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Ecopharmacolovigilance: current need and future scope

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Abstract
Ecopharmacovigilance is the science related to understanding, detection, assessment, and activities for prevention of adverse effects or other problems due to the existence of pharmaceuticals in the environment. These pharmaceuticals come into the environment through a variety of routes causing harmful effects. Due to increasing pharmaceutical pollution, “ecopharmacovigilance” has been an area of interest. Its objective is to ensure that significant environmental issues associated with pharmaceuticals in the environment are identified and managed in a timely way. Ecopharmacovigilance has become a recent topic of research in India, and regulatory requirements governing the comprehensive environmental risk assessment of pharmaceuticals are the need of the hour.

Keywords: Ecopharmacovigilance (EPV), drugs, environmental pollution, environmental risk assessment (ERA), India

Introduction
Ecopharmacovigilance can be defined as science and activities concerning detection, assessment, understanding and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment [1]. Some prominent examples of drugs causing harmful effects on environment are that of vultures' death after consuming carcass of animals treated with Diclofenac sodium [2, 3, 4], Ethinyl estradiol adversely affecting fish through its "feminization" of males [5]. Thus, the science of ecopharmacovigilance can be discussed under following heads:

- Pharmaceuticals in the environment
- Consequences of environmental pollution by pharmaceuticals
- Approaches to reduce amount of pharmaceuticals released in the environment
- Ecopharmacovigilance and Drug regulations

World Health Organization (WHO) defines ecopharmacovigilance as the science and activities associated with the detection, evaluation, understanding, and prevention of adverse effects of pharmaceuticals in the environment.
Compared to the west EPV in India is still in infancy, there is no formal frame-work to monitor for potential adverse effects of the pharmaceuticals on the environment. The unused or expired medicines can pose a hazard to public safety and to the environment, if they are not safely disposed of, as many drugs lead double lives: one within the body of animal/humans and one in the environment. Products of concern include both prescription and over-the-counter medications. [6, 7, 8, 9]
These environmental pharmaceutical pollutants include excretion of pharmaceuticals after human and veterinary therapeutic use. This dominates the global input of pharmaceuticals into the environment and are a much more difficult source to control; adding to the direct release into the wastewater system and terrestrial depositions from manufacturing or hospitals; and disposal of unused drugs.[10]. The long-term exposure to these environmental pharmaceutical pollutants could be responsible for chronic toxicity and subtle effects in animals and plants including microbial resistance, endocrine disruption, growth inhibition,

disruption of microbial ecosystems, cytotoxicity, mutagenicity, teratogenicity, and so on.

In the current times there has been a consciousness about medicines and their products contaminate the ecosystem. However, the adverse effect of therapeutic squanders on environment is yet to be comprehended and addressed gravely in India.[11] numerous pharmaceutical chemicals are nondegradable to resist the acid environment in the stomach or long-lasting, thus present a special hazard when they enter, endure, and spread in the environment including water supplies and the food chain leading to an unwitting re-entry of pharmaceutical products into human being.[12,13,14] These ecological pharmaceutical pollutants include emission of pharmaceuticals after human and veterinary therapeutic use. The long-standing exposure to these ecological pharmaceutical pollutants could be responsible for chronic toxicity and subtle impacts in animals and plants including microbial resistance, endocrine interruption, growth reticence, interruption of microbial environments, cytotoxicity, mutagenicity, teratogenicity etc.

Nowadays, pharmaceutical pollution has posed serious threat to the environment worldwide. A study in Spain found that 19 pharmaceuticals of the 27 human pharmaceuticals investigated have been identified in the aquatic environment.[15] Metabolites of carbamazepine (carbamazepine epoxide), diclofenac (4´- and 5-hydroxy diclofenac), and atorvastatin (o- and p-hydroxy atorvastatin) were detected in flow proportional 24 h composite samples of wastewater effluent collected from the Norwegian cities of Oslo and Tromsø at higher concentrations than the parent pharmaceuticals. Among them, the concentration of 5-hydroxy diclofenac determined in discharged effluent was as high as 3,700 ng/L. And certain metabolites were found in Norwegian coastal environment, marine surface waters, and sediments. [16] In this alarming situation, the concept of "ecopharmacovigilance" (EPV) has been proposed as an issue of great interest.

