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Review

A review of antiepileptic drugs: Part 1 occurrence, fate in aquatic environments and removal during different treatment technologies

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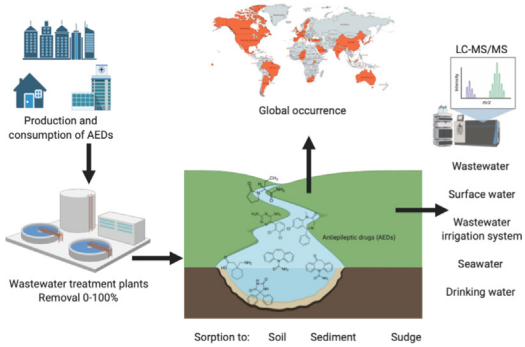
HIGHLIGHTS

- The use of antiepileptic drugs in non-epileptic disorders has steadily increased.
- Antiepileptic drugs are ubiquitously distributed in worldwide waterbodies.
- Photodegradation processes can improve the biodegradability of antiepileptic drugs.
- Little or no information is known about the antiepileptic drugs byproducts.

GRAPHICAL ABSTRACT



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ABSTRACT

Antiepileptic drugs (AEDs) are the main treatment for people with epilepsy. However, in recent years, more and more people are using them for other indications such as: migraine, chronic neuropathic pain, and mood disorders. Consequently, the prescriptions and consumption of these drugs are increasing worldwide. In WWTPs, AEDs can resist degradation processes, such as photodegradation, chemical degradation and/or biodegradation. Until now, only constructed wetlands and photocatalysis have shown good removal rates of AEDs from wastewater. However, their effectiveness depends on the specific conditions used during the treatment. Since the consumption of AEDs has increased in the last decade and their degradation in WWTPs is poor, these drugs have been largely introduced into the environment through the discharge of municipal and/or hospital effluents. Once in the environment, AEDs are distributed in the water phase, as suspended particles or in the sediments, suggesting that these drugs have a high potential for groundwater contamination. In this first part of the AEDs review is designed to fill out the current knowledge gap about the occurrence, fate and removal of these drugs in the aquatic environment. This is a review that emphasizes the characteristics of AEDs as emerging contaminants.

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1. Introduction

Epilepsy is the second most common neurological disease after stroke, affecting almost 70 million people worldwide (Ngugi et al., 2010). This disease is characterized by recurrent seizures, as well as loss of consciousness and control of bowel function.

Currently, there are more than 30 AEDs approved for the treatment of seizures. However, in recent years, more and more people are using them for other indications such as: migraine, chronic neuropathic pain, and mood disorders (Druschky et al., 2018; Liu et al.,2017). Consequently, a new group of patients are being exposed to this pharmaceutical group, which means that prescriptions and consumption of these drugs are increasing worldwide. For example, from 1999 to 2009 in U.S., the use of levetiracetam increase from 5.1% to 32%, while the use oxcarbazepine increased from 1.3% to 19.1% (Liu et al., 2017). In addition, in Norway, Baftiu et al. (2016) pointed out that the use of AEDs in non-epileptic disorders is increasing and represented 53% in the year 2012.

Due to their increasing consumption and their barely degradation in WWTPs, AEDs are widely distributed in surface water around the world. Carbamazepine, gabapentin, lamotrigine, and primidone have been the most frequently AEDs detected in the world's rivers and lakes. However, other AEDs such as topiramate, phenytoin and primidone have been also found at much lower concentrations.

In light of these considerations, the central aim of this study was to comprehensively investigate the occurrence, distribution and fate of AEDs on the different aquatic systems. Finally, we also investigated and compared the current treatment technologies used to remove AEDs from wastewater.

2. Worldwide consumption of AEDs

In recent decades there has been a significant increase in the consumption of AEDs, as is shown in Table 1. This may be due to the

Table 1
Prescriptions of anticonvulsants in different countries.

	AEDs	Year	Prescriptions per year	Source
North America	U.S.			
	Gabapentin	2017	46,043,168	Kane, 2018
	Lamotrigine		12,053,691	
	Carbamazepine		3,516,204	
	Oxcarbazepine		2,452,465	
	Phenytoin		2,348,516	
	Primidone		2,075,116	
	Levetiracetam		6,832,916	
	Topiramate		10,388,097	
	Diazepam		5,184,806	
	Pregabalin		11,152,692	
	Zonisamide		1,011,331	
South America	Brazil			
	Carbamazepine	2018	6,185,991	Pivetta et al., 2020
	Clonazepam		26,965,289	
	Diazepam		4,394,869	
	Lamotrigine		3,008,975	
	Oxcarbazepine		2,240,308	
	Clobazam		2,079,291	
	Sodium valproate		1,959,907	
Europe	Scotland			
	Carbamazepine	2016	216,405	Information Services Division National Services Scotland, 2018
	Gabapentin		694,293	
	Lacosamide		14,093	
	Lamotrigine		209,754	
	Levetiracetam		131,962	
	Ethosuximide		2576	
	Oxcarbazepine		6163	
	Phenobarbital		20,700	
	Phenytoin		63,563	
	Pregabalin		435,496	
	Primidone		12,469	
	Retigabine		253	
	Rufinamide		820	
	Sodium valproate		200,321	
	Tiagabine		343	
	Topiramate		59,160	
	Vigabatrin		1615	
	Diazepam		874,810	
	Zonisamide		9257	
	Wales			
	Pregabalin	2017	450,022	National Statistics Ystadegau Gwladol, 2018
	Levetiracetam		140,769	
	Total of prescriptions		1,523,183	
	England			
	Total of prescriptions	2017	26,649,311	Prescribing and Medicines Team Health and Social Care Information Centre, 2018
	Nederland			
	Pregabalin	2018	19,024,700	Zorginstittud Nederland, 2018
	Diazepam		11,385,741	
	Valproic acid		12,115,800	
	Levetiracetam		9,511,000	
	Carbamazepine		6,358,900	
	Lamotrigine		5,573,700	
	Gabapentin		4,554,900	
	Topiramate		1,650,500	
	Oxcarbazepine		1,607,800	
	Phenytoin		1,548,100	
	Phenobarbital		1,151,500	
	Clonazepam		1,087,700	
	Lacosamide		881,740	
	Estonia			
	Valproic acid	2018	4907	Kurvits et al., 2020
	Northern Ireland			
	Carbamazepine	2018	79,552	Mulholland, 2018
	Gabapentin		207,386	
	Lacosamide		10,292	
	Lamotrigine		112,940	
	Levetiracetam		63,811	
	Ethosuximide		1064	

Table 1 (*continued*)

AEDs	Year	Prescriptions per year	Source
Oxcarbazepine		1819	
Phenobarbital		7363	
Phenytoin		13,866	
Pregabalin		341,169	
Primidone		2915	
Sodium valproate		78,180	
Tiagabine		108	
Topiramate		23,557	
Vigabatrin		1019	
Diazepam		592,353	
Midazolam		3541	
Perampanel		2521	
Clobazam		9029	
Valproic acid		3119	
Clonazepam		20,943	
Zonisamide		8036	

extensive usage of these drugs to treat other conditions, such as chronic pain, migraine, bipolar disorder, and depression (Druschky et al., 2018; Parikh and Silberstein, 2019). Rogawski and Löscher, 2004, for instance demonstrated that in 2003 about half of the prescriptions for AEDs in the US were for conditions other than epilepsy. Furthermore, in Norway, from 2008 to 2012, AEDs use in non-epilepsy disorders accounted for 45–53% of total use (Baftiu et al. 2016). Similarly, Berman et al. (2016) demonstrated that in Israel, the AEDs used most frequently were lamotrigine and levetiracetam, followed by carbamazepine, clonazepam, valproic acid, phenobarbital and phenytoin. However, the sales data indicate that carbamazepine and phenytoin were sold more than lamotrigine, suggesting that phenytoin is prescribed to outpatients by physicians who are not epilepsy specialists.

Although the level of consumption for AEDs in Albania has shown to be very low when compared globally, Kakariqi and Vyshka (2019) pointed out that almost 43% of the patients take these drugs without prescription from the family doctor. Hence, it should be considered that such drugs are useable for other purposes apart from for epilepsy. For instance, sodium valproate is also reimbursed for the treatment of the manic phase of bipolar disorder and is also prescribed for the increase of pain tolerance for chronic pains (Druschky et al., 2018; Parikh and Silberstein, 2019).

