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RESEARCH ARTICLE

Fate of selected pharmaceuticals in hospital and municipal wastewater effluent: occurrence, removal, and environmental risk assessment

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Abstract

The concentrations and distribution of β-blockers, lipid regulators, and psychiatric and cancer drugs in the influent and effluent of the municipal wastewater treatment plant (WWTP) and the effluent of 16 hospitals that discharge into the wastewater treatment plant mentioned in this study at two sampling dates in summer and winter were examined. The pharmaceutical contribution of hospitals to municipal wastewater was determined. The removal of target pharmaceuticals was evaluated in a WWTP consisting of conventional biological treatment using activated sludge. Additionally, the potential environmental risk for the aquatic receiving environments (salt lake) was assessed. Beta-blockers and psychiatric drugs were detected in high concentrations in the wastewater samples. Atenolol (919 ng/L) from β-blockers and carbamazepine (7008 ng/L) from psychiatric pharmaceuticals were detected at the highest concentrations in hospital wastewater. The total pharmaceutical concentration determined at the WWTP influent and effluent was between 335 and 737 ng/L in summer and between 174 and 226 ng/L in winter. The concentrations detected in hospital effluents are higher than the concentrations detected in WWTP. The total pharmaceutical contributions from hospitals to the WWTP in summer and winter were determined to be 2% and 4%, respectively. Total pharmaceutical removal in the WWTP ranged from 23 to 54%. According to the risk ratios, atenolol could pose a high risk (risk quotient > 10) for fish in summer and winter. There are different reasons for the increase in pharmaceutical consumption in recent years. One of these reasons is the COVID-19 pandemic, which has been going on for 2 years. In particular, hospitals were operated at full capacity during the pandemic, and the occurrence and concentration of pharmaceuticals used for the therapy of COVID-19 patients has increased in hospital effluent. Pandemic conditions have increased the tendency of people to use psychiatric drugs. It is thought that beta-blocker consumption has increased due to cardiovascular diseases caused by COVID-19. Therefore, the environmental risk of pharmaceuticals for aquatic organisms in hospital effluent should be monitored and evaluated.

Keywords Pharmaceuticals · Risk assessment · Hospital wastewater · Conventional treatment

Introduction

The growing population and the development of urbanization and industrialization have led to an increase in the concentration of some pollutants and introduced new pollutants in the environment (Belhaj et al. 2015). As a result of advances in medical treatment methods, the emergence of new diseases, the rising demand in the field of health care and economic advancements, and the production and consumption of pharmaceuticals have inevitably risen. Pharmaceuticals are complex molecules, and due to their extensive use, they have been determined to exist in different environmental matrices, such as wastewater, surface water, groundwater, drinking water, sewage sludge, and sediments. Pharmaceutical residues impose proven or predicted risks to microorganisms, fauna, and flora (Bartrons and Peñuelas 2017; Ashfaq et al. 2017). Pharmaceuticals are subdivided into different therapeutic groups, such as analgesics/anti-inflammatories, antibiotics, β-blockers, cardiac drugs, psychiatric drugs, lipid regulators,

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and cancer drugs. These pharmaceuticals are among the commonly used drugs in hospitals and homes. Beta-blockers have been extensively taken for the treatment of abnormal heart rhythms, high blood pressure, angina pectoris, hypertension, and cardiac dysfunction (Yi et al. 2020). Atenolol, metoprolol, propranolol, and sotalol are the most widely used β-blockers (Khasawneh and Palaniandy 2021). Because β-blockers are becoming more widely used and are one of the most commonly found pharmaceuticals in the environment, it is possible to measure β-blockers and their metabolites in wastewater up to µg/L (Yi et al. 2020; Wilde et al. 2013). When studies on the occurrence of β-blockers in wastewater were examined, different concentrations were determined depending on drug use and wastewater treatment technologies in different countries (Yi et al. 2020). For example; β-blockers were detected in the range of 64–474 ng/L in Italy (Al Aukidya et al. 2012), in the range of 35–1600 ng/L in Finland (Vieno et al. 2007), in the range of 0.4–2110 ng/L in Spain (Biel-Maeso et al. 2018a), and in the range of 25–1530 ng/L in Switzerland (Alder et al. 2010) at the output of the wastewater treatment plant (WWTP).

In addition, β-blockers (atenolol, acebutolol, bisoprolol, celiprolol, metoprolol, nadolol, pindolol, propranolol, and sotalol) have a half-life of 3–8.7 days in water and are classified as "pseudopersistent" (Hernando et al. 2006; Ramil et al. 2010). Lipid regulators are widely used for the treatment of hyperlipidemia and are among the most common pharmaceuticals in wastewater. The current commonly used lipid regulators are gemfibrozil, bezafibrate, fenofibrate, and clofibric acid (Wang et al. 2019). More than 264 million people worldwide suffer from depression. The consumption of psychiatric drugs is higher than the consumption of other medical drugs (Melchor-Martínez et al. 2021). Thus, with the increasing consumption of psychiatric drugs, they have begun to be detected in wastewater, surface waters, and even drinking water around the world. For instance, the concentrations of psychiatric pharmaceuticals ranged from <dl to 3124 ng/L in WWTP influent and from <dl to 2956 ng/L in WWTP effluent (Kosma et al. 2019; Wu et al. 2015; Yuan et al. 2013; Lajeunesse et al. 2012; Oliveira et al. 2015). Psychiatric pharmaceuticals were also found in surface water (24.3 ng/L for diazepam, 0.4 ng/L for fluoxetine, 4 ng/L for lorazepam, 25.3 ng/L for carbamazepine in Chinese rivers) (Wu et al. 2015). Furthermore, psychiatric pharmaceuticals were detected at 1.9 ng/L (Wu et al. 2015) and 23.5 ng/L (Zuccato et al. 2000) for diazepam in drinking water. Psychiatric drugs can be grouped into antidepressants, anxiolytics, sedatives and hypnotics, antipsychotics, and mood stabilizers (Kosma et al. 2019). It is foreseen that there will be 21.4 million new cancer patients by 2032. Cancer medicines will be used more frequently as a result of this in forthcoming years. As cancer drugs are classified into cytotoxic and endocrine therapy drugs, they are a cause for concern (Oliveira Klein et al. 2021). Additionally, 33 emerging contaminants, including diclofenac, ibuprofen, carbamazepine, and clofibric acid, were identified in surface waters by the European Union (Hena et al. 2021).

