Pharmaceuticals in Wastewater Treatment Plants

Subjects: Others

Contributor: Gabriele Frascaroli

Pharmaceuticals (PRs) can be only partly metabolised during therapeutic use, resulting in the excretion and release of residual fractions into the sewer. Then, unchanged or in the form of metabolites or conjugates, PRs reach local municipal wastewater treatment plants (WWTPs). Indeed, most medications, designed to maintain their chemical structure during the course of the therapeutic treatment, may remain active in treatment facilities for a long time. Many studies have shown that most drugs are significantly recalcitrant, and conventional treatment solutions for wastewater (WW) are not designed to eliminate these compounds. Consequently, a consistent flow of pharmaceuticals and their metabolites reach the aquatic environment, disturbing the ecological balance of rivers, lakes and other habitats and polluting groundwater, surface water and drinking water.

Keywords: wastewater ; pharmaceutical residues ; antimicrobial resistance ; wastewater treatment plants ; occurrence ; removal ; environmental risk assessment ; classification

1. Introduction

The release of pharmaceutical residues (PRs) in the environment is arousing growing concern due to the significant risks posed towards humans, animals and microbial communities. Many studies have highlighted the ecological toxicity of PRs in waters environments [1][2][3][4][5][6][7][8]. However, the most immediate concern regarding the release of PRs in the aquatic environment is related to the spread of antimicrobial resistance (AMR) among several classes of pathogens, first and foremost bacteria and fungi [9][10]. Within PR compounds, antibiotics [11][12], antifungals [12][13][14] and personal care products [15] play a primary role in accelerating this process. Due to the selective pressure imposed on bacteria, antibiotics particularly drive the spread of antimicrobial resistance genes in environments in which there is constant contact between the microorganisms and antimicrobials [9][10]. Therefore, hospital and municipal WWTPs may be deemed potential hotspots for the development of AMR due to the high prevalence and persistence of PRs in WW teeming with bacteria and fungi.

Antimicrobial resistance undermines the efficacy of antimicrobials, causes treatments to be unsuccessful, elongates morbidity and increases mortality [16]. According to the briefing note by the Organisation for Economic Co-operation and Development (OECD) in collaboration with the European Centre for Disease Prevention and Control (ECDC), AMR causes 33,000 mortalities and costs EUR 1.1 billion per year to the health care systems in the European Union and European Economic Areas [17]. In this context, in March 2015, the European Commission considered it necessary to resort to a new mechanism to provide high-quality monitoring information on emerging pollutants in the aquatic environment. For this purpose, the Commission under the Directive 2008/105/EC [18] on Environmental Quality Standards devised a watch list with numerous substances suspected to pose a significant threat to aquatic organisms, mammals and human health via drinking water and various pathways into the food chain [19]. Among these pollutants, several antibiotics responsible for the development of AMR, such as erythromycin, clarithromycin, azithromycin and ciprofloxacin, found a place on the list.

This systematic review aimed to collate, synthesise and critically appraise all the relevant literature on the occurrence and distribution of antimicrobial substances in WW. In particular, attention has been paid to the PRs responsible for the development of the AMR, mainly antibiotics, antifungals and personal care products commonly found in municipal and hospital WWTPs. This study intended to answer the following review question: what are the main PRs relevant for the development of AMR found in hospital and municipal WWTPs? In addition to establishing the PRs of primary concern, this work attempted to define potential correlations between the presence and concentration of PRs and certain variables across studies. Emphasis has been placed on the country and season in which research was conducted, the sample source (municipal or hospital WW) and the removal performances of WWTPs. On these premises, a classification of the most harmful PRs was proposed. There is a general paucity of well-controlled studies investigating knowledge gaps in this area which this study, through constructive evaluation and criticism, hopes to address. Through due process, the present review aims to fill knowledge gaps and produce directives for future management of AMR in WWTPs.

