Environmental Pharmacology: An emerging concern

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ABSTRACT
The effect of pharmaceuticals and personal care products (PPCPs) on the environment and ecosystem is studied in environmental pharmacology. The impact of these products on environment is speculative, these substances are used by people for personal health or cosmetic reasons which enter environment due to human activities and as wastes from manufacturing units. The entry of various drugs into the aquatic ecosystem is of a concern and empirical evidences are making these concerns more convincing. Ecopharmacovigilance encourages the theory of “greener” healthcare system which protects the environment. Green pharmacy include green chemistry and green design of a pharmaceutical plant.

Keywords: environmental pharmacology, ecopharmacovigilance, green pharmacy.

INTRODUCTION
The steady increase in use of pharmaceuticals increase the amount of generated pharmaceutical waste.1 Environmental pharmacology is defined as the effect of pharmaceuticals and personal care products (PPCPs) on the environment and ecosystem.2 It includes studies of PPCPs irrespective their doses and route of entry into the environment which responsible for disturbance in the balance of ecology.1 Various other terms can be used interchangeably with environmental pharmacology such ecopharmacology, pharmacoenvironmentology, ecotoxicology.3 However, the term ‘Pharmacoenvironmentology’ deals with environmental impact of drugs given to humans and animals at therapeutic doses.4 Environmental pharmacology involves the study of environmental science, medicine, ecology as well as chemistry.3 According to WHO, about a quarter of diseases faced by humans are due to continuous exposure to environmental pollution.1

Since PPCPs tend to dissolve easily and don’t evaporate at normal temperatures, often detected in soil and water bodies. Most of the pharmaceuticals are not filtered effectively by waste water treatment plants. Pharmaceuticals may be dumped in the environment by means of improper disposal, runoff from sludge, reclaimed waste water irrigation and leaky sewage.5 The entry of various drugs into the aquatic ecosystem is of a concern and empirical evidences are making these concerns more convincing. Also, the production of illegal drugs is responsible for pollution of drinking waters resources by releasing possible carcinogens.6 These factors demand for substances that are biodegradable. However, environmental pollution by drugs may or may not have toxic effects on the ecosystem but generally there is possibility of modifying effects.7

DISCUSSION
The recent increase in awareness of environmental pollution is building an opportunity for sectors which are involved in health care such as pharmaceutical
manufacturers, hospitals, physicians and all those who are involved in health care system, pharmacies, waste management agencies, environmental protection establishments, consumers and agencies to reduce potential harm.¹

What are PPCPs?

Pharmaceuticals, prescribed as well as over the counter medications made either for human use or veterinary use are common PPCPs. Antibiotics, drugs for sexual enhancement, drugs used in veterinary, Fragrances, Cosmetics and Sun-screen products are also included in this group.¹

Historical aspects

In 1997, the decline in the population of the Asian white-backed vulture and the Indian vulture was observed which prompted the Indian Government to ban the drug ‘Diclofenac’. The total number of vultures was reduced from 150 in 1997 to 25 in 2010. It was noticed that vultures die after feeding on cattle carcasses that were treated with diclofenac. Diclofenac sodium is a nonsteroidal anti-inflammatory (NSAID) used as pain killer by veterinary doctors for treating cattle. In vultures, due to improper detoxification pathway for diclofenac, its ingestion leads to visceral gout and subsequent renal failure followed by death when they feed on carcasses of cattle treated with diclofenac.⁸ An worrying decline in number of vultures is a threat for an outbreak of epidemics as an increase in number of undecayed carcasses and feral dogs can pose a range of diseases.⁹ Another observation was the presence of narcotics in trace amounts like cocaine in Thames River.¹⁰ Recently, various classes of human pharmaceuticals have increasingly been identified in the environment at ng/l to low μg/l in surface water.¹¹ Although concentrations were in traces, the effect of this can be unpredictable.³ Enviromental pollution can be in the form of air pollution, water pollution, soil pollution or heat stress.