Another factor that may also enhance the consumption of this group of medicines could be the production of new AEDs. Liu et al.,(2017), for instance found that the annual prevalence of valproic acid decreased from 42.4% in 1999 to 26.5% in 2009, However, for the same year, the use of levetiracetam increased from 5.1% to 32%. Similarly, the use of oxcarbazepine increased from 1.3% to 19.1%, as well as the prevalence of diazepam use increased from 11.6 to 28.1%. In addition, multiple studies from different healthcare facilities have pointed out that prescriptions of third generation AEDs increased in the last years (Hsieh and Huang, 2011; Kwong et al., 2012; Lee et al., 2012; Pickrell et al., 2014; Cho et al., 2015). Jobst and Holmes (2004) compared the effectiveness of first and second generation AEDs with third generation AEDs. Their results suggest that no significant differences in efficacy, serious adverse side effects or improvement in quality of life were observed for patients using either group of drugs. Despite these data, the use of third generation AEDs has continued to increase. Among the justifications for the use of third generation AEDs are better tolerability (Koch and Polman, 2009) and less potential for drug interactions (Lyseng-Williamson, 2011).

3. Occurrence and spatial distribution of AEDs in water systems

In order to predict, regulate and understand the risks that pharmaceutical products represent to the environment, it is important to determine their fate and abundance once they enter into the environment.

AEDs are mainly introduced into the environment thought the discharge of effluents from municipal wastewater treatment plants and/or hospital effluents. This is due to AEDs cannot be completely eliminated using the current processes of WWTPs. For example, several studies have suggested that AEDs can resist degradation processes, such as photodegradation, chemical degradation or biodegradation (Bernhard et al., 2006; Tadkaew et al., 2011; He et al., 2016; Villegas-Guzman et al., 2017; Zhang et al., 2020). Furthermore, it has been also shown that after minimal degradation in WWTPs, these drugs can infiltrate groundwater and can be absorbed by living organisms (Arnold et al., 2014).

Upon their release from WWTPs, AEDs are widely distributed in worldwide surface waters (Table 2). Carbamazepine, gabapentin, lamotrigine, and primidone have been the most frequently AEDs detected in the world's rivers and lakes. However, other AEDs such as topiramate, phenytoin and primidone have been also found at much lower concentrations. This may be due to the strong adsorption of these compounds to the sediments of the rivers (Ying et al., 2013).

Until now, most of the studies that have reported about occurrence of AEDs on aquatic environments have been focused on surface waters. Another common link among these studies is the proximity of surface waters to wastewater treatment plants. This feature must be highlighted as higher concentration of AEDs have been found in surface waters that receive discharges of urban wastewater (Simazaki et al., 2015; Bai et al., 2018; Mijangos et al., 2018; Ismail et al., 2019).

Dilution may also play an important role in the abundance of AEDs. Camacho-Muñoz et al., 2010, for instance found carbamazepine reached concentrations of up to 1.1 μg/L in small water bodies. On the other hand, in large rivers, lakes or seawater, carbamazepine was found in lower concentrations (0.04 μg/L) (Klosterhaus et al., 2013). This may be due to small water bodies receive wastewater effluents with lower dilution (Ying et al., 2013). However, further studies are needed to comprehensively understand the factors that affect the abundance of AEDs on the different aquatic systems.

The spatial distribution of AEDs is presented in Fig. 2. As can be seen these drugs are widely distributed in five of the six continents of the planet. Until now carbamazepine is the most frequently detected AED, reaching concentration of up to 3.5 μg/L in Brazil (Pivetta et al., 2020). The second place is occupied by gabapentin, with concentrations as high as 9.8 μg/L in the effluents of a hospital in the US (Oliveira et al., 2015).

Lamotrigine and primidone ranks third in the list occurrence, with maximum concentrations of 2.8 μg/L (surface water) and 0.7 μg/L (urban water cycle), respectively (Hass et al., 2012; Kondor et al., 2020). Fourth and fifth places are occupied by diazepam (1.0 μg/L, irrigation water) and phenytoin (1.4 μg/L, estuary), both compounds detected in Spain (Margenat et al., 2017; Mijangos et al., 2018). Oxcarbazepine is found at the sixth place of the list, exhibiting a maximum concentration of 1.2 μg/L in wastewater in Saudi Arabia (Alidina et al., 2014).

Next places are occupied by phenobarbital (0.4 μg/L, hospital effluent), pregabalin (6.9 μg/L, hospital effluent), lacosamide (0.06 μg/L, surface water), levetiracetam (10.8 μg/L, waste water) and lastly, topiramate (0.2 μg/L, waste water) (Oliveira et al., 2015; Gurke et al., 2015; Kondor et al., 2020).

The differences in the occurrence and spatial distribution presented by these drugs could be due to the availability and consumption rates of AEDs in the different countries. Fekadu et al. (2019), for instance carried out and study to compare the occurrence of pharmaceuticals in freshwater environments in the African and European context. According to their results, one of the most important factors that governs the occurrence pattern and spatial distribution of individual pharmaceuticals in the environment is their consumption trend. Nonetheless, unlike in developed countries, the number of pharmaceuticals and their consumption trends are not readily available for Africa. Thus, it is impossible to experimentally assess the hazards and risks of these drugs in a timely manner.

Table 2
Occurrence of AEDs in worldwide water bodies.