2. Method

The literature search was conducted using four different electronic databases: Web of Science, PubMed/Medline, ProQuest and BASE on 29 January 2021. The latter two were included to minimise publication bias [20] and prevailing paradigm bias [21], as they contain grey literature reporting non-significant results. Regarding the search period, the year in which the European Commission established the first watch list [19] was chosen as the start date for the literature search. In order to reduce potential temporal bias [21], a search of references before 2015 was conducted to establish whether more than 50% of the literature would be excluded. If that were the case, 2008 (the year of the Directive 2008/105/EC [18]) would have been set as starting date. All the relevant references during the bibliographic databases searches were collated, regardless of the publication language. However, language bias and publication bias [22][23] occurred during the article screening phase, when only studies in English, Italian or Spanish were included.

The main criteria of selection and common denominator during the three screenings were based on retaining the papers dealing only with PRs responsible for AMR. A pre-determined list of 218 PRs correlated to the development of resistance was selected. Moreover, additional criteria were identified during the title and abstract sifting phases (see the chapter of results).

External validity was assessed by considering to what extent the information of the studies included in the review fulfilled the review question and whether the answers to the query could be applied directly into real-world conditions. Emphasis was given to specific information such as the environmental risk assessment: studies that contextualised the presence of PRs with the risk posed to the environment were particularly informative and considered more significant than investigations that give a simple overview of the PRs concentrations. The same applied to analyses that made use of solid-phase extraction or direct injection, a technique that increases the detection capacity of a study considerably [9]. Moreover, the number of examined treatment facilities or the size of samples were taken into account to assess the external validity.

Using a pre-set list of potential information about the significant characteristics and results of studies, relevant data were extracted from the validated studies. Results were combined in a narrative synthesis subdivided into five sections that comment on main findings, namely the PR concentrations in influents and effluents of the treatment facilities, seasonal variations of PRs, differences between hospital and municipal WW, environmental risk assessment of the antimicrobial substances and removal efficiencies of the plants. Sub-group analyses were performed to investigate significant differences between PR concentrations in effluents and influents, or municipal and hospital WWTPs, and between seasons. Statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corporation, Washington, DC, USA) and SPSS Statistics V26.0 (IBM SPSS Statistics, Armonk, NY, USA). The independent t -test, based on Levene's Test for equality of variances, was used to determine differences in PR concentrations between effluents and influents and municipal and hospital WWTPs. One-way ANOVA, following the Bonferroni correction method, was used to determine differences between seasons.

3. Main Results

Within the eighteen studies included in the review, 45 different PRs were detected. More than half of the studies (ten) analysed 10 or more different antimicrobial substances responsible for AMR. In total, the selected literature appraised in this study considered 88 WWTPs (75 municipal treatment facilities and 13 dealing with hospital WW) within 25 countries in three continents (Europe, Africa, Asia).

Among the 218 PRs ascertained responsible for the development of AMR, 45 were detected within the eighteen studies in 88 different WWTPs. The PRs belong to 16 different classes of antibiotics, antifungals, antiprotozoals and antimalarials. Among them, quinolones, sulfonamides, macrolides, tetracyclines and azoles represent 69% of all the PRs reported by the authors. Seven of those, namely ciprofloxacin, clarithromycin, erythromycin, metronidazole, ofloxacin, sulfamethoxazole and trimethoprim, occurred in more than 50% of studies (nine). In particular, ciprofloxacin, sulfamethoxazole and trimethoprim were detected in more than 75% of papers (fourteen). Azithromycin, clindamycin, norfloxacin, oxytetracycline, roxithromycin, sulfadiazine and tetracycline occurred within five and nine studies (25–50%). When looking at the highest PRs concentrations in the effluents of the 88 WWTPs (**Table 1**), sulfamethoxazole, ofloxacin and erythromycin were detected in more than 61% of studies (eleven) as the substances with the highest concentrations among the other antimicrobial substances. In studies in which sulfamethoxazole represented the most abundant PH, authors reported values ranging from 275 to 21,400 ng/L [4][6][24][25], all detected in municipal WW samples.

Table 1. List of 45 pharmaceuticals detected in 88 WWTPs, investigated in the eighteen studies. Maximum and minimum average concentrations and means were reported and expressed in ng/L.