Sources of pharmaceutical contamination¹

- Drug manufacturing effluent
- Hospital effluent
- Household effluent
- Agriculture run-off
- Municipal STP effluent
- Aquaculture

Researchers have concluded that human cells fail to grow normally in laboratory when exposed to certain pharmaceuticals in trace amount. Whenever the bacteria are exposed to a drug, there are chances that bacteria will mutate to render the drug ineffective. In India, at Patancheru near Hyderabad which is an important hub for drug production and very large number of industries are situated in a limited area. Water samples have shown presence different drugs, ranged in purpose of hypertension, heart disease, chronic liver ailments, depression and ulcers. It is named as a deadly cocktail of antibiotics.¹ The concentration of ciprofloxacin was about one million times greater than the levels that are regularly found in treated municipal sewage effluents. The probable total release of ciprofloxacin for 1 day was 44 kg, which is adequate to treat everyone in a city with 44, 000 residents.¹²

Drugs in the environment¹

Synthetic hormones

Research suggested that concentration of ethinyl estradiol in oral contraceptives can cause endocrine disruption in aquatics and amphibians like fishes, frogs, alligators and molluscs in concentrations as low as 1 ng/l which is due to increased vitallogenin production and structural change in their sex organs leading to feminization.

Cardiovascular medicines

The Non selective beta blocker (Propranolol) led to significant decrease in egg production in Medaka Fish at a concentration close to that demonstrated in a sewage treatment plant.

Antibiotics

In India, resistances to ciprofloxacin have been detected downstream pharmaceutical plants and genes for multi resistance were noted in drinking water. The term Ecoshadow is used to describe impact of antibiotics on environment. Broad spectrum antibiotics that are stable will have a greater impact on the bacterial flora (a long eco-shadow) than those with a narrow spectrum that disintegrates more rapidly (a short ecoshadow). The development of resistant bacteria is stimulated by high concentration of antibiotics in sewage plant.
Antidepressants
Fluoxetine (Serotonin reuptake inhibitor) has been shown to affect swimming activity in shell fish whether it is linked to a disturbance of serotonin function in the brain is still unknown. One laboratory study suggested that antidepressants like fluoxetine could trigger spawning in some shellfish.\(^{13}\)

Analgesics
Ketoprofan and diclofenac are non steroidal anti-inflammatory drugs (NSAIDS) often used as analgesic and frequently found in surface waters. Diclofenac affects histology of organs and gene expression in fish when exposed to a concentration of \(1 \mu g/l.\)\(^{14}\) Carbamazepine (28.3 \(\mu g/L\)) was found in the Kaveri river near Tiruchirapalli in India. Prozac was detected in Thames (UK). Cocaine was found in the Po river in Italy. \(^{15}\)Antidepressants, antiepileptic and statins were detected in Niagara river and Ontario lake in Canada. Traces of heart medications and caffeine have been found in Atlantic Ocean.\(^{15}\)

Food and Drug Administration (FDA) has regulated pharmaceuticals in the environment since 1977 under National Environmental Policy Act of 1969. If drug concentration is \(\geq 1\) part per billion, it is assumed to pose acceptable risks.\(^{16}\)

How to dispose medicines properly?
Take the drugs out of original packets and mix with cat litter or used coffee grounds. If medicine is solid, add water to dissolve it. Put the mixture into a disposable container with a lid or into a sealable bag. The sealed container with the drug mixture can now be placed in the trash.\(^{15}\)

Precautions to avoid environmental pollution
Primary focus should be to reduce the quantity of unused medications. This can be done by purchasing only the drugs that are needed and prescribed by your physician, storing medicines away from children and pets at proper temperature and humidity, as recommended on the label. Restrict taking physician samples if you are not going to use them.\(^{15}\)

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<th>Table 1: Strategies for mitigating risks by Pharmaceuticals in the environment(^{15})</th>
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<td>• Rational drug use</td>
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<td>• Medicine return programs</td>
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<td>• Raising awareness amongst patients, doctors, nurses and pharmacists</td>
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<td>• Newer effluent treatment with advanced sewage treatment plants</td>
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<td>• Incentives for the development of “green” pharmaceuticals</td>
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Measures to be taken in Pharmaceutical disposal
• Good manufacturing practice (GMP)- are required to be adapted in pharmaceutical manufacturing, quality control and other steps in which emissions into the environment are not included till now.
• Disposal of unused medicines- Medicine take back programs can really work for removing expired or unused medicine. But such programs are absent in developing economies. Medicines should be sealed in a plastic bag if to be disposed in household trash to prevent them to get entry in the environment before they reach sites of treatment. Flushing of certain medicines accidental ingestion of which can be fatal.
• European Union (EU) regulations state that there should be a collection system for unused or expired medicines. Disposal in sewage system is legally accepted route of elimination. However, incineration at high temperature (1200ºC) is a preferred alternative to avoid environmental pollution.