	Country	Occurrence media	Concentration (ng/L)	Mean concentration (ng/L)	Limit of quantification (ng/L)	Frequency of detection (%)	Method of quantification	Source
Carbamazepine								
North America	U.S.	River	42.9–113.7	NA	0.4–1.7	100	GC–MS	(Zhang et al., 2007)
		Surface water	330	302	10	100	LC-MS/MS	(Laws et al., 2011)
		Surface water	350	350	5	95	LC/Q-TOF-MS	(Ferrer and Thurman, 2012)
		Seawater	5.2–44.2	15.2	NA	100	LC-MS/MS	(Klosterhaus et al., 2013)
		River and wastewater	71–1500	360–530	10	NA	LC-MS/MS	(Writer et al., 2013)
		River	7.5–375	259	NA	100	GC–MS/MS	(Dong et al., 2015)
		Hospital effluents	210–620	240	NA	100	LC-MS/MS	(Oliveira et al., 2015)
		WWTP effluents	66.8–2300	16.4	NA	21.5–100	LC-MS/MS	(Deere et al., 2020)
	Canada	River	0.3–13.8	2.8	5.7	100	LC-MS/MS	(Challis et al., 2018)
	Mexico	Wastewater irrigation system	1.85–370	103	0.3	NA	LC-MS/MS	(Lesser et al., 2018)
		WWTP	85–476	19–381	2.3–18	100	LC-MS/MS	(Rivera-Jaimes et al., 2018)
South America	Brazil	River	115–3530	170	50	100	UPLC-MS/MS	(Pivetta et al., 2020)
	Argentina	Surface water	15–113	16–73	0.2	66.6	LC-MS/MS	(Valdés et al., 2014)
Europe	Germany	Rivers and streams	Up to 1100	250	24	100	LC-MS/MS	(Ternes, 1998)
		Surface water	Up to 762	58	2.2	100	HPLC-MS/MS	(Nödler et al., 2013)
		Groundwater	2.4–346.7	38.4	1.2–28	12.9	HPLC-MS/MS	(Reh et al., 2013)
		Wastewater	1200–2000	1900	30	100	LC-MS/MS	(Bahlmann et al., 2014)
		WWTP	893–1542.5	1310	50	100	HPLC-MS/MS	(Gurke et al., 2015)
		Urban water cycle	5–1640	NA	1	100	LC-MS/MS	(Brezina et al., 2017)
		WWTP	170–2700	800–1500	NA	100	LC-MS/MS	(Brunsch et al., 2018)
		Surface water	>1600	NA	NA	NA	LC-MS/MS	(Sanz-Prat et al., 2020)
	Spain	River	11–90	56	10	60	LC-MS/MS	(Gros et al., 2007)
		Streams and rivers	50–1110	50–150	NA	NA	LC-MS/MS	(Camacho-Muñoz et al., 2010)
		Coastal wetland	Up to 38.8	5.5	NA	26	LC-MS/MS	(Vazquez-Roig et al., 2012)
		Groundwater	7–136	115	NA	100	LC-MS/MS	(López-Serna et al., 2013)
		Urban aquifer	7.1–136	115	0.3–4.1	92–100	LC-ESI-MS/MS	(Jurado et al., 2014)
		Irrigation waters	<10–1280	10–891	0.3–80	0–100	GC–MS/MS	(Margenat et al., 2017)
		Seawater	31.1	NA	NA	75	UPLC-QqQMS/MS	(Biel-Maeso et al., 2018)
	UK	Surface water	<0.5–684	251	0.5	0–100	UPLC-MS/MS	(Kasprzyk-Hordern et al., 2008)
		Downstream of WWTP	167–334	NA	0.05–5	100	LC-MS/MS	(Zhou et al., 2009)
		WWTP	274–876	440	NA	0–100	LC-MS/MS	(Nakada et al., 2017)
		WWTP	134.7–367	156–244.7	0.93–1.37	100	UPLC-MS/MS	(Petrie et al., 2017)
		Surface water	5.6–200	NA	1	95	LC-MS/MS	(White et al., 2019)
	Portugal	Wastewater	470–520	NA	0.03	100	LC-MS/MS	(Bahlmann et al., 2014)
		Estuary	13–31	NA	NA	100	LC-MS/MS	(Gonzalez-Rey et al., 2015)
		River	24.9–214	31.7	0.02–6.40	100	UHPLC-MS/MS	(Paíga et al., 2016)
		WWTP	820–1427	689–1107	1–1.85	100	UHPLC-MS/MS	(Paíga et al., 2019)
	France	WTP	86–416	112	9.5	100	LC-MS/MS	(Leclercq et al., 2009)
		Seawater	10–40	NA	2.2	100	GC–MS, HPLC-MS/MS	(Togola and Budzinski, 2008)
	Belgium	Seawater	321	NA	5	100	LC-MS/MS	(Wille et al., 2010)
		Raw wastewater	227–1028	NA	0.5–25	NA	LC-MS/MS	(Balcerzak et al., 2015)
	Hungary	Surface water	4.7–804.6	53.2–173.1	0.10	100	SFC-MS/MS	(Maasz et al., 2019)
		Surface water	26.08–498	77.2	5	99.1	SFC-MS/MS	(Kondor et al., 2020)
	Italy	River	Up to 34.2	23.1	NA	100	HPLC-MS/MS	(Zuccato et al., 2005)
	Switzerland	Surface water	6–110	NA	2	85.36	LC-MS/MS	(Moschet et al., 2015)
	Greece	Seawater	1.4	NA	NA	77.2	LC-MS/MS	(Alygizakis et al., 2016)
	Sweden	Rivers	19.8–506.9	NA	NA	NA	NA	(Lindim et al., 2016)
Asia	China	River system	10.8–40.6	23.9	1.4	100	GG-MS	(Zhao et al., 2010)
		Irrigation water	2.2–46.9	NA	0.15	33.3	LC-MS/MS	(Chen et al., 2011)
		Tap water	0.5–38.24	NA	0.05	100	LC-MS/MS	(Cai et al., 2015)
		River	5–75.5	25.3	3	44	LC-MS/MS	(Wu et al., 2015)
		WWTP	43.4–2499	NA	NA	100	LC-MS/MS	(Zhang et al., 2018)
		Tap water	1.31–9.70	1.75	0.01	100	UPLC-MS/MS	(Liu et al., 2019a)
	South Korea	Surface water	8.4–160	44	1	100	LC-MS/MS	(Yoon et al., 2010)
		Aquifer	52.32–90.97	67.16	1	100	LC-MS/MS	(Park and Lee, 2018)
	Japan	River	Up to 15	5.6	1–3	100	LC-MS/MS	(Nakada et al., 2007)
		Rivers and drinking water	1.8–100	0.3–9	0.4	NA	LC-MS/MS	(Simazaki et al., 2015)
	India	WWTP	450–770	21.9–580	0.1–50	100	HPLC-MS/MS	(Subedi et al., 2017)
		Surface water	71.2	12.5	0.1	90	UPLC-MS/MS	(Guruge et al., 2019)
	Turkey	WWTP	6.35–245.1	NA	0.114	100	LC/MS-MS	(Aydin et al., 2017)
Africa	South Africa	River estuary	4–94	NA	0.13	100	LC-MS/MS	(Rimayi et al., 2018)
	Uganda	Wastewater	200–1300	NA	6	100	UPLS-MS/MS	(Dalahmeh et al., 2020)
	Nigeria	Surface water	<1–342	9	1	53	UPLS-MS/MS	(Ebele et al., 2020)

Table 2 (*continued*)

	Country	Occurrence media	Concentration (ng/L)	Mean concentration (ng/L)	Limit of quantification (ng/L)	Frequency of detection (%)	Method of quantification	Source
Oceania	Australia	WWTP	830-1600	NA	NA	NA	LC-MS/MS	(Cardenas et al., 2016)
		Treatment effluents	685–702	NA	NA	100	LC-MS/MS	(Roberts et al., 2016)
		Surface water	1.7–106.4	18.6	NA	13.6–100	LC-MS/MS	(Anim et al., 2020)
Gabapentin								
North America	U.S	Surface water downstream of WWTP	54	54	5	44	LC/Q-TOF-MS	(Ferrer and Thurman, 2012)
		Rivers and wastewaters	<10–3100	560–1200	10	NA	LC-MS/MS	(Writer et al., 2013)
		Hospital effluent	63,370–90,780	80,830	NA	100	LC-MS/MS	(Oliveira et al., 2015)
		Surface water	2790	NA	NA	58	GC/MS	(Elliott and VanderMeulen, 2017)
		Urban watersheds	11,200	559.5	10	99.4	UHPLC-MS/MS	(Bai et al., 2018)
		Streams and rivers	509	NA	NA	23.68	LC-MS/MS	(Weissinger et al., 2018)
Europe	UK	Surface water	<0.6–1887	1008	0.6	0–100	UPLC-MS/MS	(Kasprzyk-Hordern et al., 2008)
		Treated effluent	8541	17.4–1429	12.4	100	LC-MS/MS	(Burns et al., 2018)
		Surface water	17.4–1445					
		Surface water	160–1600	NA	10	95	LC-MS/MS	(White et al., 2019)
	Germany	WWTP	9127.5–13,400	11,175	200	100	HPLC-MS/MS	(Gurke et al., 2015)
		Surface water	110–3200	NA	30	70–100	UPLC-MS/MS	(Henning et al., 2018)
		Groundwater	210–860					
		Potable water	20–640					
		Surface water	>1000	NA	NA	NA	LC-MS/MS	(Sanz-Prat et al., 2020)
	Switzerland	Surface water	60–390	NA	2.5	48.57	LC-MS/MS	(Moschet et al., 2015)
		Surface water	3400	NA	NA	NA	LC-HRMS/MS	(Mechelke et al., 2019)
	Sweden	Rivers	0–1886.4	NA	NA	NA	NA	(Lindim et al., 2016)
	European countries	Commercially bottled water	10–12	NA	10	87	LC-MS/MS	(Lardy-Fontan et al., 2017)
Asia	Southeast Asian	Raw influent	4825.5–15,358.8	13,146.5	1.0–1.8	100	UPLC-MS/MS	(Tran and Gin, 2017)
		Treated effluent	1333–8855					
Africa	Nigeria	Surface water	<1–67	11	1	NA	UHPLS-MS/MS	(Ebele et al., 2020)
		Groundwater	<1–41					
Oceania	Australia	Surface water	<0.05–117.6	28.6	NA	0–95.2	LC-MS/MS	(Anim et al., 2020)
Lamotrigine								
North America	U.S.	Wastewater	488	NA	5	97	LC/Q-TOF-MS	(Ferrer and Thurman, 2012)
		Groundwater	324					
		Surface water	108					
		Drinking water	17					
		Surface water downstream of WWTP	455	455	5	97	LC/Q-TOF-MS	(Ferrer and Thurman, 2012)
		Rivers and wastewaters	54–1200	340–600	10	NA	LC-MS/MS	(Writer et al., 2013)
		Hospital effluent	490–720	440	NA	100	LC-MS/MS	(Oliveira et al., 2015)
		Surface water	85.2	NA	NA	65	GC/MS	(Elliott and VanderMeulen, 2017)
		Urban watersheds	2390	305.5	10	93.4	UHPLC-MS/MS	(Bai et al., 2018)
		Streams and rivers	34.3	NA	NA	10.52	LC-MS/MS	(Weissinger et al., 2018)
Europe	Germany	WWTP	582–1117.5	752	50	100	HPLC-MS/MS	(Gurke et al., 2015)
		Rivers and streams	Up to 730	NA	25	100	LC-MS/MS	(Bollmann et al., 2016)
		WWTP	158–1653					
	Switzerland	Surface water	6.1–220	NA	2	97.2	LC-MS/MS	(Moschet et al., 2015)
	Spain	Irrigation waters	<6–46	12	0.3–80	0–20	GC–MS/MS	(Margenat et al., 2017)
	Sweden	Drinking water	7.4–12	6.3	0.24–0.26	87.5	UPLC-MS/MS	(Tröger et al., 2018)
		Surface water	89	50	0.07–4	100	UPLC-MS/MS	(Golovko et al., 2020)
	Hungary	Surface water	5.7–1734.8	57.8–240.2	5	90–100	SFC-MS/MS	(Maasz et al., 2019)
		Surface water	13.9–2780	171	5	92	SFC-MS/MS	(Kondor et al., 2020)
		Well water	5.18–849					
	United Kingdom	Surface water	1.2–280	NA	1	100	LC-MS/MS	(White et al., 2019)
Primidone								
North America	U.S.	Surface water	220	168	10	100	LC-MS/MS	(Laws et al., 2011)
		River	9.2–228	134	NA	100	GC–MS/MS	(Dong et al., 2015)
		Hospital effluent	50–120	40	NA	66	LC-MS/MS	(Oliveira et al., 2015)
Europe	Spain	Raw water	200	39	0.15	NA	UPLC-MS/MS	(Huerta-Fontela et al., 2011)
		Drinking water	–					
		Irrigation waters	<4–215	7–145	0.3–80	0–100	GC–MS/MS	(Margenat et al., 2017)
	Germany	Urban water cycle	430–710	80	20	100	UPLC-MS/MS	(Hass et al., 2012)
		Groundwater	3.3–397.3	15.1	1.2–28	10.4	HPLC_MS/MS	(Reh et al., 2013)
		WWTP	180–325.8	223	100	100	HPLC-MS/MS	(Gurke et al., 2015)
		Surface water	600	NA	NA	NA	LC-MS/MS	(Sanz-Prat et al., 2020)
Asia	South Korea	Surface water	<0.50–4.7	0.81	1	50	LC-MS/MS	(Yoon et al., 2010)
		Aquifer	5.50–6.33	5.56	1	75	LC-MS/MS	(Park and Lee, 2018)
	China	Irrigation water	17.4	NA	0.59	70	LC-MS/MS	(Chen et al., 2011)