Class	Pharmaceutical	No. of Studies in Which the PR Was Detected (% of the Total)	Max. Average Conc. (ng/L) Detected in Effluents	Min. Average Conc. (ng/L) Detected in Effluents *	Mean across Studies (ng/L)
Amphericols	Chloramphenicol	3 (16.7)	97 [3]	5.9 [26]	50
Azoles	Fluconazole	3 (16.7)	170 [27]	3 [28], H	73
	Metronidazole	10 (55.6)	3000 [2], H	1.2 [29]	330
	Tinidazole	1 (5.6)	12 [25]	9.1 [25]	10
Cephalosporins	Cefalexin	2 (11.1)	308 [1]	5.0 [28]	117
	Ceftazidime	1 (5.6)	1600 [2], H	1600 [2], H	1600
Dehydropeptidase Inhibitors	Cilastatin	1 (5.6)	4100 [2]	4100 [2], H	4100
Diphenylethers	Triclosan	1 (5.6)	7.4 [3]	0.9 [3]	4.2
Folic Acid Inhibitors	Trimethoprim	14 (77.8)	26,100 [30]	1.6 [8]	1979
Glycopeptide antibiotics	Vancomycin	2 (11.1)	162 [4]	81 [5]	119
Lincosamides	Clindamycin	5 (27.8)	290 [4]	0.5 [29]	71
	Lincomycin	4 (22.2)	56 [4]	1.5 [3]	26
Macrolides	Azithromycin	8 (44.4)	56,666 [8]	0.1 [29]	4387
	Clarithromycin	12 (66.7)	15,000 [2], H	0.2 [29]	750
	Erythromycin	11 (61.1)	1187 [31]	0.1 [29]	304
	Roxithromycin	6 (33.3)	6272 [8]	3.6 [8]	882
Penicillins	Ampicillin	4 (22.2)	790 [7], H	60 [7]	254
Penicillins-Like	Amoxicillin	4 (22.2)	1600 [6]	40 [3]	463
Quinolones	Ciprofloxacin	15 (83.3)	24,000 [2], H	0.6 [8]	1137
	Flumequine	3 (16.7)	63 [3]	3.0 [28], H	28
	Lomefloxacin	2 (11.1)	4.6 [8]	0.3 [8]	1.6
	Marbofloxacin	1 (5.6)	<LOD [28]	<LOD [28]	<LOD
	Nalidixic Acid	2 (11.1)	50 [1]	7.8 [25]	24
	Norfloxacin	8 (44.4)	2900 [6]	0.5 [29]	221
	Ofloxacin	12 (66.7)	200,000 [2], H **	2.7 [8]	7405
	Oxolinic Acid	3 (16.7)	60 [3]	4.6 [3]	19
	Sparfloxacin	1 (5.6)	<LOD [30]	<LOD [30]	<LOD
	Sulfamerazine	1 (5.6)	28 [8]	0.3 [8]	8.0
Rifamycins	Rifampicin	1 (5.6)	2.9 [4]	2.9 [4]	2.9
	Rifaximin	2 (11.1)	12 [3]	3.8 [3]	7.0

Class	Pharmaceutical	No. of Studies in Which the PR Was Detected (% of the Total)	Max. Average Conc. (ng/L) Detected in Effluents	Min. Average Conc. (ng/L) Detected in Effluents *	Mean across Studies (ng/L)
Sulfonamides	Sulfadiazine	8 (44.4)	373 [32], H	0.8 [8]	53
	Sulfadimidine	2 (11.1)	106 [3]	3 [3]	54
	Sulfadoxine	1 (5.6)	<LOD [28]	<LOD [28]	<LOD
	Sulfamethazine	4 (22.2)	21 [8]	0.8 [8]	7.0
	Sulfamethizole	2 (11.1)	19 [8]	0.04 [16]	3.6
	Sulfamethoxazole	16 (88.9)	21,400 [6]	1.0 [28], H	1217
	Sulfamoxole	1 (5.6)	<LOD [28]	<LOD [28]	<LOD
	Sulfathiazole	1 (5.6)	138 [8]	0.9 [8]	21
	Sulfisoxazole	1 (5.6)	20 [8]	1.6 [8]	8.1
Tetracyclines	Chlortetracycline	2 (11.1)	12 [32], H	0.5 [8]	4.0
	Doxycycline	3 (16.7)	1500 [6]	0.4 [8]	191
	Minocycline	1 (5.6)	210 [3]	21 [3]	116
	Oxytetracycline	5 (27.8)	416 [8]	0.1 [4]	65
	Tetracycline	6 (33.3)	231 [1]	0.6 [8]	41
Thioamides	Ethionamide	1 (5.6)	9.3 [29]	0.2 [29]	4.8

* LOQ values were not considered; H, Hospital; ** the effluent WW of this facility undergoes treatment in a municipal biological WWTP, of which data were not available [2]. The second-highest concentration of ofloxacin in effluent WW was 3051 ng/L [3].

