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A Study of the Most Prescribed Pharmaceuticals in Indian Context and Their Removal Efficiency

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ABSTRACT: *Pharmaceuticals have gained much of the attention in the present scenario due to two chief reasons; first because of their therapeutic power and second because of their ecotoxicity levels. We thus planned this study so as to not only consolidate a list of the most usually consumed drugs in the Indian hospitals but also monitor their risk values, which would help in assessing their ecotoxicity. For this out of the 198 most frequently consumed drugs, 127 were given the risk values based on PEC and PNEC. The risk values highlighted that 77 out of 127 drugs were in the Hazardous category and 50 were Non hazardous. Also out of these 127, 70 were bioaccumable. Next, since antibiotics and anti-inflammatory drugs are the most prescribed ones in India, some of the important drugs of these two classes were monitored for their physicochemical properties and concentrations. When the treatment options for the removal of pharmaceuticals from the hospital wastewaters were studied , it was found that two treatment options ASP and MBR, when combined with other treatments gave better results for their removal. Lastly to conclude each drug has its own removal efficiency which could differ in different treatment plants depending upon a multitude of factors.*

KEY WORDS: Pharmaceuticals, Risk value, Hazardous, Bioaccumable, ASP and MBR

I. INTRODUCTION:

Pharmaceuticals are chemicals having specific biological activities and so are used for the treatment of a wide variety of diseases [1]. During the manufacturing of 1 kg of an active pharmaceutical compound, the waste that is generated is app. 50 - 100 kg [2]. Efforts are made to adopt a greener and sustainable approach to reduce the quantity of waste generated but the bigger problem that is to be tackled in this context is that the medicinal drugs themselves are posing newer types of environmental pollution and health risks. More than 3000 active pharmaceutical ingredients (APIs) have been reported till date which can enter into the environment at any stage of their life cycle i.e. during manufacturing in the industries or during consumption by the patients or at the final disposal site. The worst thing is that these APIs can exist in their original forms, as metabolites or as transformed products and so evaluating their ecotoxicity becomes all the more difficult [3]. App.30 - 90% of the orally administered drugs are actively secreted into the faeces and urine of the patients and find their way into the wastewaters [4]. Because the wastewater treatment plants are so designed to eliminate traditional pollutants as such these "Imminent contaminants" which are present in nanograms to micrograms ultimately find their way into the water cycle [5]. Though the share of the hospital wastewaters (HWWs) in the total volumes of municipal wastewaters (MWWs) is comparatively less yet due to the consumption of a broad range of specialised drugs and that too in larger proportions, hospitals have become the hot spots of pharmaceutical pollution. Pharmaceutical problems in HWWs have been addressed previously by many researchers but due to the structural complexities of these compounds, their low concentrations, high rate of transformations and variable chemical behaviours they are unfavourable explored pollutants [6 - 9]. Earlier studies have attempted to highlight the ecotoxicity of the pharmaceuticals but the data is incomplete and not fully understood [10]. It has been documented that the pharmaceutical compounds (PCs) are responsible for microbial genotoxicity and mutagenicity but who and how questions are still a maze puzzle. Due to large variations in their concentrations and types, different wastewater treatment plants (WWTPs) show different removal capacities for each PC. Also in the majority of cases the original compound and its derivatives do exist in the effluent released from WWTP and seep into the ground contaminating the water cycle to pose adverse effects on human health [11]. This study aims to analyse the most frequently prescribed PCs in terms of their risk potential, secondly the frequently encountered concentrations of the above PCs would be summarised and their removal methods would be discussed. This would help to generate a picture of the PCs that are mostly consumed in our city and that ought to be studied so that their ecotoxicology effects could be minimised.

II. METHOD:

Selection of priority pollutant pharmaceutical compounds (PCs) for risk assessment:

The first step adopted was to demarcate the drugs that are most frequently prescribed and then associate a risk factor with that particular drug. For this the local health statistics office was contacted and data about the pharmaceuticals maximally consumed during the year 2021 - 2022 were procured. When the drugs that are maximally prescribed and so have a high environmental load were studied, it was found that 198 PCs should be regularly present in the HWWs, of which 172 were detected in one or more studies. So now the approach was to assign a risk factor value to each of these drugs, for which 2 values are needed- **PEC and PNEC** [12]**.**

PEC means predicted environmental (surface water) concentration of a drug: For the calculation of this value the following formula has been used -