Pharmaceuticals can enter environmental matrices in different ways, such as pharmaceutical production plants, hospitals, improper disposal, households and WWTPs, irrigation with treated or untreated wastewater, and atmospheric wet deposition (Ma et al. 2018; Ferrey et al. 2018; Martínez-Alcala et al. 2021). After the COVID-19 pandemic, which emerged at the end of 2019, the consumption of pharmaceuticals has increased worldwide. The detection frequency and concentration of some pharmaceuticals post pandemic in Wuhan surface water increased before the pandemic. Additionally, some antibiotics pose a medium/high risk for aquatic organisms (Chen et al. 2021). The concentrations of antiviral drugs and paracetamol in wastewater increased 170% and 198% compared to prepandemic concentrations in Greece, respectively (Galani et al. 2021). Kuroda et al. (2021) reported that the removal efficiency of antiviral drugs used to treat coronavirus disease with conventional wastewater processes is below 20%. These drugs pose a high risk for aquatic organisms in the receiving environment. In particular, due to the increase in the number of patients receiving therapy in hospitals during the COVID-19 pandemic, the pharmaceutical contribution of hospitals to urban wastewater has increased (Khan et al. 2021). Commonly used conventional WWTPs, which include primary and secondary treatment processes to remove pollutants such as organic matter and suspended matter, are not designed to eliminate these compounds; therefore, many pharmaceuticals go through conventional WWTP without adequate treatment. In addition, the main sources of pharmaceuticals in WWTPs are households and hospital wastewater. Hospital wastewater containing a large number of pharmaceuticals is generally discharged into sewer networks and treated together with domestic wastewater in WWTPs. Hospitals produce different amounts of wastewater containing different types and numbers of pharmaceuticals according to hospital characteristics. Determining the contribution of hospitals to the pharmaceutical load in WWTPs is important for the pretreatment of hospital wastewater (Tormo-Budowski et al. 2021; Semerjian et al. 2018; Santos et al. 2013). Pharmaceuticals have been detected worldwide at ng/L, ng/g, or µg/L levels and at µg/g levels in wastewater and the receiving environment, respectively (Maniakova et al. 2020). Pharmaceuticals have effects significantly reducing fertility in species such as cladoceran *Daphnia magna* and fish, endocrine disruption in receiving environments, and development of bacterial pathogen resistance (Semerjian et al. 2018).

In this context, a total of 18 commonly used pharmaceuticals of different therapeutic classes (β-blockers, lipid regulators, psychiatric and cancer drugs) were analyzed in sixteen

hospital effluents and the influent and effluent of municipal WWTP in Konya (Turkey) at two sampling dates in summer and winter Konya urban wastewater and examined 16 hospitals discharge to the Konya WWTP. For this reason, wastewater samples were taken from the Konya WWTP to determine the pharmaceutical load of the examined hospitals to the WWTP and to determine the treatment efficiency of pharmaceuticals. The plants have screening, grit removal, preliminary sedimentation, biological treatment with activated sludge process, and secondary sedimentation.

Pharmaceutical concentrations discharged into the sewer system of the examined hospitals were determined. Generally, hospital wastewater is an important source of pharmaceuticals in WWTPs. In this study, the pharmaceutical pollution load of the examined hospitals to the WWTP was revealed. The pharmaceutical removal of Konya WWTP was calculated with detected concentrations at influent and effluent of Konya WWTP. Konya WWTP effluent is discharged into the salt lake. Pharmaceuticals have some proven and predicted risks to the receiving environment. So, the potential ecotoxicological risk for pharmaceuticals was determined by using the risk quotient for aquatic organisms in the receiving environment.

Material and methods

Chemicals and equipment

Atenolol, sotalol, timolol, bezafibrate, pravastatin, tamoxifen, ifosfamide, and etoposide were obtained from Sigma (Switzerland), and metoprolol, propranolol, clofibric acid, fenofibrate, gemfibrozil, carbamazepine, diazepam, fluoxetine, lorazepam, and cyclophosphamide standards were obtained from Fluka (Switzerland). The physicochemical properties of the investigated pharmaceuticals are presented in the supplementary material (Table S1). HPLC-grade methanol, hydrochloric acid (37%), formic acid (98%), and ethylenediaminetetraacetic acid disodium salt solution (Na_2EDTA) were obtained from Merck (Darmstadt, Germany). While a glass fiber filter with a 1.2 µm pore diameter was acquired from Whatman (USA), a 0.45-µm nylon membrane filter was acquired from Sartorius (Göttingen, Germany). The Oasis HLB cartridge (60 mg, 3 mL) used for solid phase extraction (SPE) was obtained from Waters Corporation. Deionized water was supplied from a Millipore brand ultrapure water device. High-purity nitrogen gas was provided by a nitrogen generator (Peak Scientific).

Wastewater samples

Hospital effluents were collected from 5 state hospitals and 5 private hospitals in Selcuklu District, 2 state hospitals and 3 private hospitals in Meram District, and 1 private hospital in Karatay District and the influent and effluent of the municipal WWTP, which receives wastewater from the three districts in Konya. Effluent samples were taken from the discharge points of the hospitals into the sewage system. The bed capacities of the sampled hospitals vary between 27 and 1298 beds. The Konya sewerage system is a combined sewerage system in which wastewater and rainwater are collected in the same channel. There are physical treatments, biological treatments, and disinfection processes in the WWTP. Wastewater samples were gathered twice a year in summer and winter using a composite micro sampler (Durko, Turkey) and were stored at 4 °C until analysis.

Analytical procedures

Wastewater samples before extraction were passed through a glass fiber filter and a nylon membrane filter. The Oasis HLB SPE cartridge was conditioned with 5 mL of deionized water followed by 5 mL of methanol at a flow rate of approximately 2 mL/min. Samples were loaded into the cartridge at a flow rate of approximately 1 mL/min. After preconcentration of the sample, the cartridge was washed with 5 mL of deionized water at a flow rate of approximately 2 mL/min, and air was passed through the cartridge for 5 min to remove excess water from the cartridge. Elution of the compounds in the cartridge was carried out with 10 mL of methanol at a flow rate of approximately 1 mL/min. The extract obtained was redissolved in 400 µL methanol/water (50/50, v/v) after drying under a rotary evaporator and gentle stream of nitrogen gas.

Quantitative analyses of target compounds were carried out with LC-MS/MS systems. The mobile phase was eluent A (deionized water with 0.1% formic acid and 5 mM ammonium formate) and eluent B (methanol) for positive ion mode and eluent A (deionized water with 10 mM ammonium acetate) and eluent B (methanol) for negative ion mode. The most suitable carrier phase flow rate was determined to be 0.6 mL/min. The column temperature was 35 °C, and the injection volume was 2 µL. Analytical parameters determined for the pharmaceuticals are given in Table S2.

Physicochemical analyses such as pH, electrical conductivity (EC), total suspended solids (TSS), and chemical oxygen demand (COD) of wastewater taken from hospitals and the influent and effluent of municipal WWTP were carried out. The pH and EC measurements of the wastewater samples were performed with a Hach brand portable pH and EC measuring device. TSS measurements were carried out according to standard methods (APHA 1992). COD values were measured with a WTW brand spectrophotometer using ready kits. The pH, EC, TSS, and COD values of wastewater samples

ranged from 6.58 to 8.63, from 525 to 7970 µS/cm, from 18 to 1218 mg/L, and from 183 to 819 mg/L in hospital wastewater and from 7.2 to 7.93, from 1706 to 2510 µS/cm, from 592 to 644 mg/L, and from 539 to 944 mg/L in municipal wastewater, respectively. The pH, EC, and TSS values were higher in hospital wastewater than in municipal wastewater.

Environmental risk assessment

An environmental risk assessment approach was used to assess the impact of pharmaceutical pollution on the aquatic environment. Risk quotient (RQ) values were calculated for three different trophic levels (algae, crustaceans, and fish) using Eq. (1):

$$RQ = MECmax/PNEC \quad (1)$$

The meanings of the MEC_{max} and PNEC are as follows: maximum measured environmental concentration and predicted no-effect concentration, respectively. The PNEC values used for the calculations are presented in Table S3. The risk assessment criteria, where RQ < 0.1, suggest no adverse effect with insignificant risk. A value of 0.1 < RQ < 1.0 suggests a low risk, and there is a potential adverse effect. Values of RQ between 1 and 10 indicate a moderate risk, while a high ecological risk indicates values equal to or above 10 (Gomez et al. 2006; Deblonde and Hartemann 2013).