Out of the 45 antimicrobial substances detected amongst the target studies, ciprofloxacin, clarithromycin, erythromycin, metronidazole, ofloxacin, sulfamethoxazole and trimethoprim constitute a considerable risk in terms of ubiquitous distribution. In particular, sulfamethoxazole frequently appeared in the studies as the compound with the most worrying high concentrations, RQ values and capacities to resist removal treatments. However, in order to establish a classification of the most concerning antimicrobial substances relevant to the question of this review, it is crucial to consider the potentialities of the PRs to induce AMR. Looking at the classification, ciprofloxacin, clarithromycin and ofloxacin are the most worrying antimicrobial substances that may lead to AMR.

4. Conclusions and Recommendations

The present study aimed to appraise all relevant literature for the presence of pharmaceuticals responsible for the development of antimicrobial resistance in wastewater and to provide detailed and updated information valuable for the management of AMR dissemination in wastewater treatment plants.

The review of 18 studies covered 25 countries; 21 are European. Therefore, it can be asserted that notwithstanding that the discharge of harmful antimicrobials is a widespread global issue, research is of particular significance to Europe.

Here, a list of the seven most concerning pharmaceuticals commonly found in the influents and effluents of wastewater treatment plants is proposed. Ciprofloxacin, clarithromycin, erythromycin, metronidazole, ofloxacin, sulfamethoxazole and trimethoprim constitute a considerable risk in terms of ubiquitous distribution, worrying concentrations and RQ values and capacities to resist removal treatments. Especially concerning were the PRs ciprofloxacin, clarithromycin and ofloxacin as these were frequently detected at levels above the predicted no-effect concentrations for resistance selection, which make these compounds the most concerning antimicrobials that encourage the development of antimicrobial resistance.

In conclusion, based on the gaps in knowledge identified during this systematic review, the main recommendations are as follows: The reliability of study outcomes must be improved through the implementation of standardised guidelines for the suitable selection of analytical procedures, data representation, and statistical analysis. The experiments should not be based on daily campaigns composing of a singular grab sample, but instead, values for concentrations should be the

result of the mean of at least three replicates. The need remains for time-weighted screenings to capture seasonal variations in both the influent levels of pharmaceuticals and the effluent levels discharged into aquatic matrices to better assess the impact of wastewater treatment plants on the environment. The necessity of studies dealing specifically with the presence of antimicrobial substances in hospital wastewater or correlating the removal efficiencies of wastewater treatment plants with treatments used is stressed. Call for awareness about the problem of pharmaceuticals compounds in wastewater and the related spread of antimicrobial resistance: the research in this field needs to be expanded to a global level.