PEC_{sw}= A x (100 - R) / 365 x P x V x D x 100

A = the quantity of particular drug consumed

R = the removal rate in the STP (sewage treatment plant, which is taken as 0)

P = the population of that city

V = volume of waste water produced in terms of per capita per day(taken as 120 L)

D = dilution factor in the environment (taken as 10)

(population data was taken from statistics deptt and sales of drugs was taken from the health statistics deptt)

PNEC: prediction of no effect concentration, which means to assess that concentration of a particular drug which will not cause any ecotoxicity. For this a 2 step methodology has been adopted

1) The maximum prescribed therapeutic dose of a particular drug, $PNEC_D$ was calculated as max. Dose in mg / 1000

2) The chemical structure of the concerned drug is studied for its ecotoxicity potential, $PNEC_T$ which is calculated as giving a numerical value to each drug (0 - 100).

Therefore risk factor can be calculated as PEC_{sw} / $PNEC_D$ or PEC_{sw} / $PNEC_T$. Next the literature was explored for risk values assigned to each of these PCs.

III. RESULTS AND DISCUSSIONS:

Out of the 172 PCs detected in HWWs, Risk factor for only 127 PCs could be found as it was calculated for these PCs, because for the remaining 45 PCs PNEC values could not be calculated. These drugs were then arranged as per their therapeutic classes and it was found that app. 22% PCs in each category did not have a PNEC value & so no risk factor value has been assigned to them [13].

Table 1: Lists the drugs most frequently prescribed

Code/frequency n	Therapeutic class	Drugs most prescribed
A (7)	Alimentary canal drugs & metabolites	ranitidine, omeprazole, clofibric acid, demethyl diazepam
B	Blood & blood forming organs	ancestim
C (20)	Blood Vascular System	atenolol, enalapril
D (3)	Subcutaneous	furosemide, hydrochlorothiazide
G (4)	Genito urinary sys & sex hormones	17 estradiol, estrone
H	Systemic hormonal preparations(excluding sex hormones & insulin)	catecholamines
J(35)	Antibiotics / anti infective drugs	clarithromycin, erythromycin, spiramycin, lincomycin, ciprofloxacin, ofloxacin, amoxycillin, azithromycin, chloramphenicol, metronidazole
L (9)	Anti cancer/ immunomodulating agents	Oxytetracycline, tamoxifen
M (10)	Anti inflammatory/ painkillers / musculo skeletal system	Ibuprofen, salbutamol, acetaminophen, codeine, diclofenac, indomethacin, ketoprofen, mefenamic acid, naproxen, salicylic acid
N (30)	Nervous system drugs	diazepam, carbamazepine, fluoxetine, lorazepam, paroxetine, lofepramine, procyclidine
P	Anti parasitic drugs	albendazole

R (5)	Respiratory sys	Cetirizine, fexofenadine
V(4)	Various	bezafibrate

PC classification presented here is as per the ATC (Anatomic Therapeutic and Chemical Classification given by WHO collaborating center for drug statistics methodology WHOCC, 2011)

Based on the Risk factor value three categories of most prescribed 127 drugs were obtained. The first category included 50 PCs which had a Risk value < 1, and consequently were termed as" Non Hazardous."(As per the European Union, 1996 compounds having a risk factor > 1 are of " potential concern") In this category the PCs assigned N & J code were maximally to be found, with none of the D code PC being found in the non hazardous list.

Risk factor between 1 - 1000, "Hazardous PCs" : this category has 62 drugs , with high numbers from D code PC's and lower number of G & A code compounds.

Risk factor < 1000: "Very Hazardous PCs": 15 most frequently prescribed drugs are kept in this category (33% are hormones), with max. 5 drugs from J code. Thus out of the 127 PCs 77 were listed as hazardous i.e. having ecotoxic effects [13].