Results and discussion

Pharmaceutical concentration in wastewater

Table 1 demonstrates the minimum, average, and maximum concentrations of the pharmaceuticals detected in the wastewater samples. All compounds investigated were present in at least one influent, effluent, and hospital wastewater, with the exception of timolol and diazepam. This result indicates the widespread presence of pharmaceuticals in wastewater even after treatment. Pharmaceutical concentrations detected in previous studies are given in Tables 2, 3, 4, and 5. In this

Table 1 Range of concentrations, mean, and median concentrations of pharmaceuticals in hospital effluents and WWTP influent and effluent (ng/L)

Pharmaceuticals	Summer					Winter				
	Hospital effluent			WWTP		Hospital effluent			WWTP	
	Range	Mean	Median	Influent	Effluent	Range	Mean	Median	Influent	Effluent
Atenolol	<dl–163	35.3	13.3	424	163	47.2–919	156	67.8	154	138
Metoprolol	<dl–176	18.2	0.01	86.8	39.7	<dl–48.7	6.69	2.43	7.43	<dl
Propranolol	<dl–118	14.9	<dl	3.31	<dl	0.57–5.14	0.97	0.59	7.43	0.64
Sotalol	<dl–6.60	0.41	<dl	81.0	30.4	<dl–78.5	7.54	0.22	7.43	0.03
Timolol	<dl	<dl	<dl	<dl	<dl	<dl	<dl	<dl	<dl	<dl
Carbamazepine	<dl–7008	509	20.8	136	101	<dl–85.9	10.8	<dl	11.9	<dl
Diazepam	<dl	<dl	<dl	<dl	<dl	<dl	<dl	<dl	<dl	<dl
Fluoxetine	<dl	<dl	<dl	<dl	<dl	2.48–4.21	2.85	2.75	2.57	2.51
Lorazepam	<dl–0.10	<dl	<dl	<dl	<dl	2.88–65.3	16.3	9.91	4.83	2.53
Bezafibrate	0.04–0.63	0.18	0.14	0.41	0.15	4.44–8.79	6.40	6.08	8.24	8.18
Clofibric acid	0.03–0.16	0.08	0.07	0.26	0.04	<dl	<dl	<dl	<dl	<dl
Fenofibrate	0.01–0.82	0.13	0.08	0.15	0.07	1.03–2.02	1.31	1.29	1.46	1.45
Gemfibrozil	0.03–0.28	0.12	0.11	3.61	0.89	2.96–6.76	4.40	3.07	13.5	6.30
Pravastatin	0.17–1.76	0.56	0.47	0.81	0.10	3.45–26.4	5.87	3.77	5.49	5.43
Tamoxifen	0.001–0.17	0.04	0.02	0.01	<dl	1.74–3.93	2.48	1.77	3.37	3.31
Cyclophosphamide	0.009–2.17	0.17	0.02	0.38	0.07	1.11–2.41	1.71	1.75	2.44	2.37
Ifosfamide	0.01–0.31	0.06	0.03	0.38	0.11	1.80–2.87	2.26	1.88	2.83	2.80
Etoposide	0.04–5.69	0.61	0.25	0.30	0.07	<dl	<dl	<dl	<dl	<dl
Total β-blocker	<dl–209	68.8	32.6	595	233	48.1–924	171	95.2	169	139
Total psychiatric drugs	<dl–7009	509	20.8	136	101	6.50–154	61.9	17.2	19.3	5.04
Total lipid regulators	0.56–2.28	1.09	0.93	5.24	1.25	11.9–41.8	17.9	13.8	28.7	21.4
Total cancer drugs	0.22–5.73	0.89	0.41	0.96	0.25	4.65–8.95	6.44	5.45	8.64	8.48
Total pharmaceutical	0.83–7127	580	33.7	737	335	86.3–993	226	139	226	174

<dl means below the limit of detection

Table 2 Beta-blockers detected in hospital effluent, WWTP influent, and effluent in the literature

Country	Atenolol	Metoprolol	Propranolol	Sotalol	Timolol	Reference
Hospital effluents						
Denmark	170–250	2900–3700	260–360	16–28	–	Nielsen et al. (2013)
Portugal	59–1069	<dl–35.6	18.0–98.9	<dl–89.1	–	Santos et al. (2013)
Italy	5100, 2400–5800	830, 740–1100	23, 43–85	4800, 48–5100	<dl, <dl–33	Verlicchi et al. (2012a)
USA	1370–3790	750–3540	10–200	100–530	nd–30	Oliveira et al. (2015)
Spain	1361[a], 3400[b]	46[a]	279[a], 1350[b]	235[a]	–	Mendoza et al. (2015)[a]; Gomez et al. (2006)[b]
Taiwan	–	–	54	–	–	Lin and Tsai 2009
Switzerland	2315	1325	–	–	–	Kovalova et al. (2012)
Finland	2300	1700	–	–	–	Ajo et al. (2018)
France	796–2134	–	30–603	–	–	Perrodin et al. (2013)
Mexico	200	2020	–	–	–	Perez-Alvarez et al. (2018)
Turkey	<dl–919	<dl–176	<dl–118	<dl–78.5	<dl	In this study
WWTP influent						
Portugal	522[a]	<dl[a]	8.98[a], 344[b]	117[a]	–	Santos et al. (2013)[a]; Paíga et al. (2019)[b]
Italy	2100	260	26	530	14	Verlicchi et al. (2012b)
USA	1340–6030	600–3020	20–70	120–510	nd–20	Oliveira et al. (2015)
Spain	1620[a], 1391[b]	128[b]	123[a], 13[b]	–	13[a], 5[b]	Biel-Maeso et al. (2018a)[a]; Villar-Navarro et al. (2018)[b]
China	–	114	<dl	–	–	Dai et al. (2014)
UK	12,913, 14,223	75, 94	557, 638	–	–	Kasprzyk-Hordern et al. (2009)
Turkey	154–424	7.43–86.8	3.31–7.43	7.43–81.0	<dl	In this study
WWTP effluent						
Portugal	600[a]	11.9[a]	8.27[a], nd[b]	154[a]	–	Santos et al. (2013)[a]; Paíga et al. (2019)[b]
Italy	73	180	18	320	10	Verlicchi et al. (2012a)
USA	130–650	500–2110	nd–100	50–470	nd–20	Oliveira et al. (2015)
Spain	1140[a], 775[b]	94[b]	73[a], 12[b]	–	13[a], 4[b]	Biel-Maeso et al. (2018a)[a]; Villar-Navarro et al. (2018)[b]
China		157	6	–	–	Dai et al. (2014)
UK	2870, 2123	69, 41	265, 264	–	–	Kasprzyk-Hordern et al. (2009)
Turkey	138–163	<dl–39.7	<dl–0.64	0.03–30.4	<dl	In this study

En dash means not analyzed, and <dl means below the limit of detection

nd not detected

study, the maximum concentrations of β-blockers detected in hospital wastewater were 175 ng/L for metoprolol during the summer and 920 ng/L for atenolol during the winter. The concentrations of β-blockers in the influent and effluent of the municipal WWTP were <dl–424 ng/L in summer and <dl–153 ng/L in winter, and <dl–162 ng/L in summer and <dl–138 ng/L in winter, respectively. At the WWTP, atenolol was determined at maximum concentration in both summer and winter periods. Additionally, timolol compounds were not detected in hospital, influent, or effluent wastewater. When looking at the physicochemical properties of the β-blockers investigated, the atenolol compound has higher solubility than other β-blockers. In addition, the atenolol compound is excreted from the body at a rate of 40–50% in the main form and has a low log K_{ow} value (0.16). Therefore, it has high mobility in aquatic environments. Due to these properties, it was detected in high concentrations in hospital and WWTP wastewaters. Even though the removal rates of the metoprolol, propranolol, and timolol compounds in the main form are low, the log K_{ow} values are high. However, the sotalol compound is excreted in the main form at a rate higher than 75%, and the log K_{ow} value is low. Atenolol was detected at high concentrations because there are many drugs containing atenolol as an active ingredient, and it is used in the treatment of more common diseases.