References

1. Rodriguez-Mozaz, S.; Vaz-Moreira, I.; Varela Della Giustina, S.; Llorca, M.; Barceló, D.; Schubert, S.; Berendonk, T.U.; Michael-Kordatou, I.; Fatta-Kassinos, D.; Martinez, J.L.; et al. Antibiotic residues in final effluents of European wastewater treatment plants and their impact on the aquatic environment. Environ. Int. 2020, 140, 105733.
2. Yilmaz, G.; Kaya, Y.; Vergili, I.; Beril Gönder, Z.; Özhan, G.; Ozbek Celik, B.; Altinkum, S.M.; Bagdatli, Y.; Boergers, A.; Tuerk, J. Characterisation and toxicity of hospital wastewaters in Turkey. Environ. Monit. Assess. 2017, 189, 55.
3. Alygizakis, N.A.; Besselink, H.; Paulus, G.K.; Oswald, P.; Hornstra, L.M.; Oswaldova, M.; Medema, G.; Thomaidis, N.S.; Behnisch, P.A.; Slobodnik, J. Characterisation of wastewater effluents in the Danube River Basin with chemical screening, in vitro bioassays and antibiotic resistant genes analysis. Environ. Int. 2019, 127, 420–429.
4. Giebułtowicz, J.; Nałęcz-Jawecki, G.; Harnisz, M.; Kucharski, D.; Korzeniewska, E.; Płaza, G. Environmental Risk and Risk of Resistance Selection Due to Antimicrobials' Occurrence in Two Polish Wastewater Treatment Plants and Receiving Surface Water. Molecules 2020, 25, 1470.
5. Castiglioni, S.; Zuccato, E.; Fattore, E.; Riva, F.; Terzaghi, E.; Koenig, R.; Principi, P.; Di Guardo, A. Micropollutants in Lake Como water in the context of circular economy: A snapshot of water cycle contamination in a changing pollution scenario. J. Hazard. Mater. 2020, 384, 141441.
6. Kairigo, P.; Gachanja, A.; Ngumba, E.; Sundberg, L.; Tuhkanen, T. Occurrence of antibiotics and risk of antibiotic resistance evolution in selected Kenyan wastewaters, surface waters and sediments. Sci. Total Environ. 2020, 720, 137580.
7. Kimosop, S.J.; Getenga, Z.M.; Orata, F.; Okello, V.A.; Cheruiyot, J.K. Residue levels and discharge loads of antibiotics in wastewater treatment plants (WWTPs), hospital lagoons, and rivers within Lake Victoria Basin, Kenya. Environ. Monit. Assess. 2016, 188, 532.
8. Ren, B.; Geng, J.; Wang, Y.; Wang, P. Emission and ecological risk of pharmaceuticals and personal care products affected by tourism in Sanya City, China. Environ. Geochem. Health 2021.
9. Jones, H.O.A.; Voulvoulis, N.; Lester, J.N. Human pharmaceuticals in wastewater treatment processes. Crit. Rev. Environ. Sci. Technol. 2005, 35, 401–427.
10. Wang, Y.; Lu, J.; Engelstädter, J.; Zhang, S.; Ding, P.; Mao, L.; Yuan, Z.; Bond, P.L.; Guo, J. Non-antibiotic pharmaceuticals enhance the transmission of exogenous antibiotic resistance genes through bacterial transformation. ISME J. 2020, 14, 2179–2196.
11. WHO. The 2019 WHO AWaRe Classification of Antibiotics for Evaluation and Monitoring of Use; World Health Organization: Geneva, Switzerland, 2019; Available online: https://www.who.int/medicines/news/2019/WHO_releases2019AWaRe_classification_antibiotics/en/ (accessed on 1 November 2020).
12. CDC. Antibiotic Resistance Threats in the United States; US Department of Health and Human Services, CDC: Atlanta, GA, USA, 2019. Available online: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf (accessed on 1 November 2020).
13. CDC. Antifungal Resistance. Atalanta: Centers for Disease Control and Prevention, 2020. Available online: https://www.cdc.gov/fungal/antifungal-resistance.html#what-causes (accessed on 1 November 2020).
14. NHS. Antifungal Medicines; National Health System: London, UK, 2020; Available online: https://www.nhs.uk/conditions/antifungal-medicines/ (accessed on 1 November 2020).
15. Yadav, S.; Jadeja, N.B.; Dafale, N.D.; Purohit, H.; Kapley, A. 17-Pharmaceuticals and personal care products mediated antimicrobial resistance: Future challenges. In Pharmaceuticals and Personal Care Products: Waste Management and Treatment Technology; Prasad, M.N.V., Vithanage, M., Kapley, A., Eds.; Butterworth-Heinemann: Oxford, UK, 2019; pp. 409–428.
16. Brown, E.D.; Wright, G.D. Antibacterial drug discovery in the resistance era. Nature 2016, 529, 336–343.