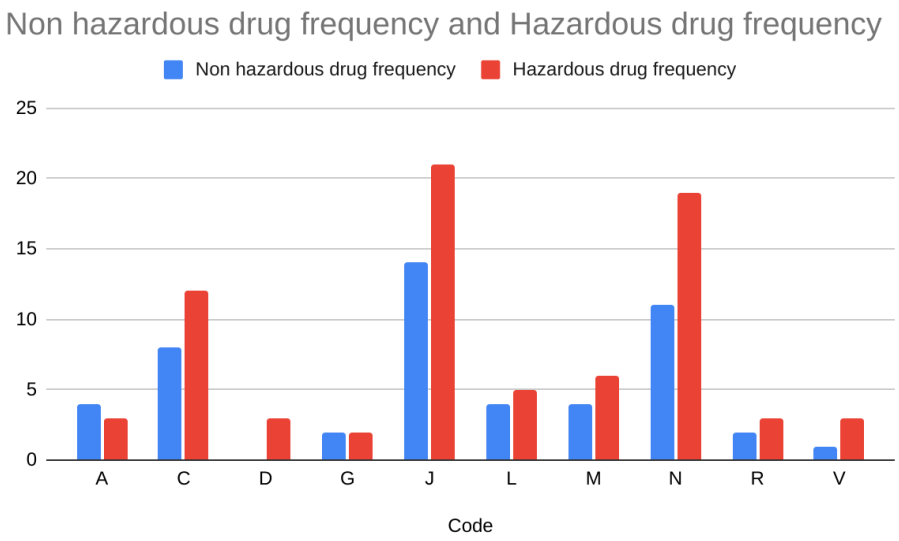

Fig 1: depicts the hazardous and non hazardous PCs of each code that are usually prescribed.

Apart from the hazardous 77 PCs, 70 of the 127 most prescribed drugs were recognised as Bioaccumable drugs [14,15]. These are listed as below

Table 2: States the Bioaccumable drugs that are most frequently prescribed.

Code	No. of bioaccumable drugs (BA)	Specific therapeutic class with frequency of BA drugs
A	9	Vitamins (6)
B	1	Haematopoietic drug
C	9	Lipid regulators (3)
D	7	Anti fungal (4)
G	8	Sex hormones (6)
H	2	Corticosteroids (1)
J	10	Anti viral (7)
L	6	Anti cancerous (6)

N	9	Anti depressant (4)
P	2	Insecticides (2)
R	7	Anti histamines (5)

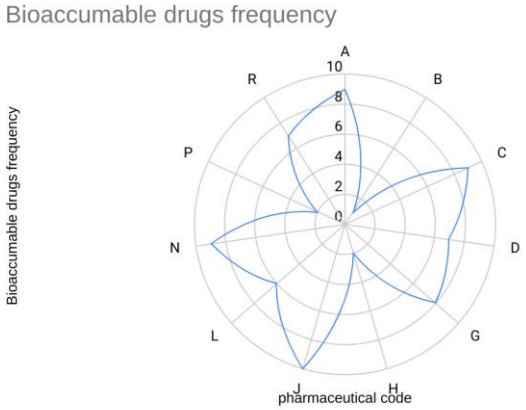

Fig 2: Depicts the Bioaccumable PCs of each code that are usually prescribed.

After compiling the list of priority pharmaceutical pollutants, their status was monitored in the environment as per the literature studies.

The major PCs detected in the HWWs belonged to class J & N. Out of the 60 PCs frequently prescribed in class J 47 were detected in HWWs, as for the class N 47 are most frequently prescribed of which 46 have been detected in the samples of HWWs. (most of the compounds of N class do not have any PNEC value recorded). The ecotoxicity of J class compounds have been studied maximally, followed by M class compounds. The classes N, V and G have least explored ecotoxicological data.

J class drugs: Among the antibiotics, most frequently used are beta lactams 52% (amoxicillin, penicillin), followed by sulfonamides 25% (sulfamethoxazole), cephalosporins 15% and 2% each of quinolones (ofloxacin, ciprofloxacin), macrolides (erythromycin, azithromycin). The most detectable antibiotics of HWWs are sulfonamides, quinolines and tetracyclines, with beta lactams being the rarely detected group (may be because of their hydrolysis)[16, 17]. Resistance to antibiotics has become a new threat and requires global efforts. The issue is critical as hospitals consume a broad spectrum of these drugs from mild to severe making the HWWs as the most challenging pollutants to be dealt with. It was found that globally the consumption of antibiotics has increased by 30 - 40% from 2000 - 2020, and about three quarters of this increase is concentrated in India, China, South Africa, Brazil and Russia. India is also one of the leading producers of antibiotics. The problem of consumption of antibiotics is further aggravated by self medication in the Indian scenario. Among the antibiotics the highest conc's in descending order were recorded for ofloxacin (19µg/L to 300µg/L), ciprofloxacin (237µg/L), trimethoprim, sulfamethoxazole (1- 5µg/L), and erythromycin. Usually ciprofloxacin is the most abundant antibiotic found in the HWW effluents, probably because it is the one of the most prescribed and also because it is nonbiodegradable. Ciprofloxacin at the concentrations 25µg/L can cause genotoxicity [10]. Sulfamethoxazole , ofloxacin and lincomycin exert mutagenic effects in microbial populations of WWTPs. The higher loads of antibiotics in HWWs have been found to be associated with the antibiotic resistant genes [22]. Higher levels of these genes in the HWWs suggest existence of multiple drug resistant microbes [4, 16, 23]. Two of the most frequently encountered AR genes of HWWs are bla_{KPC} and vanA [14], these genes when horizontally transferred pose a heightened risk.