The minimum concentration of lipid regulators in hospital wastewater was 0.011 ng/L (fenofibrate) in summer and below the detection limit (clofibric acid) in winter. The maximum concentration in hospital wastewater was determined to be 1.76 ng/L (pravastatin) in the summer and 26.38 ng/L (pravastatin) in the winter. Lipid regulators were 0.15–3.61 ng/L in summer, <dl–13.51 ng/L in winter, 0.084–0.89 ng/L

Table 3 Lipid regulators detected in hospital effluent, WWTP influent, and effluent in the literature

Country	Bezafibrate	Clofibric acid	Fenofibrate	Gemfibrozil	Pravastatin	Reference
Hospital effluent						
Denmark	< 10	< 10	< 12–28	–	–	Nielsen et al. (2013)
Portugal	<dl–258	–	–	nd–125	<dl–306	Santos et al. (2013)
Italy	950, <dl–200	17, <dl–13	10, <dl	19, <dl–33	620, 77–170	Verlicchi et al. (2012b)
USA	nd	nd	–	150–3250	30–480	Oliveira et al. (2015)
Spain	126	–	103	–	–	Mendoza et al. (2015)[c]
Taiwan	–	–	–	760	–	Lin and Tsai (2009)
Switzerland	63[a]	–	–	–	1600[b]	Kovalova et al. (2012)[a]; Escher et al. (2011)[b]
Turkey	0.04–8.79	<dl–0.16	0.01–2.02	0.03–6.76	0.17–26.4	In this study
WWTP influent						
Portugal	490[a]	–	–	<ql[a], 59[b]	218[a]	Santos et al. (2013)[a]; Paiga et al. (2019)[b]
Italy	90	10	6	200	110	Verlicchi et al. (2012a)
USA	nd	nd	–	760–5380	nd–350	Oliveira et al. (2015)
Spain	297[a], 188[b]	65[b]	78[a], 1[b]	2870[a], 3108[b]	406[a], nd[b]	Biel-Maeso et al. (2018a)[a]; Villar-Navarro et al. (2018)[b]
China	36	–	–	94	–	Dai et al. (2014)
UK	420, 600	19, 1	–	–	< 60	Kasprzyk-Hordern et al. (2009)
Slovenia	–	–	–	–	–	Isidori et al. (2016)
Turkey	0.41–8.24	<dl–0.26	0.15–1.46	3.61–13.5	0.81–5.49	In this study
WWTP effluent						
Portugal	4409[a]	–	–	<dl[a], 27[b]	239[a]	Santos et al. (2013)[a]; Paíga et al. (2019)[b]
Italy	36	20	3	110	540	Verlicchi et al. (2012b)
USA	nd	nd	–	230–540	nd	Oliveira et al. (2015)
Spain	73[a], 24[b]	2[b]	24[a], 1[b]	1910[a], 2578[b]	138[a], nd[b]	Biel-Maeso et al. (2018a)[a]; Villar-Navarro et al. (2018)[b]
China	15	–	–	117	–	Dai et al. (2014)
UK	231, 177	15, 6	–	–	< 60	Kasprzyk-Hordern et al. (2009)
Turkey	0.15–8.18	<dl–0.04	0.07–1.45	0.89–6.30	0.10–5.43	In this study

En dash means not analyzed, and <dl means below the limit of detection

nd not detected

in summer, and <dl–8.18 ng/L in the influent and effluent of the WWTP, respectively. Gemfibrozil was detected at the highest concentrations in wastewaters taken from the influent and effluent of the WWTP in summer and winter. The lowest concentrations in the wastewater treatment plant were determined for fenofibrate compound in the influent, clofibric acid compound in the effluent in the summer, and clofibric acid compound in the influent and effluent in the winter. Lipid regulators have high persistence (log K_{ow}: 2.5–5.2; half-life: 15–100 days). Bezafibrate and pravastatin compounds are excreted in the main form at high rates from the body. Lipid regulators have low water solubility, high log K_{ow} values, and half-lives. Fenofibrate compounds are usually detected in wastewater at low concentrations due to their very small excretion from the body in the form of the parent compound. The oral doses of bezafibrate and pravastatin, which were predominantly detected in the samples, were excreted from the body at approximately 30% unchanged. Higher concentrations of lipid regulators were determined in all hospitals during the winter. This result can be explained by the tendency of the patients' blood fat to increase during cold seasons (Ockene et al. 2004). Consumption of lighter foods during the summer months, depending on eating habits, reduces the consumption of cholesterol reducers.

In hospital wastewater, carbamazepine was detected at maximum concentrations of 7008 ng/L in summer and 85.9 ng/L in winter. In hospital wastewater, fluoxetine and diazepam were determined to be below the detection limit in all samples during the summer period. Lorazepam was determined to be below the detection limit in samples taken from hospitals, except for one hospital. Carbamazepine compounds were detected at 135 ng/L in the influent of the municipal WWTP and 100 ng/L in the effluent and in the summer period, while other compounds were detected to be below the detection limit. In the winter period, carbamazepine compound was determined as 11.9 ng/L, fluoxetine compound as 2.57 ng/L, lorazepam compound as 4.83 ng/L at the influent of the municipal WWTP, fluoxetine compound as 2.51 ng/L, and lorazepam compound as 2.53 ng/L at the effluent of the municipal WWTP. When the physicochemical

Table 4 Psychiatric drugs detected in hospital effluent, WWTP influent, and effluent in the literature

Country	Carbamazepine	Diazepam	Fluoxetine	Lorazepam	Reference
Hospital effluent					
Denmark	2300–3200	–	–	–	Nielsen et al. (2013)
Portugal	64.5–771	<ql–18.5	19.3–70.1	110–441	Santos et al. (2013)
Italy	730, 950–970	<dl, <dl–31	5, 27–56	670, 60–180	Verlicchi et al. (2012a)
USA	20–620	nd–10	20–230	30–100	Oliveira et al. (2015)
Spain	271[a], 40[b]	33[a]	–	609[a]	Mendoza et al. (2015)[a]; Gomez et al. (2006)[b]
Switzerland	222[a], 500[b]	–	30[a]	–	Kovalova et al. (2012)[a]; Escher et al. (2011)[b]
Finland	100	–	–	–	Ajo et al. (2018)
Turkey	<dl–7009	<dl	<dl–4.21	<dl–65.3	In this study
WWTP influent					
Portugal	565[a], 689[b]	6.46[a], 56[b]	<dl[a], 76[b]	299[a], nd[b]	Santos et al. (2013)[a]; Paiga et al. (2019)[b]
Italy	580	76	110	220	Verlicchi et al. (2012b)
USA	160–570	nd–100	10–80	nd–50	Oliveira et al. (2015)
Spain	291[a], 215[b]	–	326[a], 3[b]	–	Biel-Maeso et al. (2018a)[a]; Villar-Navarro et al. (2018)[b]
China	94	–	–	–	Dai et al. (2014)
UK	1694, 950	–	–	–	Kasprzyk-Hordern et al. (2009)
Turkey	11.9–136	<dl	<dl–2.57	<dl–4.83	In this study
WWTP effluent					
Portugal	460[a], 1107[b]	7.16[a], 35[b]	<dl[a], 67[b]	294[a], 74[b]	Santos et al. (2013)[a]; Paiga et al. (2019)[b]
Italy	370	<dl	44	120	Verlicchi et al. (2012b)
USA	170–580	nd–20	nd–130	nd–30	Oliveira et al. (2015)
Spain	232[a], 182[b]	–	326[a], nd[b]	–	Biel-Maeso et al. (2018a)[a]; Villar-Navarro et al. (20182018)[b]
China	117	–	–	–	Dai et al. (2014)
UK	2499, 826	–	–	–	Kasprzyk-Hordern et al. (2009)
Turkey	<dl–101	<dl	<dl–2.51	<dl–2.53	In this study