(*continued on next page*)

Table 2 (*continued*)

	Country	Occurrence media	Concentration (ng/L)	Mean concentration (ng/L)	Limit of quantification (ng/L)	Frequency of detection (%)	Method of quantification	Source
		Tap water	6.26–32.85	8.86	0.01	100	UPLC-MS/MS	(Liu et al., 2019a)
	Saudi Arabia	WWTP	<3–3000	645	3	100	LC-MS/MS	(Alidina et al., 2014)
	Malaysia	Estuarine water	<0.38	NA	0.38	NA	LC-MS/MS	(Ismail et al., 2019)
		River	0.12–0.35	0.21	0.08	100	LC-MS/MS	(Wee et al., 2019)
Phenytoin								
North America	U.S.	Wastewater	287–402	NA	1	100	LC-MS/MS	(Vanderford and Snyder, 2006)
		Drinking water	1.3					
		Surface water	150	103	20	100	LC-MS/MS	(Laws et al., 2011)
		Hospital effluent	60–100	30	NA	66.6	LC-MS/MS	(Oliveira et al., 2015)
		Urban watersheds	145	22.2–27.5	10	45.5–51.4	UHPLC-MS/MS	(Bai et al., 2018)
Europe	Spain	Raw water	140	56	0.02	100	UPLC-MS/MS	(Huerta-Fontela et al., 2011)
		Drinking water	10					
		Groundwater	78					
		Estuary	6–1401	3–13	NA	6–34	LC-MS/MS	(Mijangos et al., 2018)
Asia	Korea	Surface water	1.1–8.9	4.3	1	75	LC-MS/MS	(Kim et al., 2007)
		Surface water	1.8–54	9.5	1	100	LC-MS/MS	(Yoon et al., 2010)
	Japan	River	4	NA	2	NA	LC-MS/MS	(Hoshina et al., 2009)
		Rivers and drinking water	3.1–23	10	2.1	NA	LC-MS/MS	(Simazaki et al., 2015)
	Saudi Arabia	WWTP	<20–440	60	20	NA	LC-MS/MS	(Alidina et al., 2014)
	China	Tap water	1.93	0.59	0.5	100	UPLC-MS/MS	(Liu et al., 2019b)
Diazepam								
North America	U.S.	Surface water	5	2	5	NA	LC-MS/MS	(Laws et al., 2011)
	Mexico	Wastewater irrigation system	6.5–24.6	10.7	0.3	NA	LC-MS/MS	(Lesser et al., 2018)
Europe	Slovenia	Hospital effluent	17–11	NA	3	100	GC–MSD	(Kosjek et al., 2012)
		River	9–69					
	Spain	Coastal wetland	Up to 8.6	1.6	NA	32	LC-MS/MS	(Vazquez-Roig et al., 2012)
		Groundwater	1–35.1	17.6	NA	23–100	LC-MS/MS	(López-Serna et al., 2013)
		Irrigation waters	<1–1019	3–163	0.3–80	0–100	GC–MS/MS	(Margenat et al., 2017)
	Hungary	Surface water	0.1–2	0.1–1.1	0.10	10–20	SFC-MS/MS	(Maasz et al., 2019)
Asia	China	Wastewater	1–16	2–7	0.3–10	100	LC-MS/MS	(Shao et al., 2009)
		River	4.6–75.5	24.3	0.2	NA	LC-MS/MS	(Wu et al., 2015)
		Drinking water	1.9					
	South Korea	Surface water	<0.25–1.7	0.38	1	50	LC-MS/MS	(Yoon et al., 2010)
	India	WWTP	6–100	9.5–36	0.1–50	100	HPLC-MS/MS	(Subedi et al., 2017)
Africa	Nigeria	Surface water	<0.3–42	<0.3	0.3	18	UPLS-MS/MS	(Ebele et al., 2020)
		Groundwater	<0.3–26					
Oxcarbazepine								
North America	U.S.	Rivers and wastewaters	<10–480	110	10	NA	LC-MS/MS	(Writer et al., 2013)
		Urban watersheds	273	32.5–34.2	10	45.8–55.7	UHPLC-MS/MS	(Bai et al., 2018)
South America	Argentina	Surface water	39–51	18–23	0.2	NA	LC-MS/MS	(Valdés et al., 2014)
Europe	France	WWTP	51–505	476	20.1	100	LC-MS/MS	(Leclercq et al., 2009)
	Germany	Wastewater	220.8–781	397	50	100	HPLC-MS/MS	(Gurke et al., 2015)
		Urban water cycle	8–570	NA	1	100	LC-MS/MS	(Brezina et al., 2017)
Phenobarbital								
North America	U.S.	Hospital effluent	110–440	240	NA	100	LC-MS/MS	(Oliveira et al., 2015)
Europe	Germany	Urban water cycle	<30–210	NA	30	100	UPLC-MS/MS	(Hass et al., 2012)
	Spain	Groundwater	3.42–47.2	9.69	NA	8–69	LC-MS/MS	(López-Serna et al., 2013)
Asia	Japan	River	15	NA	15	NA	LC-MS/MS	(Hoshina et al., 2009)
Pregabalin								
North America	U.S.	Hospital effluent	3630–6870	4190	NA	100	LC-MS/MS	(Oliveira et al., 2015)
		Urban watersheds	252	42.2	10	53.3–58.3	UHPLC-MS/MS	(Bai et al., 2018)
Europe	Germany	WWTP	810-2357.5	2015	100	100	HPLC-MS/MS	(Gurke et al., 2015)
		Surface water	110	NA	NA	NA	LC-MS/MS	(Sanz-Prat et al., 2020)
Lacosamide								
Europe	Hungary	Surface water	9.3	9.3	0.50	10	SFC-MS/MS	(Maasz et al., 2019)
		Surface water	0.81–60.32	8.45	0.5	34	SFC-MS/MS	(Kondor et al., 2020)
Levetiracetam								
Europe	Germany	WWTP	8157–10,825	8920	200	50	HPLC-MS/MS	(Gurke et al., 2015)
	Switzerland	Surface water	9–95	NA	15	96.8	LC-MS/MS	(Moschet et al., 2015)
Topiramate								
Europe	Germany	WWTP	107.9–162	145	50	100	HPLC-MS/MS	(Gurke et al., 2015)

NA: not available.