Current global status of EPV:

Differing from the highly regulated "pharmacovigilance" (PV) in patients, EPV is an emerging science concerning detection, assessment, understanding, and prevention of adverse effects related to the presence of pharmaceuticals in the environment, which affect human and other animal species.[3,4] The definition of EPV by Holm et al.,[6] based on the World Health Organization (WHO) definition of PV is "the science and activities associated with the detection, evaluation, understanding, and prevention of adverse effects of pharmaceuticals in the environment". The approaches of EPV include green drug design, green chemistry in process development, development of biodegradable products, minimization of manufacturing emissions, education over rational use of drugs, improved prescribing practices, the management of unused drugs, etc.[17, 18, 19] And these new EPV approaches have been introduced into the environment monitoring of antidepressants,[20] antibacterials like flouroquinolones, hormones, paracetamol, and diclofenac.

The European Commission (EC) is recently evaluating data on pharmaceuticals in the environment and the impending effect on the environment and public health, as well as a evaluation of the current legislation for human and veterinary medications. The Society of Environmental Toxicology and Chemistry (SETAC) have currently published the results of a collaborative workshop that recognized the top 20 questions associated to pharmaceuticals in the environment. The American Senate has approved a legislation to screen the pharmaceutical products in environment. United Kingdom also has observed the effect of rigorous regulations. EC has issued a numeral of appropriate legislations and regulatory supervision in the area of EPV, which incorporate Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters (KNAPPE), environmental risk assessment of pharmaceuticals (ERAPharm), Pharmas, and Cytothrea. Amongst all the projects on EPV, pharmaceuticals ERA, which is by characterization predictive evaluation of prospective risks usually based on investigational laboratory studies, is a recognized regulation system as crucial to apply strategies to reduce the potential pharmaceutical environmental effect. The EU ERA regulations are presently the most demanding and statistics intensive. In the EU, the ERA must normally be in place previous to authorization of a new drug, and if an environmental hazard is recognized, "specific provision to limit it should be envisaged.[20]

The proportion of the predicted environmental concentration (PEC) to the predicted no-effect concentration (PNEC) ration (PEC: PNEC). The PEC provides an estimation of the maximum concentration predictable to occur in the environment, consequential from patient use and subsequent emission into the wastewater system. The PNEC is derivate from ecotoxicological tests, usually on algae, Daphnis and fish (representing three trophic levels), mutually with an assessment feature that accounts for interspecies differences in toxicity. Characteristically, worst-case assumptions are primarily made in deriving the PEC (e.g., 100% excretion by patients, no removal during sewage treatment), and generally if the PEC:PNEC is <1 no further information is required. Conversely, if PEC: PNEC is >1 then additional testing is in general required to refine the PEC or PNEC. If this fails to refine the risk quotient to <1 then appropriate risk management measures might need to be put in place. [21]

EPV in the India:

In India, ecopharmacovigilance is in a growing state. It isn't backed up by ample information to disclose the data of pharmaceuticals found in the environment. Indian government has been estimating the amounts of minerals and heavy metals as contaminations in environment but has not prevailing to distinguish pharmaceuticals as contaminants. India is a center of pharmaceutical organizations and manufacturing units and has become one of the world's biggest hubs for bulk drug manufacture, supplying over 65 nations. This leads to unprecedented drug pollution of surface, ground, drinking water and the atmosphere. A Swedish research team exposed that pharmaceutical levels in water downstream of a wastewater treatment plant in Patancheru, Andhra Pradesh, India was 150 times the highest levels of that originate in the USA. Water samples were as well taken from wells in six closes by villages. The samples were investigated for the occurrence of 12 pharmaceuticals amidliquid chromatography–mass spectrometry. All wells were determined to be contaminated with drugs. [22]

Strengthening the Policy-guided and Scientific Researches of EPV:

EPV is a comprehensive research area involving pharmacy, environics, chemistry, and management, and should be further studied by experts from academia, governments, and industry from around the world to bridge the current knowledge gaps. Related researches including administrative supervision and management over pharmaceutical pollutants, the analysis of current distribution levels and fate in different environmental matrices, better sewage treatment plants, development of biodegradable products, the impact of drug over environment, and potential ecotoxicity risks may be further investigated to develop EPV in india. It will be pertinent for regulatory as well as scientific society to work hand in hand to address this vital issue. Pharmaceutical firms, who play a vital role in managing the safety of medicines, should actively involve in the policy-guided and scientific researches of EPV.

Conclusion:

India is struggling to balance economic development and environmental protection. EPV provides useful reference for the disposal of environmental issues associated with pharmaceuticals in the environment in a timely way. Compared to the west, EPV in india is in infancy. We have to build some perfect laws and regulation system on EPV, defining the evaluation index for EPV, continuing the clinical rational medication, and the pharmaceutical take-back programs popularizing the concept of EPV and strengthening the policy-guided and scientific researches of EPV in pharmaceutical firms and academia.

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