En dash means not analyzed, and <dl means below the limit of detection

nd not detected

properties of psychiatric drugs were examined, the water solubility of the fluoxetine compound was quite high compared to other compounds, and all of the investigated psychiatric compounds had high persistence (log K_{ow}: 2.45–4.08). Most carbamazepine appears to be excreted from the body without being metabolized. Summer term sampling was carried out at the end of August. During the change of seasons, the rate of people experiencing depression increases, which may raise the use of psychiatric drugs. In addition, one factor affecting the pharmaceutical concentrations in wastewater is dilution during the rainy seasons. The most commonly detected carbamazepine compound is the most commonly used psychiatric drug in psychiatric conditions such as epilepsy, mania, bipolar disorder, and anxiety, and it is eliminated from the body in its main form at a rate of approximately 28–72% of the dose taken. It remains in the water phase due to its low adsorptive rate in the sludge.

The detected maximum concentrations of the cancer drugs in hospital wastewater were 5.59 ng/L for etoposide in summer and 3.93 ng/L for tamoxifen in winter in the present study. In the summer, tamoxifen was detected at 0.17 ng/L, which was the minimum concentration. The maximum concentrations in influent wastewater were 0.38 ng/L for cyclophosphamide in summer and 3.37 ng/L for tamoxifen in winter. The maximum concentrations in effluent wastewater were 0.11 ng/L for ifosfamide in summer and 3.31 ng/L for tamoxifen in winter. Etoposide was found below the limit of quantification in all the samples analyzed in winter. Concentrations of etoposide and cyclophosphamide in WWTP were lower than their concentrations in hospital effluent. Other cancer drugs have been detected in close concentrations in hospital wastewater and WWTP samples. Etoposide is a medicine that is supplied to hospitalized patients rather than for domestic use, and it is excreted from the body in the form of the parent compound at a rate of 5–22%. The log K_{ow} value is quite low and tends to remain in the water phase. Etoposide can react rapidly with chlorine and decompose (Santana-Viera et al. 2019). Tamoxifen, which was detected at high concentrations in the winter period,

Table 5 Cancer drugs detected in hospital effluent, WWTP influent, and effluent in the literature

Country	Tamoxifen	Cyclophosphamide	Ifosfamide	Etoposide	Reference
Hospital effluents					
Denmark	<5	12–14	62–70	–	Nielsen et al. (2013)
Italy	<dl	–	–	–	Verlicchi et al. (2012a)
Spain	<dl–7.4	<dl–32	<dl	nd	Isidori et al. (2016)
Spain		1218		375.8–619.9	Santana-Viera et al. (2019)
Slovenia	<dl–10	1080–22,100	<dl–48	<ql	Isidori et al. (2016)
Canada		nd–2.17	nd–144		Vaudreuil et al. (2020)
Turkey	0.001–3.93	0.009–2.41	0.01–2.87	<dl–5.69	In this study
Influent of WWTP					
Portugal	–	nd–80	nd–50	nd–62	Gouvei et al. (2020)
Italy	<dl	–	–	–	Verlicchi et al. (2012b)
USA	–	–	–	–	Oliveira et al. (2015)
Spain	6.7[a]	<dl[a]	<dl[a]	nd[a]	Isidori et al. (2016)[a]
Sapin				874.9–5141	Santana-Viera et al. (2019)
Slovenia	11	19	<dl	<ql	Isidori et al. (2016)
Canada		<LOD–118	<LOD		Vaudreuil et al. (2020)
Turkey	0.01–3.37	0.38–2.44	0.38–2.83	<dl–0.30	In this study
Effluent of WWTP					
Portugal	–	nd–42	nd–71	nd	Gouvei et al. (2020)[c]
Italy	<dl	–	–	–	Verlicchi et al. (2012a)
Spain	<dl	<dl	<dl	nd	Isidori et al. (2016)
Sapin		55.94–91.25			Santana-Viera et al. (2019)
Slovenia	7.1	17	<dl	nd	Isidori et al. (2016)
Canada		<LOD–18.2	nd		Vaudreuil et al. (2020)
Turkey	<dl–3.3	0.07–2.37	0.11–2.80	<dl–0.07	In this study

En dash means not analyzed, and <dl means below the limit of detection

nd not detected

has a longer half-life than other cancer drugs and was found at higher concentrations than other cancer drugs due to its persistence. Tamoxifen has a high consumption amount in breast cancer treatment. Additionally, it is used in reproductive control and hormone treatments for animals (Ferrando-Climent et al. 2014; Negreira et al. 2015). Cyclophosphamide is the most common drug and is a compound resistant to ozonation. Ifosfamide is prescribed less than the other investigated cancer drugs. Some studies have indicated that hospital wastewater and WWTPs contain low concentrations of cancer drugs (Santana-Viera et al. 2019; Ferrando-Climent et al. 2014; Ferre-Aracil et al. 2016). Santana-Viera et al. (2019) detected etoposide at concentrations of 376 ng/L and 620 ng/L in hospital wastewater in influent wastewater ranging from 620 to 5141 ng/L. Cyclophosphamide was detected in hospital wastewater at a concentration of 1218 ng/L and in effluent wastewater at a concentration of 91.3 ng/L. However, even at low concentrations, they can have a negative effect on aquatic biota, flora, and fauna. Additionally, continuous discharge, even at low concentrations, may cause their accumulation (Oliveira Klein et al. 2021).

In some studies, it has been determined that the pharmaceutical concentrations in wastewater show seasonal changes. For example, studies conducted in Switzerland and the USA have found that concentrations in winter were higher than those in summer (Valcarcel et al. 2013; Yu et al. 2013). Golovko et al. (2014) investigated 21 pharmaceuticals in WWTPs and reported that the total concentrations of target pharmaceuticals in WWTPs were higher during winter than during summer. Sui et al. (2011) and Yu et al. (2013) found higher pharmaceutical concentrations in wastewater in winter season. Seasonal conditions, regional factors, average age of the population, and processes of WWTPs can affect the presence of pharmaceuticals in wastewater (Golovko et al. 2014; Bueno et al. 2012). While the concentrations of pharmaceuticals in wastewater are generally higher in the winter season, the removals are higher in the summer season.