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<th>Table 2: World Health Organization (WHO) guidelines for safe disposal of pharmaceutical wastes(^{3})</th>
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<td>• Disposal methods</td>
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<td>i. Returning the drugs to manufacturers</td>
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<td>ii. Dispatch to landfill or sewers</td>
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<td>iii. Encapsulation and inertization</td>
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Ecopharmacovigilance (EPV)

Ecopharmacovigilance can be defined as science and activities regarding detection, assessment, understanding and prevention of adverse effects or any other problems which are related to the presence of pharmaceuticals in the environment, which affect human and other animal species.\(^{17}\) EPV has an environmental focus and is environment as well as public health oriented. EPV commences from point of production to the point of disposal.\(^{3}\) In developed countries, EPV is being considered and helping in reducing the environmental pollution. But in developing countries, EPV is still neglected which is responsible for harmful effects of pharmaceutical waste. It is necessary that regulatory and scientific society work hand in hand to address this vital issue.\(^{18}\) Ecopharmacovigilance can redesign the healthcare system in such a way that only the most efficacious medicines are produce in minimal doses and dispersed in limited quantities and for limited durations to ensure full consumption. EPV encourages the theory of “greener” healthcare system which protects the environment and ensure more official utilization of healthcare resources, reduced costs, improved outcome and reduced incidence of drug abuse and accidental poisonings.\(^{3}\) Also, there is a crying need of Pharmacovigilology, watching for drug interaction with the environment in terms of both benefit as well as risk.\(^{19}\)

Green Pharmacy

In attaining green challenges for pharmaceutical industry, green pharmacy has a vivacious role to play. Green pharmacies include green chemistry and green design of a pharmaceutical plant. Green chemistry includes design of PPCPs and processes which are environment friendly to cut down negative impacts on humans as well as environment. Also, it supports invention of more eco-friendly chemical processes reducing generation of hazardous substances.\(^{1}\)

### Table 1: Safe disposal methods

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<td>iv. Burning in open containers: for small quantities</td>
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<td>v. Medium temperature or Novel high temperature incineration</td>
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<td>vi. Chemical decomposition.</td>
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- Sorting should be done e.g. anti-neoplastics, anti-histamines, expired or hazardous pharmaceutical materials like aerosol cans and recyclable materials.
- Use recommended disposal methods by sorting different pharmaceutical products.

Green design involve monitoring of work place environment, waste minimization by refining materials and Organizations adapting to ISO-14001, Environmental management system (EMS) for persistent improvement of a pharmaceutical plant. According to ISO-14000, Environmental management system (EMS) standard comprises of five sections namely environmental policy, planning, implementation and operations, checking and corrective action and management review.\(^{1}\)

**CONCLUSION**

The range of human exposures to PPCPs from the environment is a complex. In India, pollution of water, air and land due to pharmaceutical products is on a higher side due to absence of ecofriendly production measures in Indian pharmaceutical set up. Manufacturers should design new drugs which are more ecologically sensitive and that biodegrade more quickly and yield less harmful end products. Concentrations only in surface water are not sufficient for assessing the risk of negative environmental effects of these PPCPs. Bioaccumulation in fish and other aquatic foods consumed by humans should also be considered. Also, synergistic effects between pharmaceuticals and chemicals in the contaminated water should be looked for.

A proposed new drug has never been turned down based on estimated environmental concentrations and no actual testing is conducted after a drug is marketed to see if the environmental concentration was estimated correctly. During clinical trials of newer drugs, ecopharmacovigilance need to be added to ensure restriction of environmental pollution due to the drugs released in environment. Those drugs which are not biodegradable should not be manufactured if other alternatives can serve their purpose. Herbal drugs have certain useful pharmacological properties and it is assumed that plants are generally natural entities and therefore
Green Pharmacy aims at zero waste production that will greatly benefit our environment at all levels of our society. To purchase drugs in small amounts, limiting expired medications, use medications with low environmental impact, disposal of unused or unwanted medications at take-back sites are the immediate measures to be taken. Pharmacies should have recycle bins allowing consumers to bring unused/expired medicines back whenever they shop. Hospitals should implement methods for proper disposal of waste. Green Pharmacy can prove to be a powerful approach with a fast developing solution for limiting environmental pollution.

REFERENCES