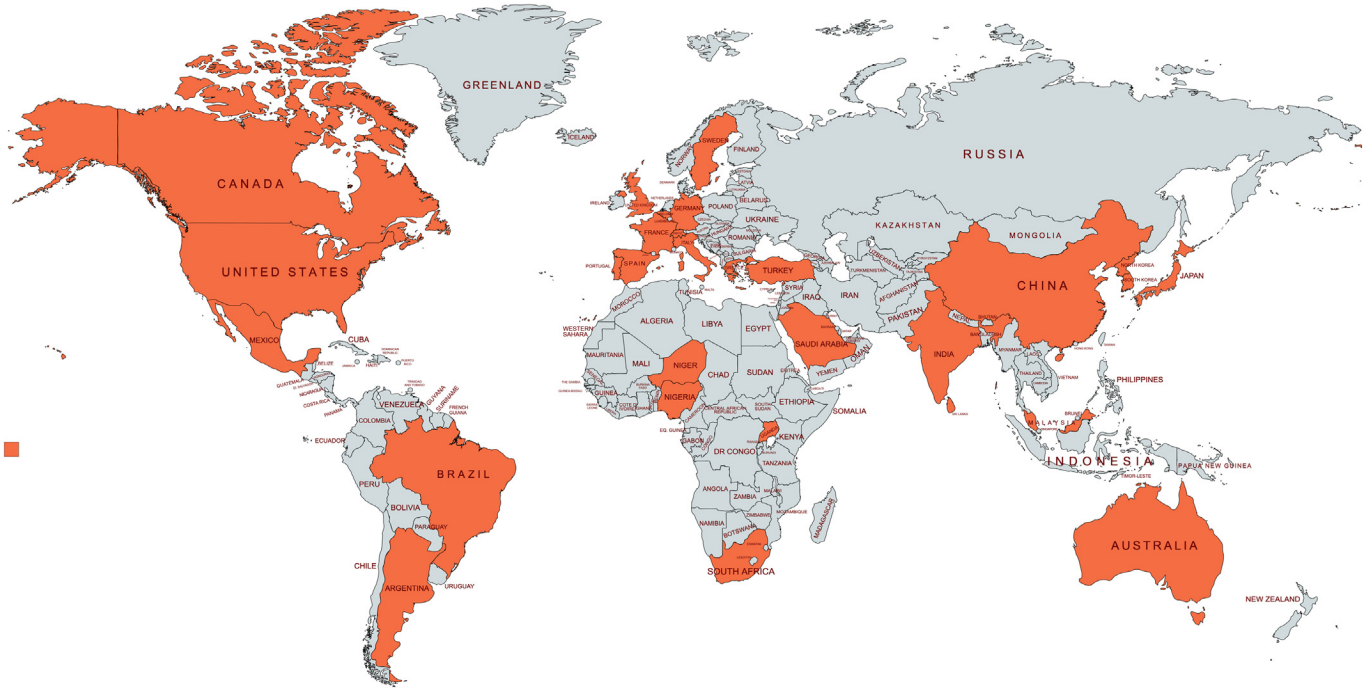

Fig. 2. Spatial-distribution of AEDs detected in worldwide waterbodies.

Differences in removal and quantification technologies may also be an important reason for which developing countries have not reported the occurrence of these drugs in aquatic environments. Many studies have emerged from developed and middle-income countries in the past two decades, while developing countries are still lagging behind in terms of identifying and quantifying AEDs in environmental samples (see Table 2). Notably in review articles from an African perspective is the mention of some difficulties such as poor sanitation systems, lack of infrastructure for routine trace analysis of environmental pollutants and shortage of well-trained personnel for operation of state of the art equipment required for water analysis of emerging pollutants (Gwenzi and Chaukura, 2018; Madikizela et al., 2017). Thus, the differences in technology and the inefficiency of the processes presented in the different WWTPs may also fluctuated the abundance of these drugs.

Other factors that may also play an important role in the occurrence and distribution of these drugs in freshwater and marine ecosystems are: uncontrolled wastewater treatment, discharge of drug manufacturing processes, domestic discharges from informal settlements without proper sanitation facilities, seasonal variation in pharmaceutical consumption, dilution factors, prescription rates of individual pharmaceuticals in the country, cost of pharmaceuticals, animal farm wastewater, resistance of individual pharmaceuticals to biodegradation, pharmacokinetics of individual pharmaceutical and transformation of pharmaceuticals into degradation products during metabolism.

4. Transport and fate of AEDs in solid matrices

Sediments originate from the erosion of minerals and soil, and just like water, are a very dynamic part of river systems (Babić and Mutavdžić Pavlović, 2013). These are transported downstream to the coast, where they are discharged into seas and oceans. Furthermore, in lowland areas where river flow velocity decreases, sediments are deposited along the banks and beds.

Once in the environment, AEDs are distributed in the water phase, as suspended particles or in the sediments, depending on their physicochemical properties. Most of the AEDs are hydrophobic compounds, so they are absorbed by the water particles (Qiu, 2011). Thus, when particles fall, anticonvulsants enter the sediments. Adsorption and desorption may be affected by several environmental properties, such as temperature, salinity, and pH values. Furthermore, water flow velocity, particle size and shape and riverbed morphology may also affect particle fall. Consequently, particles that fall into the sediment can be resuspended in the water.

Since sediments accumulate contaminants and can be transported through the different water bodies, these remain potential sources of adverse effects on surface and groundwater (Babić and Mutavdžić Pavlović, 2013). In addition, sewage sludge, the final product of WWTPs, are used in soil as a source of nutrients or as a soil conditioner. However, lipophilic and not readily biodegradable compounds, such as AEDs, are retained in the sludge where they are accumulated. This way, sewage sludge may also be a potential source of substances that are harmful to humans and animals. On the other hand, upon the application of contaminated sewage sludge to the soil, the compounds that contain may also be partially released, reaching deeper soil layers or groundwater through runoff and leaching (Babić and Mutavdžić Pavlović, 2013).

Due to the aforementioned, anticonvulsants have been widely detected in worldwide soils, sediments and sludge. In the last decade, the studies that evaluated the presence, fate and behavior of AEDs in solid environmental matrices have increased. However, such research is even less numerous in relation to the studies carried out in aqueous matrices.

Data about AEDs concentrations in solid matrices are shown in Table 3. In several countries of the world, the use of wastewater as irrigation water for agricultural land is a well-established practice. However, this habit may lead to the accumulation of AEDs in the soil and their further leaching into the groundwater. Gibson et al., 2010 for instance, reported the persistence and leaching potential of several drugs, including carbamazepine in the soils of Valle de Tula in Mexico. According to their results, carbamazepine was the most persistent drug in the soil, with concentrations equivalent to several years of irrigation (2.6–7.5 μg/kg). Furthermore, it should be noted that this drugs were also present in the deeper soil, and that concentration patterns were highly and positively correlated with soil organic matter concentration. Based on these results, it can be suggested that carbamazepine has a high potential for groundwater contamination. (See Tables 4 and 5.)