Pharmaceutical contribution from hospitals to municipal WWTP

The wastewater flow rate per bed was accepted as 1000 L/day for the purpose of determining the load brought by medicines used in hospitals in WWTPs (Metcalf and Eddy 2003), and the contributions from each hospital were calculated. The flow to the WWTP is 170,000 m^3/day, with industrial flow accounting for 6%. Excluding industrial wastewater flow, the WWTP receives 159,800 m^3/day. It is known that the foremost route of entry of pharmaceuticals into ecological systems is wastewater. Domestic usage, industry, and hospitals are thought to be the principal pharmaceutical sources in wastewater. According to some studies, hospitals are the most significant source of pharmaceutical load in municipal WWTPs, and it is recommended that their wastewater be discharged after pretreatment (Corre et al. 2012; Hawkshead 2008; Ternes et al. 2006). The pharmaceutical load and their contributions originating from each hospital are given in Table 6. In this study, the total pharmaceutical solids made from hospitals to the influent of WWTP were found to be 1.9% in the summer and 4.32% in the winter. Thomas et al. (2007) reported that the contribution from hospitals to municipal wastewater was less than 2% for other pharmaceuticals, excluding paracetamol compounds. Santos et al. (2013) determined the pharmaceutical contribution from hospitals to be between 0.03 and 8.9% for β-blockers, between 0.001 and 7.3% for lipid regulators, and between 0.009 and 11% for psychiatric drugs. Langford and Thomas (2009) discovered that hospitals contributed 11% of propranolol, 2% of atenolol, and less than 1% of carbamazepine and metoprolol. Azuma et al. (2016) detected 38 pharmaceutical compounds in the effluent of a hospital. The pharmaceutical contribution to the influent of the treatment plant at the effluent of the hospital ranged from < 0.1 to 14.8%. Ort et al. (2010) determined the contribution from hospitals to be 1.8%, 0.4%, 4.1%, and 4.1% for atenolol, carbamazepine, gemfibrozil, and metoprolol compounds, respectively. The contribution of analgesics and anti-inflammatories made to the municipal WWTP from 16 hospitals was determined to be 0.01–3.23% in the summer period and 0–1.74% in the winter for each hospital. The total contribution from hospitals was determined to be 11.3% and 7.09% in the summer and winter, respectively (Aydin et al. 2019a). The contribution of antibiotic for each hospital was determined to be 0.01–3.57% in the summer and 0.003–11.4% in the winter. The total contribution from hospitals was determined to be 13.07% and 28.19% in the summer and winter, respectively (Aydin et al. 2019b). When the previous studies and the results of this study were taken into account, it was concluded that the main pharmaceutical source in WWTPs was not hospitals.

Table 6 The contribution of each hospital effluent to the load of pharmaceuticals in WWTP

HE	Number of beds	Type of hospital	Flow rate (m^3/day)	Concentration of pharmaceuticals (ng/L)		Load of pharmaceuticals (mg/bed day)		Contribution (%)	
				Summer	Winter	Summer	Winter	Summer	Winter
HE1	1298	UH	1298	315	507	0.31	0.51	0.35	1.82
HE2	1040	GH	1040	174	187	0.17	0.19	0.15	0.54
HE3	82	GH	82	721	90.4	0.72	0.09	0.05	0.02
HE4	194	UH	194	7127	91.7	7.13	0.09	1.17	0.05
HE5	376	PH	376	136	87.7	0.14	0.09	0.04	0.09
HE6	75	GH	75	0.83	140	0.0008	0.14	0.00005	0.03
HE7	27	GH	27	14.99	92.4	0.01	0.09	0.001	0.01
HE8	38	GH	38	14.15	86.3	0.01	0.08	0.0005	0.009
HE9	201	GH	201	236	993	0.24	0.99	0.04	0.55
HE10	47	GH	47	19.03	96.0	0.02	0.09	0.001	0.02
HE11	45	GH	45	272	112	0.27	0.11	0.01	0.02
HE12	103	GH	103	77.6	319	0.08	0.32	0.007	0.09
HE13	600	GH	600	27.7	222	0.03	0.22	0.01	0.37
HE14	420	GH	420	125	270	0.12	0.27	0.04	0.31
HE15	74	UH	74	11.1	181	0.01	0.18	0.001	0.04
HE16	903	UH	903	7.88	139	0.008	0.14	0.006	0.35
Total HE	5584		5584	9280	3615	0.40	0.28	1.90	4.32

HE hospital effluent, *UH* university hospital, *PH* pediatric hospital, *GH* general hospital

Removal of pharmaceuticals in the WWTP

Pharmaceuticals are biologically active and resistant chemicals and are found in aquatic environments at levels of ng/L. The formation and concentration of pharmaceuticals in WWTP influents depend on socioeconomic status, consumption pattern, climatic conditions, and water consumption. However, the pharmaceutical concentrations in WWTP effluents depend on the properties of the pharmaceuticals and wastewater and the treatment processes applied (Khasawneh and Palaniandy 2021). The removal rates of pharmaceuticals in WWTPs are affected by the physicochemical properties of pharmaceuticals, such as polarity, volatility, persistence, adsorption, and lipophilicity (Majumder et al. 2019; Khasawneh and Palaniandy 2021). The removal performances of the four groups of pharmaceuticals in Konya WWTP are summarized in Fig. 1. It seems that pharmaceuticals had removal efficiencies between 0.68 and 100%. The Konya WWTP is designed to treat discharges from the equivalent of a population of 1,600,000. Its maximum treatment flow rate will be 300,000 m^3/day by 2030. Considering the results, it can be said that the treatment provided the high removal of metoprolol, sotalol, and carbamazepine from target compounds in winter and propranolol, clofibric acid, gemfibrozil, pravastatin, tamoxifen, cyclophosphamide, and etoposide in summer. Low removal efficiencies were observed in winter for compounds with high removal rates in summer.

Temperature is one of the foremost environmental factors inducing low removal efficiencies in cold seasons (Evgenidou et al. 2015). Biodegradation kinetic is slower than the one in summer on account of low temperatures in cold seasons on biological wastewater treatment processes (Ma et al. 2013). In distinct studies, it was reported that seasonal conditions have an influence on the elimination of pharmaceutical compounds found in wastewater treatment plants. For instance, it was reported that pharmaceutical compounds were removed in higher yields in summer in Greece (Kosma et al. 2014). Vieno et al. (2005) assigned a decrease in the removal efficiency of pharmaceutical compounds for the rate of biodegradation in winter. While Castiglioni et al. (2006) pointed out that the removal rates of pharmaceuticals are higher in summer than in winter, Yu et al. (2013) did not observe a substantial difference between the removal efficiencies obtained in both periods. Sun et al. (2014) determined that some pharmaceuticals were removed in the activated sludge biological treatment process at a higher rate in winter than in summer, and a positive correlation was found between hydraulic holding time and removal rates and it was stated that the treatment efficiency of some pharmaceuticals may decrease owing to the reduced hydraulic holding time in hot seasons. Similarly, in our study, most of the pharmaceuticals investigated were eliminated at higher rates during the summer period. Some pharmaceuticals showed higher removal rates in winter. Similar to the literature studies, these removals were observed in the biological treatment plant due to the temperature and hydraulic holding time.

