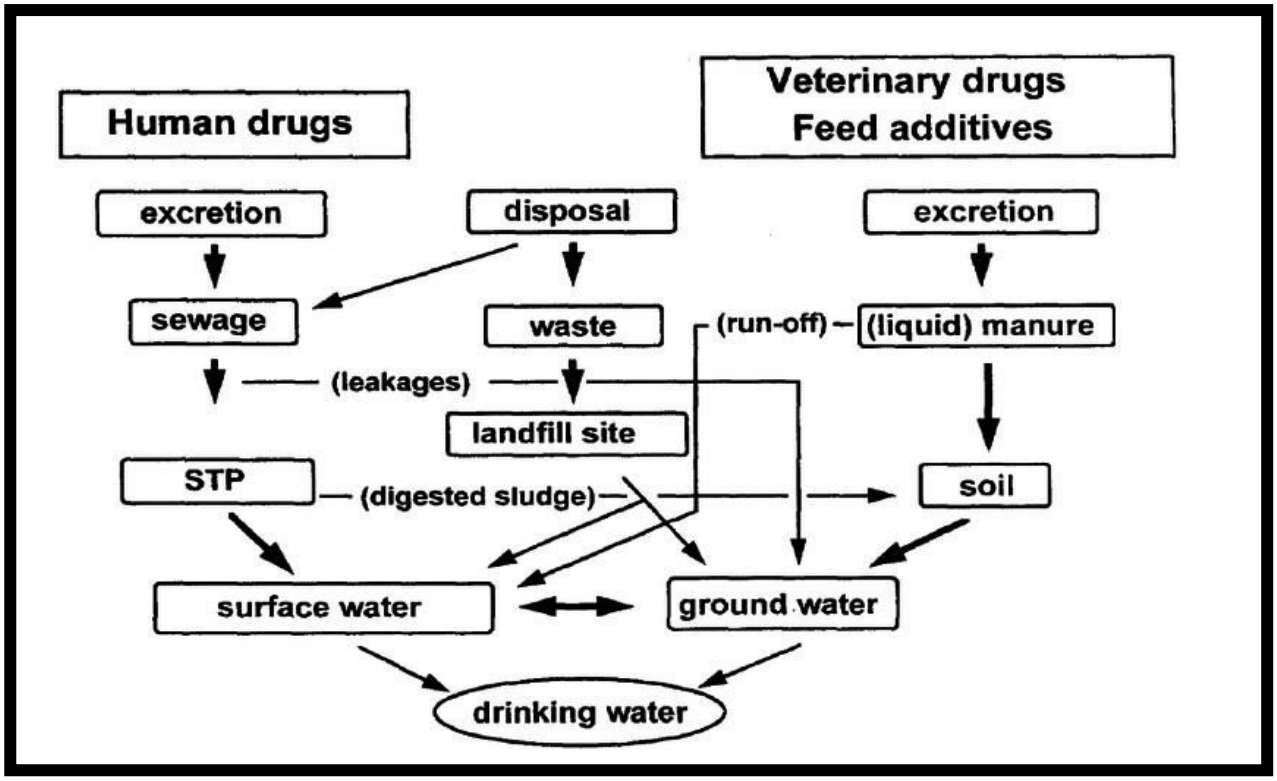

Fig.2:Pharmaceuticalsourcesand entrypointsintotheenvironment.(20)

GlobalEcopharmacovigilanceperspective:

Pharmaceutical use patterns in the US and the EU, as well as any possible risks connected tomedications in those areas, are displayed by current ERA practices. Any area where drugs areused should be protected from them and have regional variations addressed by EPV. The riskassociated with different medications may vary depending on the disease prevalence and culturalcustomsinagivenregion.

Oneofthemajorglobalchallengesisthatanyobservedeco logicaltrendsornegativeenvironmental effects will initially be linked to a specific one. The causes of fish intercourse andthe declineinvultures take years touncoverandaddress[20].