Table 3
Anticonvulsants in solid matrices.

Country	Matrix	Method of quantification	Min–max concentrations (μg/kg)	Mean concentration (ng/g)	Limit of quantification (ng/g)	Frequency of detection (%)	Source
Carbamazepine							
Mexico	Soil	GC–MS	5.14–6.48	NA	0.5	100	(Durán-Alvarez et al., 2009)
Mexico		GC–MS	2.6–7.5	3.7	0.5	100	(Gibson et al., 2010)
United sates		LC-ESI-MS/MS	0.7–1.1	0.7–1.1	NA	100	(Wu et al., 2010)
Israel		SPE-LC-MS	21.1–326.1	560, 1094	4	100	(Arye et al., 2011)
Tunisia		HPLC	0.28–0.94	0.1–0.3	0.25	100	(Fenet et al., 2012)
Czech Republic		LC-MS/MS	96–144	NA	5	100	(Koba et al., 2016)
Israel		HPLC-MS/MS	2.2–6	NA	100	NA	(Paz et al., 2016)
Spain		UPLC-MS/MS	0.08–1.36	NA	NA	NA	(Biel-Maeso et al., 2018)
Spain		LC-QTOF-MS	0.10–8.2	0.27	0.1	100	(Martínez-Piernas et al., 2018)
United states		LC-ESI-MS/MS	50	NA	NA	NA	(Thelusmond et al., 2018)
Spain	Sediment	LC-ESI-MS/MS	1.43–6.85	2.93	0.5	100	(Vazquez-Roig et al., 2010)
United states		HPLC-MS/MS	1–4	1.6	0.3	65	(Lara-Martín et al., 2015)
South Africa		HPLC-MS/MS	<0.535–6.07	1.37	0.5352	100	(Matongo et al., 2015)
Portugal		UHPLC-MS/MS	1.82	NA	1.20	NA	(Santos et al., 2016)
Baltic sea		LC-MS/MS	6.3–14	NA	0.1	86	(Björlenius et al., 2018)
India		GC–MS	3–519	22–67	NA	100	(Chakraborty et al., 2019)
Serbia/Romania		LC-MS	0.5–0.9	NA	0.1	NA	(Matić Bujagić et al., 2019)
Sweden		UPLC-MS/MS	<0.064–1.1	0.62	0.042–1.5	100	(Golovko et al., 2020)
Spain	Sludge	HPLC-DAD	18.4–460	66.6	14.8	91.6	(Martín et al., 2012)
China		LC-MS/MS	74–44,941	NA	13.8	100	(Dong et al., 2016)
Australia		HPLC	300	154	NA	100	(Yang et al., 2016)
Diazepam							
Spain	Soil	LC-QTOF-MS	0.14–0.81	0.65	0.1	42.8	(Martínez-Piernas et al., 2018)
Spain	Sediment	LC-ESI-MS/MS	2.50–4.65	2.86	2.3	100	(Vazquez-Roig et al., 2010)
Lamotrigine							
Israel	Soil	HPLC-MS/MS	1.5–8.5	NA	100	NA	(Paz et al., 2016)
Spain		LC-QTOF-MS	0.04–2.6	0.09	0.01	50	(Martínez-Piernas et al., 2018)
Primidone							
China	Soil	LC-MS/MS	1.6–3.3	NA	1.1	69	(Chen et al., 2011)
Spain		LC-QTOF-MS	5.6–6.5	5.6	0.1	25	(Martínez-Piernas et al., 2018)

NA: not available.

Another study that must be highlighted was carried out by Martínez-Piernas et al. (2018). They quantified organic micropollutants in agricultural soils irrigated with recovered wastewater for more than ten years.

Among the AEDs detected in this study were carbamazepine, primidone, lamotrigine and diazepam, with maximum concentrations of 8.2, 6.5, 2.6 and 0.81 μg/kg respectively. These concentrations could be explained by their recurrent presence and high concentrations reported in wastewater treatment plant effluents.

Lastly, Paz et al. (2016) reported the behavior of two of the most persistent anticonvulsant drugs (lamotrigine and carbamazepine) as well as of two of their metabolites, in agricultural soil. According to their results, the sorption of the compounds with the soils was the following: lamotrigine > carbamazepine > EP-CBZ > DiOH-CBZ. On the other hand, they also found that the sorption followed a reversible process without competition between the sorbates.

In addition, the detection of carbamazepine and one of its metabolites in wheat, agrees the reversibility of its uptake, leading to its possible leaching and availability for plant uptake.

5. Methods of quantification of AEDs

The method of choice to monitor the fate of CBZ (log KOW of 2.4) and its metabolites in trace levels is liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Here, it is important to emphasize that samples must be preconcentrated using solid phase extraction (SPE), in order to enhance the detection limit and reduces matrix effects (Bahlmann et al., 2014).

The separation of AEDs has been carried out with reversed-phase chromatography using high-performance liquid chromatography (HPLC) (Bai et al., 2018; Gurke et al., 2015; Nödler et al., 2013; Reh et al., 2013; Zuccato et al., 2005) and/or ultra-performance liquid chromatography (UPLC) (Biel-Maeso et al., 2018; Dalahmeh et al., 2020; Ebele et al., 2020; Kasprzyk-Hordern et al., 2008; Petrie et al., 2017; Pivetta et al., 2020) columns. Elution of the analytes from the chromatographic column has been achieved with an organic gradient using either ACN or MeOH. The mobile phase has been acidified with formic acid or ammonium formate to enhance the formation of molecular (protonated) ions in the positive mode. Until now, no mobile phase modifiers have been used in the negative mode. However, a basification of the mobile phase pH with ammonium hydroxide or ammonium bicarbonate generally favors analyte deprotonation (Borova et al., 2014; López-García et al., 2018).

Molecular ions of AEDs amenable to mass spectrometry detection have been produced by means of electrospray ionization (ESI). This has usually been performed in the positive ESI mode. However, a few AEDs are only amenable to negative polarity ESI ionization. This is the case of the phenytoin and valproic acid, and the barbiturates pentobarbital and phenobarbital, which are only amenable to negative ionization (Borova et al., 2014; López-García et al., 2018).

MS determination of the ESI-produced molecular ions has been performed with different analyzers. Instruments equipped with triple quadrupole (QqQ) analyzers have been the most commonly used (Borova et al., 2014). They were operated in the selected reaction monitoring (SRM) mode, acquiring a minimum of two SRM transitions per compound. The recent development of benchtop HRMS instruments and the growing installation of this technology in many laboratories have boosted the creation of highly selective analytical methods for the targeted analysis of organic compounds, including psychoactive pharmaceuticals. Besides improving method selectivity due to the use of a mass tolerance window of 5 ppm, the main advantages of using HRMS hybrid analysers such as quadrupole time of flight (Q-ToF) or quadrupole Orbitrap (Q-Exactive mass spectrometer) compared to conventional QqQ analysers is that non-targeted full scan screening can be

Table 4
Removal rates of AEDs using biological treatments.