17. OECD. EU Health Ministerial Meeting—Next Steps towards Making the EU a Best Practice Region in Combating AMR. Bucharest, Romania. 2019. Available online: https://www.oecd.org/health/health-systems/AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.pdf (accessed on 1 November 2020).
18. Directive 2008/105/EC of the European Parliament and of the Council. Available online: https://eur-lex.europa.eu/eli/dir/2008/105/oj (accessed on 1 November 2020).
19. Carvalho, R.; Ceriani, L.; Ippolito, A.; Lettieri, T. Development of the First Watch List under the Environmental Quality Standards Directive, 2015. Report EUR 27142. Available online: https://publications.jrc.ec.europa.eu/repository/bitstream/JRC95018/lbna27142enn.pdf (accessed on 1 November 2020).
20. Leimu, R.; Koricheva, J. What determines the citation frequency of ecological papers? Trends Ecol. Evol. 2005, 20, 28–32.
21. Bayliss, H.R.; Beyer, F.R. Information retrieval for ecological syntheses. Res. Synth. Methods 2015, 6, 136–148.
22. Song, F.; Parekh, S.; Hooper, L.; Loke, Y.K.; Ryder, J.; Sutton, A.J.; Hing, C.; Kwok, C.S.; Pang, C.; Harvey, I. Dissemination and publication of research findings: An updated review of related biases. Health Technol. Assess. 2010, 14, 1–220.
23. Dickersin, K. Publication Bias: Recognising the Problem, Understanding Its Origins and Scope, and Preventing Harm. Chapter 2. In Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments; Rothstein, H.R., Sutton, A.J., Borenstein, M., Eds.; Wiley: Hoboken, NJ, USA, 2006; pp. 9–33.
24. Afonso-Olivares, C.; Sosa-Ferrera, Z.; Santana-Rodriguez, J.J. Occurrence and environmental impact of pharmaceutical residues from conventional and natural wastewater treatment plants in Gran Canaria (Spain). Sci. Total Environ. 2017, 599, 934–943.
25. Huang, H.; Zeng, S.; Dong, X.; Li, D.; Zhang, Y.; He, M.; Du, P. Diverse and abundant antibiotics and antibiotic resistance genes in an urban water system. J. Environ. Manag. 2019, 231, 494–503.
26. Kot-Wasik, A.; Jakimska, A.; Śliwka-Kaszyńska, M. Occurrence and seasonal variations of 25 pharmaceutical residues in wastewater and drinking water treatment plants. Environ. Monit. Assess. 2016, 188, 661.
27. Qi, W.; Singer, H.; Berg, M.; Mueller, B.; Pernet-Coudrier, B.; Liu, H.; Qu, J. Elimination of polar micropollutants and anthropogenic markers by wastewater treatment in Beijing, China. Chemosphere 2015, 119, 1054–1061.
28. Paulus, G.K.; Hornstra, L.M.; Alygizakis, N.; Slobodnik, J.; Thomaidis, N.; Medema, G. The impact of on-site hospital wastewater treatment on the downstream communal wastewater system in terms of antibiotics and antibiotic resistance genes. Int. J. Hyg. Environ. Health 2019, 222, 635–644.
29. Faleye, A.C.; Adegoke, A.A.; Ramluckan, K.; Fick, J.; Bux, F.; Stenström, T.A. Concentration and reduction of antibiotic residues in selected wastewater treatment plants and receiving waterbodies in Durban, South Africa. Sci. Total Environ. 2019, 678, 10–20.
30. Dalahmeh, S.; BjöRnberg, E.; Elenström, A.; Komakech, A.J.; Niwagaba, C.B. Pharmaceutical pollution of water resources in Nakivubo wetlands and Lake Victoria, Kampala, Uganda. Sci. Total Environ. 2020, 710, 136347.
31. Moslah, B.; Hapeshi, E.; Jrad, A.; Fatta-Kassinos, D.; Hedhili, A. Pharmaceuticals and illicit drugs in wastewater samples in north-eastern Tunisia. Environ. Sci. Pollut. Res. 2018, 25, 18226–18241.
32. Li, C.; Lu, J.; Liu, J.; Zhang, G.; Tong, Y.; Ma, N. Exploring the correlations between antibiotics and antibiotic resistance genes in the wastewater treatment plants of hospitals in Xinjiang, China. Environ. Sci. Pollut. Res. 2016, 23, 15111–15121.