Ecopharmacovigilanceinuse:

The Environment Risk Management Plan, which offersaframeworkfor documenting any environmental riskof productsfrom development to marketing and beyond,isoneof the challenges that must be overcome if ecopharmacovigilance is to be effective inpractice. It contains details about the prenatal toxicology, metabolism, pharmacokinetics, physio-chemistry, and environmental aspects of the active pharmaceutical ingredient.

Antimicrobial resistance (AMR) is gaining special attention because it is a clinically significantissue. The World Health Organization has determined ways to combat the growing threat ofantibiotic resistance. Reducing the use of antibiotics and looking for antimicrobial resistance areamong the control measures, but it doesn't seem that they are looking at natural reservoirs ofresistance or the potential influence of other chemical co-selectors on the increased burden andtransmission of antimicrobial resistance. Evidence suggests that environmental bacteria are thesourceofthe resistance-encoding genes found in clinicallyrelevantbacteria.

The antiviral medication oseltamivir, sometimes known as Tamiflu, has also been shown in studies to have little chance of harming the environment despite being widely used due to the bird flupandemic[21].

Ecopharmacovigilance and Drug Regulations:

The following are some of the steps regulatory bodies have taken tolessen theimpactof

drugsontheenvironment:

1. Resource Conservation and Recovery Act(RCRA):

According to RCRA, hazardous waste is any combination of chemicals or materials that poses asignificant risk to the environment and needs to be disposed of separately, not in landfills orsewers.

Health care waste disposal is governed by the federal Resource Conservation and Recovery Act(RCRA), which was passed in 1976. Enforced by the EPA, it establishes stringent guidelines for facilities that produce, transport, store, and dispose of hazardous waste. It also tracks and controls the disposal of solidwaste[22].

2. Risk Mitigation Measures (RMM):

An authorization for a Veterinary Medicinal Product (VMP) may be denied if the environmentalrisk (ERA) of the product is determined to be unacceptable, i.e., if the risk quotient (RQ) of theproduct, which is the ratio of PEC (Predicted Environmental Concentration) to PNEC (Predicted No Effect Concentration), is greater than or equaltoone, and/or if the risk-benefit balanceis negative, meaning that the risks to the environment, safety, or efficacy out weight he therapeutic benefit.

Three categories are available for the RMMs:

- Short-term measures; e.g., enhanced methods for disposal and sewage treatment, as well as arefusalto spread contaminated manure.
- Mid-termmeasures;e.g.,producersandconsumersofpharmaceuticalitemshavealteredtheirperceptions of and communication about risk.
- Long-term measures; e.g., choices that support sustainable pharmacyasaconcept[23].

3. Environmental Risk Assessment (ERA) of drugs:

As a crucial component of its regulatory process, the Food and Drug Administration (FDA) musttake the effects of drug approval on the environment into account. Environmental Assessments (EAs) are required to be submitted with some new drug applications, according to FDA regulations found in 21 CFR part 25. The FDA mandates that the manufacturer perform a risk assessment that projects the concentration that will be present in the environment whenever a new drug is proposed for sale. If the risk assessment determines that the concentration will beless than one part perbillion, it is considered that the risks associated with the drug are acceptable[22].

Conclusion:

Thestudy,evaluation,comprehension,andmitigationof drugs'harmfulimpactsontheenvironmentareknownasecopharmacovigilance.EPVshouldprimarilyconcentrateonidentifying potential risks following the drug's debut. Effective strategies for addressing intimate partner violence (EPV) are still in the early stages of development, requiring significant global and national effort.

It can be challenging to establish a causal link between amedication and an adverse drugreaction (ADR) for a patient, but it is not nearly as challenging to link a single drug to negative effects in environmental species.

For ecopharmacovigilance to become a significant aspect of pharmacovigilance, pharmaceutical companies, government agencies, andchemists must take the initiative to become involved.

Drugs exposed to humans and animals through the environment may have direct or indirecteffects.Themostdiscussedtopicthesedaysismicrobiologicalresistance.Long-termexposureto extremely low doses of antibiotics through drinking water can lead to the development ofantibiotic resistance. The issue might get worseif pharmaceutical companies stop makinginnovative antimicrobialsinfavoroffancydrugs.

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