Biological treatment	Conditions	Initial concentration (ng/L)	Removal rate (%)	Source
Carbamazepine				
Activated sludge/membrane bioreactor	The submerged MBR was equipped with three membrane plates, each having a surface of 0.1 m^2 and a mesh with width of 0.4 μm.	1273–1287	0–13	(Bernhard et al., 2006)
Biological treatment/ozonation	A2O multi-stage configuration with nitrification-denitrification/The gas containing about 9.7 g/Nm^3 ozone was bubbled by means of a porous glass disk with a gas flow of 0.36 Nm^3/h	173	100	(Rosal et al., 2010)
Activated sludge	Nitrifying (aerobic) and denitrifying (anoxic) conditions	20,000	<25	(Suarez et al., 2010)
Membrane bioreactor	Pore size of 0.04 μm, effective membrane surface area of 0.047 m^2	2000	13.4	(Tadkaew et al., 2011)
Membrane bioreactor/reverse osmosis	Pore size of 0.4 μm, 8 m^2 of flat sheet membranes, 10 bar	64–99	>99	(Dolar et al., 2012)
Membrane bioreactor/granular activated carbon	pH 7.2–7.5, HRT 24 h, 20 °C, 7.5 g GAC	5000	>98	(Nguyen et al., 2012)
Suspended activated sludge and moving bed biofilm process	Hydro-dynamic cavitation with addition of H_2O_2 and UV irradiation. 20 mL, 30% H_2O_2, 30 min, 6 bar/UV	1000	0–>98	(Zupanc et al., 2013a, b)
Constructed wetland	Three horizontal subsurface flow, operation of 5 years, pretreatment unit, gravel to a depth to 0.8 m, vegetation: phragmites and phalaris	<LOD	100	(Chen et al., 2016)
Constructed wetland	Two pilot-scale constructed operated in parallel, with *P. australis* and Leca	2370–58,430	89.23–95.94	(Özengin and Elmaci, 2016)
Ultrafiltration membrane bioreactor	Membrane module with a nominal pore size of 0.04 μm and a total membrane area of 0.93 m^2	1×10^6	36.2	(Chtourou et al., 2018)
Staged anaerobic fluidized membrane bioreactor	Anaerobic fluidized bed reactor and anaerobic fluidized-bed reactor connected in series, zeolite (0.6–2 mm diameter), each membrane module held 100 cm long polyvinylidene fluoride (PVDF) membrane, pore size of 0.1 μm	1000	16.6–18.5	(Chen et al., 2019)
Sequencing batch reactor	9 cm diameter and a height of 47 cm, fungal consortium of five isolated South African indigenous fungi inoculated at 30% (v/v) of mycelium solution	1×10^6	89.77	(Kasonga et al., 2019)
Constructed wetland/photo-phenton	Fiberglass container (0.375 m^2 surface area), six seedling rhizomes, HRT 2.5 days/Three Fe^{2+}/H_2O_2 ratios (0.1, 0.3, and 0.8)	15,000	86	(Casierra-Martinez et al., 2020)
Moving bed biofilm reactors	12 L, air flow of 0.09 m^3/h, cubic polyurethane sponges (15 mm, 28 kg/m^3, 0.846 m^2/g), HRT 12 h	1–5 × 10^6	28.3	(Zhang et al., 2020)
Diazepam				
Constructed wetland	240 m^2, depth of 110 cm, HRT 10 days, vegetation *Phragmites australis* and *Iris pseudacorus*	48	70	(Auvinen et al., 2017)
Gabapentin				
Constructed wetland	Three horizontal subsurface flow, operation of 5 years, pretreatment unit, gravel to a depth to 0.8 m, vegetation: Phragmites and Phalaris	>100	53–88	(Chen et al., 2016)
Constructed wetland	240 m^2, depth of 110 cm, HRT 10 days, vegetation Phragmites australis and Iris pseudacorus	7910	>90	(Auvinen et al., 2017)
Phenytoin				
Membrane bioreactor	Pore size of 0.04 μm, effective membrane surface area of 0.047 m^2	2000	5.4	(Tadkaew et al., 2011)
Sequencing bath reactors	1.8 L, SRT 10 days, HRT 24 h,	70	Recalcitrant	(Stadler et al., 2015)
Primidone				
Membrane bioreactor	Pore size of 0.04 μm, effective membrane surface area of 0.047 m^2	2000	12.4	(Tadkaew et al., 2011)
Membrane bioreactor/granular activated carbon	pH 7.2–7.5, HRT 24 h, 20 °C, 7.5 g GAC	5000	>98	(Nguyen et al., 2012)

combined with targeted analysis in the same analytical run. Thus, a retrospective analysis of the sample can be performed any time in the future without the need of reanalyzing the extract (López-García et al., 2018).

6. Removal of AEDs from WWTPs

Since AEDs are ubiquitously distributed in worldwide water bodies, it is suggested that wastewater treatment processes are not effective in eliminating these drugs from effluents. In addition, several studies have demonstrated that these drugs may result harmful to aquatic organisms at environmentally relevant concentrations. Thus, new alternatives for the removal of these drugs from effluents should be urgently investigated.

The following section briefly discuss the removal rates achieved under different treatment technologies.

6.1. Biological treatment technologies

These treatment technologies have been considered as the main treatment process to eliminate organic contaminants from wastewater in WWTPs. However, several studies have suggested that biological treatment technologies are not effective to remove AEDs from wastewater. Bernhard et al., 2006, for instance assessed the biodegradation of certain group of contaminants, using a laboratory-scale membrane bioreactor that worked in parallel with activated sludge. In their results, carbamazepine was reported as a non-degradable micro-contaminant, as this was not removed at all during wastewater treatment. Similarly,

Table 5
Removal rates of AEDs using chemical treatments.

Chemical treatment	Conditions	Initial concentration (ng/L)	Removal rate (%)	Source
Carbamazepine				
Photocatalytic degradation	P25 (0.5 g/L), 5 mM of H_2O_2 or 50% O_2 (v/v), with rate constants ca. 0.3144 min^{-1} and 0.2005 min^{-1}	8×10^6	100	(Martínez et al., 2011)
Advanced oxidation/biodegradation	UV/H_2O_2, biomass concentration was 32 ± 1 mg/L	26×10^4–1×10^6	100	(Keen et al., 2012)
UV-photolysis	Bench scale UV photoreactor with a circulating flow system. 120 min irradiation period. Steel container (8 L), a waterpump (85 L/h), and a medium pressure metal-halogen UV lamp (690 W).	6×10^6	~99	(Donner et al., 2013)
Photocatalysis	Sand was sieved to obtain 200–500 μm fractions, mixed with DI, stirred for 24 h, and air-dried prior to being used as the immobilization substrate, TiO_2 was coated on the sand.	5×10^6	76	(He et al., 2016)
Green photo-Fenton process	Surface of 560 cm^2 and 600 W/m^2 of solar intensity, 0.5% of UVB (290–320 nm) and 5–7% of UVA (320–400 nm), while after 400 nm the solar spectrum was simulated	164	16.43–40.92	(Villegas-Guzman et al., 2017)
Photocatalytic degradation	Immobilized TiO_2 coatings, under controlled and natural solar irradiation	248.8–381.1	~20	(Rueda-Márquez et al., 2020)
Gabapentin				
Photo-Fenton process	60 min of UV254/H_2O_2/Fe(II)	342.47	<24	(Neamțu et al., 2014)
Green photo-Fenton process	Surface of 560 cm^2 and 600 W/m^2 of solar intensity, 0.5% of UVB (290–320 nm) and 5–7% of UVA (320–400 nm), while after 400 nm the solar spectrum was simulated	1467	6.48–29.16	(Villegas-Guzman et al., 2017)
Primidone				
Green photo-Fenton process	Surface of 560 cm^2 and 600 W/m^2 of solar intensity, 0.5% of UVB (290–320 nm) and 5–7% of UVA (320–400 nm), while after 400 nm the solar spectrum was simulated	60.5	16.71–33.50	(Villegas-Guzman et al., 2017)
Photocatalytic ozonation	Cubic chamber with 44 LEDs, 25–455 W m^{-2} with a maximum wavelength of 425 nm, O_2 or O_3:O_2 mixture: 0.5% O_3	20×0^6	70–>82	(Checa et al., 2019)

Tadkaew et al., 2011 studied the relationship between the structural characteristics of organic contaminants and their removal efficiency by a laboratory-scale membrane bioreactor. Since three AEDs shared similar removal efficiencies (carbamazepine 13.4%, phenytoin 5.4% and primidone 12.4%), they concluded that there is a correlation between chemical structures and contaminant removal.

Not only activated sludge and membrane bioreactors processes have demonstrated poor removal rates for AEDs, but also moving bed biofilm reactors processes. Casas et al. (2015), for instance evaluated the removal efficiency of three moving bed biofilm reactors used for the treatment of drugs in hospital waste water. The removal of the compounds was studied in two experiments, the first one in batches, in which the drugs were introduced in each reactor and the second one, a continuous flow experiment. Carbamazepine in both experiments showed low removal rates, with values of less than 20%. Analogously, Zhang et al., 2020 constructed four laboratory-scale moving bed biofilm reactors to treat synthetic wastewater polluted with pharmaceutical and personal care products. Their results showed that the average disposal efficiency for carbamazepine was 28.3 ± 7.4%.