The average removal efficiency was found to be 50–77% for atenolol and fluoxetine and < 50% for metoprolol, as

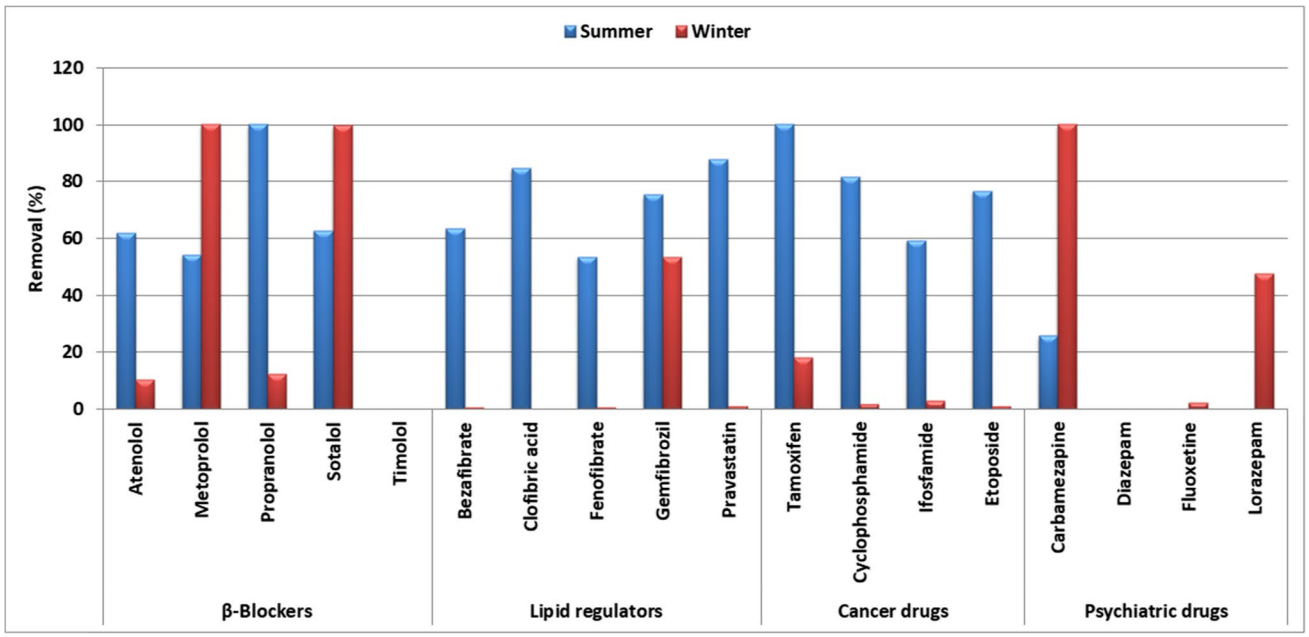

Fig. 1 Removal efficiency of selected pharmaceuticals in municipal WWTP

reported by Kumar et al. (2019). A WWTP from which the samples were taken had a primary treatment and a secondary treatment containing a five-stage Bardenpho process and a membrane bioreactor (MBR). Papageorgiou et al. (2016) reported negative removal rates and high removal rates for 55 pharmaceuticals in different therapeutic groups. They reported that the investigated WWTP is not able to efficiently remove complex mixtures of pharmaceuticals. In our study, it was reported that the removal efficiencies varied in a wide range (0.73–100%). Similar to the work of Papageorgiou et al. (2016), WWTPs are said to be insufficient in pharmaceutical treatment. Pharmaceuticals cannot be completely removed from wastewater in conventional treatment processes. Advanced treatment processes can be applied to remove pharmaceuticals from wastewater. Successful results have been acquired in the removal of pharmaceuticals by advanced oxidation methods (Bautitz and Nogueira, 2007; Wang and Wang 2016). For example, diazepam and bezafibrate removed 100% (Bautitz and Nogueira, 2010; Trovo et al. 2008), carbamazepine removed > 90% (Mohapatra et al. 2013), and gemfibrozil removed > 80% (Li et al. 2012) from wastewater by the Fenton oxidation process. Kim et al. (2009) investigated that 100% removal of bezafibrate, atenolol, metoprolol, propranolol, diazepam, and carbamazepine and more than 90% removal of clofibric acid were achieved with the UV/H_2O_2.

Environmental risk assessment

More than 200 pharmaceuticals have been detected in environmental matrices, such as different water sources and wastewater. The fate of pharmaceuticals and their effects on humans and the environment are uncertain (Couto et al. 2019). Most pharmaceutical compounds have high polarity and low volatility. Even at extremely low concentrations in the aquatic environment, they can have substantial ecotoxicological consequences, such as bioaccumulation, endocrine disruption, and drug resistance. Pharmaceutical concerns include an increase in the prevalence of cancer, antibiotic resistance, reproductive harm, and aberrant physiological processes (Wang et al. 2021). Table 7 comprises the pharmaceutical risk assessments for effluent wastewater in this study and literature studies. When "insignificant risk" is identified, the result is "acceptable" for the receiving environment; when "low risk" is identified, "more research" is necessary, and "detailed assessment" is required for the receiving environment in cases where "medium and high risk" is detected. Additionally, in this study, hospital wastewater and influent wastewater were evaluated in terms of risk. In the summer period, atenolol compounds showed a medium risk for fish in hospital wastewater and a high risk in the influent of WWTP. In hospital wastewater, propranolol and carbamazepine compounds showed a low risk for fish, *Daphnia magna*, and algae. During the winter, while atenolol compounds showed a high risk for fish in hospital wastewater and a moderate risk in the effluent municipal WWTP, the fluoxetine compound demonstrated a low risk for algae both in hospital wastewater and in the influent of the municipal WWTP. When Table 7 was examined, atenolol showed a moderate risk for fish in the summer and winter periods in this study. Fluoxetine showed a low risk for algae, and an insignificant risk was detected with other pharmaceuticals in this study. Mendoza et al. (2015) showed a high environmental risk for fish from propranolol and a medium risk for *Daphnia magna* from bezafibrate. Biel-Maeso et al. (2018b) identified a moderate risk for algae from propranolol.

Conclusions

This study addresses the analysis of four groups of pharmaceutical concentrations in hospital wastewaters and WWTP in summer and winter. The 18 target pharmaceuticals were detected at different concentrations (maximum, 7008 ng/L for carbamazepine). Beta-blockers and psychiatric pharmaceuticals were detected at higher concentrations in wastewater. The total concentrations of pharmaceutical groups in hospital wastewater were higher during winter than during summer, except psychiatric pharmaceuticals. In the WWTP, the total concentrations of lipid regulators and cancer pharmaceutical groups were higher in winter. It is still necessary to perform detailed studies on seasonal change. The contribution of the 16 hospitals to WWTP influent varied between 0.00005 and 1.818%. Flow rates of hospital wastewater remained at very low levels compared to WWTP influent. Therefore, pharmaceuticals detected in high concentrations in hospital wastewater are a small contribution. It has been concluded that pharmaceutical discharge from hospitals does not create a serious load on WWTPs. However, it is thought that the continuous discharge of pharmaceuticals from hospitals should be controlled. In this study, the environmental risk for *Daphnia*, fish, and algae was evaluated. The obtained results highlight that pharmaceuticals in WWTP effluent may pose a medium–high risk to aquatic life. However, more studies are still needed to identify the toxicities of pharmaceuticals for nontarget organisms. The observed removal efficiencies vary over a wide range for the investigated pharmaceuticals in WWTPs. Some compounds (metoprolol and carbamazepine in winter seasons and propranolol and tamoxifen in summer seasons) were completely eliminated during treatment. Our current research has shown that conventional treatment can be efficient for pharmaceutical removal. However, pharmaceutical removal depends on many factors, such as social and environmental conditions. Conventional systems under different operating conditions should be examined in detail.