The most notable concentrations of the drugs among the analgesics (M) / NSAIDs (non steroidal anti inflammatory drugs) that were found in almost all the surveys were Ibuprofen (19.2 µg/L [18] diclofenac, and salicylic acid. Ibuprofen was always detected at significantly higher concentrations (in 84% of the effluent samples observed), probably due to the amount of ibuprofen used as a prescription combined with a low degree of human metabolism, this was followed by diclofenac (in 69% of the effluent samples studied)[12, 19] ,however it was reported by [20] that the highest conc among the painkillers was found for ketoprofen 5.0 µg/L followed by acetaminophen 4.5 µg/L Paracetamol was found at a conc of 27 µg/L in HWW of Mexico, followed by naproxen 9.22 µg/L as reported by Calderon et al., 2019. These drugs are consumed the most after antibiotics and are excreted as parent compounds or their metabolites. Because they are soluble in water and have polar functional

groups they are not completely removed from WWTPs and so are present in surface waters; sometimes these may also show negative removal [21]. Regarding the ecotoxicological effects of NSAIDs, ibuprofen is the most ecotoxic drugs among all the NSAIDs [8, 11, 21], for other drugs of this class low to medium ecotoxicity have been reported [9, 20]. Diclofenac ecotoxicity has been well documented in literature of India and Pakistan [10].

Table 3: Highlights the physicochemical properties of pain killer drugs.

NSAID	Water solubility(mg/ L)	%age excretion as parent compound
Ibuprofen	58	15
Diclofenac	10	10 - 15
Ketoprofen	51	80

Treatment Options:

Biological and chemical methods have been designed for the removal of imminent contaminants of HWWs. These methods include the traditional activated sludge process (ASP), membrane bioreactors (MBRs), moving bed biofilm reactors (MBBRs), advanced oxidation(ozone treatment along with disinfection), advanced nanotechnological process and electrochemical processes [24, 25]. Removal of pharmaceuticals does not mean its complete degradation. It can be partial degradation and or adsorption or its volatilisation Removal of PCs from wastewaters depends on a number of factors i.e. chemical structure, treatment methodology and physical and biological conditions. Nevertheless, removal efficiency determination is very crucial for the reuse of such wastewaters [26].

1) ASP:

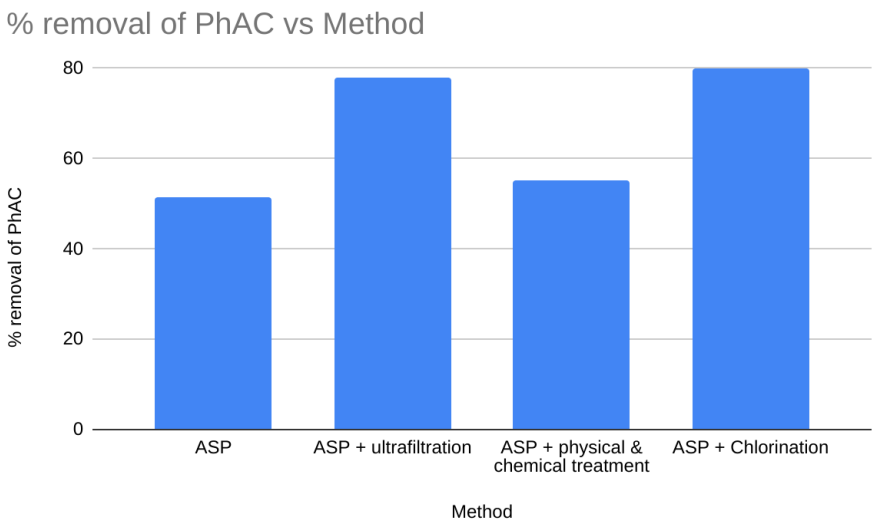

Fig 3: Depicts the removal capacities of PCs when ASP is combined with other treatment options.