In the last decade, algae-based bioreactors have gained special interest as a promising way to remove emerging contaminants from wastewater. In laboratory-scale studies, high removal rates have been achieved for most selected pharmaceuticals, but not for AEDs. In a study carried out by Xiong et al. (2016), degradation capacity of two microalgae species (*Chlamydomonas mexicana* and *Scenedesmus obliquus*) was assessed. Results showed that removal rates of both microalgae were lower than 35%. Similarly, de Wilt et al. (2016) demonstrated that the removal of AEDs with algae-based bioreactors (*Chlorella sorokiniana*) was incomplete and did not exceed 30%. Concerned about the persistence and fate of pharmaceuticals and personal care products in the Lake Mead, Bai and Acharya (2017) evaluated the elimination of five drugs using the green algae Nannochloris sp. Their results showed that almost 100% of the carbamazepine applied dose was found after 14 days of incubation.

Until now the only biological treatment technology that has shown to be useful for the removal of AEDs are constructed wetlands (CW's). Dordio et al. (2010), for instance used a constructed wetland system (planted with Typha spp.), established with a light expanded clay aggregate matrix (LECA) to evaluate their ability to remove pharmaceutical products. Their results demonstrated that carbamazepine was eliminated in a 97%, after 7 days of retention. Similarly, two pilot-scale artificial wetlands were constructed using LECA as a substrate and operated in parallel. The first as an experimental unit (planted with *Phragmites australis*) and the second as a control, which was not planted. The elimination efficiency for carbamazepine was 89.23% in the planted reactor and 95.94% in the non-planted reactor. These results demonstrate LECA has a high adsorption capacity for pharmaceutical products that area resistant to biodegradation. On the other hand, Auvinen et al., 2017 assessed the removal efficiency of a wetland with a large-scale hybrid aerated groundwater flow system. According to their results, carbamazepine, diazepam and gabapentin were efficiently removed from hospital wastewater. Furthermore, it was concluded that the efficiency of elimination depended on the aeration applied.

6.2. Photo-based treatment technologies

Since biological processes have shown variable removal rates for AEDs, chemical treatment technologies emerge as an alternative to achieve higher removal efficiencies of these drugs.

Several studies have pointed out that photocatalysis may be a promising post-treatment process for eliminating AEDs from wastewater. Martínez et al., 2011, for instance evaluated the photocatalytic degradation of carbamazepine under UV radiation, using TiO_2 and ZnO as catalysts. Their results demonstrated a complete elimination of carbamazepine. Similarly, Haroune et al. (2014) evaluated the effects of environmental parameters, such as pH, ionic strength and organic matter content, in the photodegradation of carbamazepine. According to their results TiO_2 was more efficient than ZnO to degrade carbamazepine. However, in both processes, the photodegradation of carbamazepine was significantly affected by the pH and by the presence of organic matter.

In order to achieve the aqueous mineralization of primidone with ozone and LED visible light, Checa et al., 2019 synthesized a compound of graphite oxide and titanium (GO/TiO_2). According to their results, GO and ozone improved TiO_2 activation under visible light, reaching a

mineralization rate of up to 82% in 2 h. It is suggested hydroxyl radicals were the main species responsible for the elimination of primidone.

Unlike photocatalysis, photo-Fenton process has shown low removal rates of AEDs in wastewater. A comparative study of photolytic degradation under UV254 nm exposure and solar simulator irradiation in the presence of H_2O_2 and Fe(II) corroborated the chemical stability of these drugs under UVC irradiation. Gabapentin was one of the most persistent compounds, with less than 24% was eliminated after 60 min of treatment with UV254/H_2O_2/Fe(II). Taking into account these findings, Villegas-Guzman et al., 2017 proposed a new green photo-Fenton process for wastewater treatment, which involves the use of natural iron and additives that act as iron chelators. The process was able to eliminate 40% of the total identified micro-contaminants from a municipal wastewater treatment plant. However, the removal efficiency for AEDs was lower than 41%.

One of the most important natural processes for the removal of pharmaceuticals is photo transformation driven by solar irradiation. Primidone was chosen as a model "photorefractory" compound to assess whether the reactive intermediates inhibited or enhanced the photochemical transformation of this drug under simulated solar irradiation. The results indicate that hydroxyl radicals plays a key role in the photodegradation of primidone and that dissolved oxygen can affect the rate of degradation. In addition, 28 photochemical transformation products were identified for this anticonvulsant (Liu et al., 2019a, b).

6.3. Combined treatment processes

Among the pharmaceuticals that prove to be more persistent, suffering little or no degradation during treatment, is carbamazepine. Coupled systems combining biological treatments and advanced oxidation technologies represent an alternative to reduce the risk of these compounds in the environment. For example, Rosal et al., 2010 demonstrated that advanced oxidation processes coupled to a biological treatment improved the removal rates for this drug, with a removal efficiency of up to 100%. Thus, it is suggested that ozonation can improve the biodegradability of carbamazepine. Kosjek et al. (2012) carried out the evaluation of different benzodiazepine drugs, including diazepam, in wastewater treatment plants and in surface water. Removal efficiencies with respect to biological treatment of diazepam were 16–18% (oxic), 18–32% (anoxic/oxic), 53–76% (oxic/anoxic) and 83% (oxic/ anoxic/oxic/anoxic cascade bioreactors). Coupled biological and photo-chemical treatment followed by the adsorption to activated carbon resulted in a removal efficiency of 99.99%, suggest that only combinational treatment is sufficient to remove them. Analogously, Wang and Wang (2017) used a combination of gamma irradiation and biodegradation to remove carbamazepine from wastewater. Their results showed that removal efficiency for carbamazepine increased during the irradiation process, reaching a maximum removal of 99.8%. In addition, Casierra-Martinez et al., 2020 evaluated the performance of a photo-Fenton process coupled to a constructed wetland for the removal of carbamazepine from domestic wastewater. According to their results, significantly higher efficiencies were achieved with the photo-Fenton constructed wetland coupled system (40% CW only and up to 92% of the coupled system). In addition, the coupled system showed a total organic matter and nitrogen removal efficiency greater than 61%. Together, these results demonstrate that the combined process of irradiation with biological treatments may be an alternative to remove recalcitrant organic contaminants such as carbamazepine from wastewater.

Significant progress has been made so far in the removal of AEDs from wastewater. However, some problems remain to be solved such as the analytical detection and quantification of unknown compounds. For example, little or no information is known about the degradation and/or transformation products of AEDs. Moreover, during the degradation of AEDs, several intermediaries are formed, which may be more toxic than the original compounds, making them more dangerous. It is therefore necessary to evaluate them in order to reduce, as far as possible, the ecotoxicological effects of these by-products before treating them. Finally, it is recommended to work with real wastewater samples instead of those simulated in the laboratory to provide solutions that are close to reality.

7. Conclusions and perspectives

A solid understanding for the occurrence and fate in aquatic environments for most of the pharmaceutical products has been gained in the last decade. However, it is necessary to expand this knowledge on other pharmaceutical groups, such as AEDs.

AEDs have been found in several water bodies around the world, and carbamazepine has been the most frequently anticonvulsant detected in most of the studies. However, in the last decade, the use of AEDs has changed, showing an important increase in the number of prescriptions for lamotrigine, gabapentin, levetiracetam and topiramate. Thus, the occurrence and distribution of these anticonvulsants should be further monitored, not only in surface waters, but also in sediments, as more data on waste and surface waters are available in the literature.

As we aforementioned, there is a lack of interest and necessity for monitoring the occurrence of AEDs degradation products. However, it is necessary to increase attention about these byproducts as in most of the cases these may be more toxic than the parent compounds. Therefore, identification and real-time monitoring of these compounds becomes today's challenge.

Until now, only CW's and photocatalysis have shown good removal rates of AEDs from wastewater. However, their effectiveness depends on the specific conditions used during the treatment. In CW's, for example, it is suggested that its removal capacity improved when this is established with a light expanded clay aggregate matrix (LECA). Thus, these conditions must be taken into account to reach high removal rates. On the other hand, chemical processes have shown to improve the biodegradability of this type of compounds, as well as break down non-biodegradable compounds into simpler and smaller molecules. Therefore, combination treatment strategies have proven to be the most efficient and ecological methods to eliminate recalcitrant compounds such as carbamazepine.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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