Table 7 Risk assessment of pharmaceuticals in this study and previous studies

Pharmaceuticals	RQ	Species	Result	Reference
Beta-blockers				
Atenolol	12×10^{-2}	Fish	Low risk	Mendoza et al. (2015)
	54×10^{-4}	*Daphnia magna*	Insignificant risk	Gros et al. (2010)
	7×10^{-4}	Algae	Insignificant risk	Cleuvers (2005)
	1×10^{-2}	Algae	Insignificant risk	Biel-Maeso et al. (2018b)
	8.13	Fish	Moderate risk	In this study
	5×10^{-3}	*Daphnia magna*	Insignificant risk	
	2×10^{-4}	Algae	Insignificant risk	
Metoprolol	14×10^{-3}	*Daphnia magna*	Insignificant risk	Mendoza et al. (2015)
	1×10^{-5}	Fish	Insignificant risk	Gros et al. (2010)
	2×10^{-4}	*Daphnia magna*	Insignificant risk	
	1×10^{-3}	Algae	Insignificant risk	
	286×10^{-3}	Algae	Low risk	Cleuvers (2005)
	4×10^{-4}	Fish	Insignificant risk	In this study
	45×10^{-4}	*Daphnia magna*	Insignificant risk	
	2×10^{-4}	Algae	Insignificant risk	
Propranolol	115×10^{-1}	Fish	High risk	Mendoza et al. (2015)
	81×10^{-2}	Algae	Low risk	Cleuvers (2005)
	18×10^{-1}	Algae	Moderate risk	Biel-Maeso et al. (2018b)
	3×10^{-4}	Fish	Insignificant risk	In this study
	8×10^{-4}	*Daphnia magna*	Insignificant risk	
	9×10^{-4}	Algae	Insignificant risk	
Sotalol	3×10^{-2}	Algae	Insignificant risk	Mendoza et al. (2015)
	5×10^{-5}	Fish	Insignificant risk	In this study
	1×10^{-4}	*Daphnia magna*	Insignificant risk	
	11×10^{-4}	Algae	Insignificant risk	
Timolol	1×10^{-2}	Algae	Insignificant risk	Biel-Maeso et al. (2018b)
	nd	Fish	Insignificant risk	In this study
	nd	*Daphnia magna*	Insignificant risk	
	nd	Algae	Insignificant risk	
Lipid regulators				
Bezafibrate	12×10^{-1}	*Daphnia magna*	Moderate risk	Mendoza et al. (2015)
	75×10^{-3}	Fish	Insignificant risk	Gros et al. 2010)
	18×10^{-3}	*Daphnia magna*	Insignificant risk	
	15×10^{-4}	Fish	Insignificant risk	In this study
	2×10^{-4}	*Daphnia magna*	Insignificant risk	
	4×10^{-4}	Algae	Insignificant risk	
Clofibric acid	27×10^{-2}	*Daphnia magna*	Low risk	Gros et al. 2010)
	15×10^{-5}	Algae	Insignificant risk	
	4×10^{-7}	Fish	Insignificant risk	In this study
	5×10^{-7}	*Daphnia magna*	Insignificant risk	
	5×10^{-7}	Algae	Insignificant risk	
Fenofibrate	2×10^{-1}	*Daphnia magna*	Low risk	Mendoza et al. (2015)
	18×10^{-4}	Fish	Insignificant risk	In this study
	4×10^{-3}	*Daphnia magna*		
	14×10^{-3}	Algae		

Table 7 (continued)

Pharmaceuticals	RQ	Species	Result	Reference
Gemfibrozil	57×10^{-2}	Fish	Low risk	Gros et al. 2010)
	5×10^{-2}	*Daphnia magna*	Insignificant risk	
	13×10^{-2}	Algae	Low risk	
	7×10^{-3}	Fish	Insignificant risk	In this study
	6×10^{-4}	*Daphnia magna*	Insignificant risk	
	2×10^{-4}	Algae	Insignificant risk	
Pravastatin	1×10^{-4}–21×10^{-3}	Algae	Insignificant risk	Escher et al. (2011)
	22×10^{-2}	Fish	Low risk	Gros et al. 2010)
	3×10^{-3}	Fish	Insignificant risk	In this study
	6×10^{-4}	*Daphnia magna*	Insignificant risk	
	6×10^{-4}	Algae	Insignificant risk	
Psychiatric drugs				
Carbamazepine	2×10^{-1}	*Daphnia magna*	Low risk	Mendoza et al. (2015)
	4×10^{-4}–283×10^{-3}	Algae	Insignificant risk	Escher et al. (2011)
	1×10^{-4}	Fish	Insignificant risk	Gros et al. 2010)
	47×10^{-4}	*Daphnia magna*	Insignificant risk	
	43×10^{-4}	Algae	Insignificant risk	
	3×10^{-3}	Fish	Insignificant risk	In this study
	7×10^{-3}	*Daphnia magna*	Insignificant risk	
	3×10^{-3}	Algae	Insignificant risk	
Diazepam	6×10^{-4}–4×10^{-2}	Algae	Insignificant risk	Escher et al. (2011)
	22×10^{-4}	Fish	Insignificant risk	Gros et al. 2010)
	44×10^{-4}	*Daphnia magna*	Insignificant risk	
	38×10^{-4}	Algae	Insignificant risk	
	nd	Fish	Insignificant risk	In this study
	nd	*Daphnia magna*	Insignificant risk	
	nd	Algae	Insignificant risk	
Fluoxetine	1×10^{-3}–78×10^{-3}	Algae	Insignificant risk	Escher et al. (2011)
	12×10^{-3}	Fish	Insignificant risk	Gros et al. 2010)
	41×10^{-3}	*Daphnia magna*	Insignificant risk	
	26×10^{-3}	Algae	Insignificant risk	
	1.04×10^{-1}	Algae	Low risk	In this study
	3×10^{-3}	Fish	Insignificant risk	In this study
	5×10^{-3}	*Daphnia magna*	Insignificant risk	
	104×10^{-3}	Algae	Low risk	
Lorazepam	5×10^{-1}	Algae	Low risk	Mendoza et al. (2015)
	3×10^{-3}	Fish	Insignificant risk	In this study
	5×10^{-3}	*Daphnia magna*	Insignificant risk	
	1×10^{-3}	Algae	Low risk	
Cancers drugs				
Tamoxifen	1×10^{-1}	*Daphnia magna*	Low risk	Negreira et al. (2014)
	24×10^{-3}	Fish	Insignificant risk	Ferrando-Climent et al. (2014)
	1×10^{-3}	Fish	Insignificant risk	In this study
	2×10^{-3}	*Daphnia magna*	Insignificant risk	
	–	Algae	Insignificant risk	

Table 7 (continued)

Pharmaceuticals	RQ	Species	Result	Reference
Cyclophosphamide	3×10^{-5}	*Daphnia magna*	Insignificant risk	Negreira et al. (2014)
	25×10^{-6}	*Daphnia magna*	Insignificant risk	Ferrando-Climent et al. (2014)
	4×10^{-6}	*Daphnia magna*	Insignificant risk	Gouvei et al. (2020)
	3×10^{-5}	Fish	Insignificant risk	In this study
	1×10^{-6}	*Daphnia magna*	Insignificant risk	
	2×10^{-4}	Algae	Insignificant risk	
Ifosfamide	5×10^{-3}	Fish	Insignificant risk	Negreira et al. (2014)
	5×10^{-1}	*Daphnia magna*	Low risk	
	1×10^{-4}	Algae	Insignificant risk	
	2.11×10^{-5}	*Ceriodaphnia dubia*	Insignificant risk	Gouvei et al. (2020)
	2×10^{-5}	Fish	Insignificant risk	In this study
	1×10^{-6}	*Daphnia magna*	Insignificant risk	
	2×10^{-4}	Algae	Insignificant risk	
Etoposide	nd	Fish	Insignificant risk	In this study
	nd	*Daphnia magna*	Insignificant risk	
	nd	Algae	Insignificant risk	

nd means the concentration of compound in wastewater is below the limit of detection, and en dash means the PNEC value of tamoxifen on algae was not found

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