2) MBR:

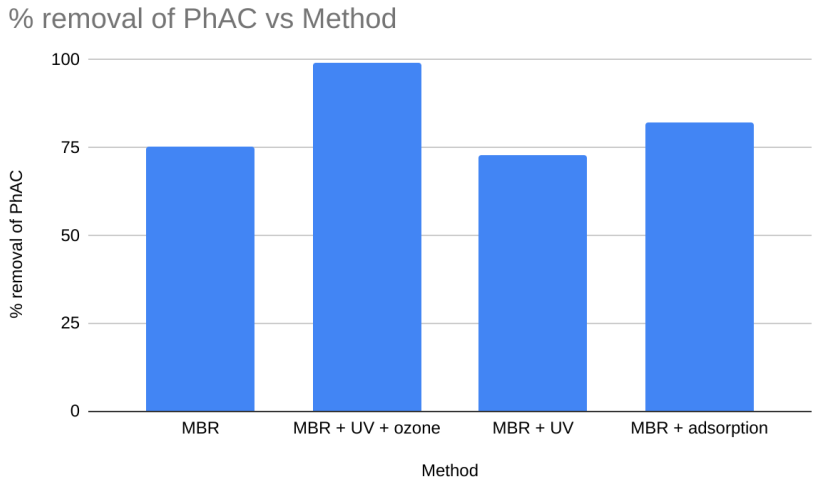

Fig 4: Compares the removal capacities of MBR + various treatment options for PCs

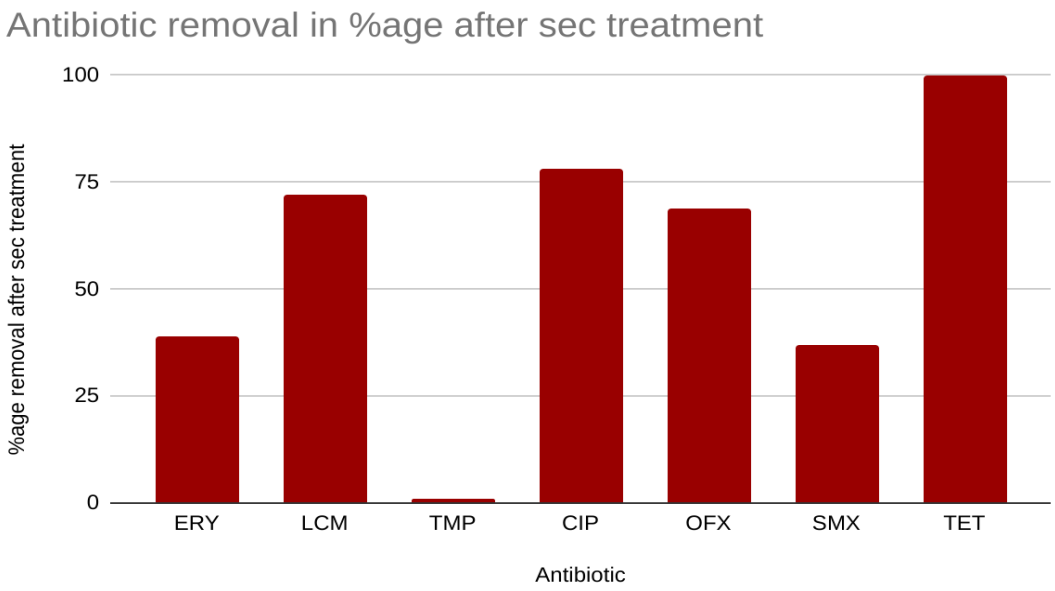

Fig 5: Highlights the antibiotic removal efficiency of secondary treatment options.

ERY: erythromycin, LCM: lincomycin, TMP: trimethoprim, CIP: ciprofloxacin, OFX: ofloxacin, SMX: sulfamethoxazole, TET: tetracycline.

IV. CONCLUSIONS:

The usually prescribed drugs can be hazardous, nonhazardous and bioaccumable. The removal of PCs does not mean that it has been lost from the environment, it simply emphasises that it exists in some other form or in some other solvent. This means that PCs from HWWs on entering into the municipal wastewaters (MWWs) can be biotransformed or partially removed. Thus a thorough study of PCs is a must as the WWTPs should be accordingly designed because ultimately the water discharged from them is either reused or finds its way into the water bodies.

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