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Review

Consumption and ocurrence of antidepressants (SSRIs) in pre- and post-COVID-19 pandemic, their environmental impact and innovative removal methods: A review

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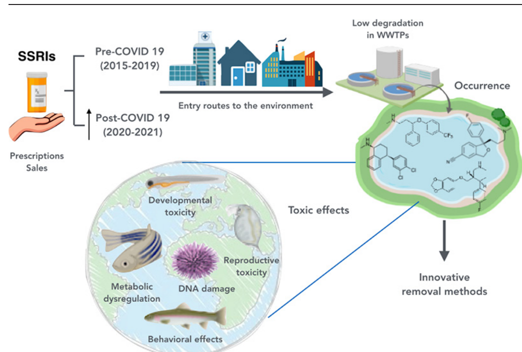
HIGHLIGHTS

- During the COVID-19 pandemic, the consumption of SSRIs increased worldwide.
- The consumption and occurrence of SSRIs pre-COVID-19 and post-COVID-19 were compared.
- Concentrations of SSRIs in the environment also increased.
- Its main effects are alterations in genetic transcription, deficiency in reproduction and motility.
- UV photolysis, activated carbon, electron beam irradiation, and molecular polymers have shown a removal greater than 99.9%

GRAPHICAL ABSTRACT



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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are pharmaceuticals whose consumption has increased significantly. They are prescribed as first-line treatment in mental disorders such as depression, obsessive-compulsive disorder, phobias, and anxiety; also, they are indicated as adjuvants in diseases such as fibromyalgia and bulimia nervosa. In addition to being linked to the illegal market to be consumed as recreational drugs. The relevance of this review lies in the fact that worldwide consumption has increased significantly during the COVID-19 pandemic, due to the depression and anxiety that originated in the population. As a consequence of this increase in consumption, concentrations of SSRIs in the environment have increased, and these have become a relevant issue for toxicologists due to the effects that they could generate in different organisms, both aquatic and terrestrial. For this reason, the objective of this article was to do a critical evaluation of the existing data on the characteristics and physicochemical properties of SSRIs, consumption data during the COVID-19 pandemic, its occurrence in the environment and the reports of toxic effects that have been generated in different organisms; we also conclude with an updated review of different methods that have been used for their removal. With this analysis, it can be concluded that, despite SSRIs are pharmaceutical products widely studied since their launching to the market, still currently under investigation to clarify their mechanisms of action to understand the different effects on the organisms, adverse reactions, as well as possible toxicological effects on non-target organisms. On the other hand, it has been proven that although it is already possible to eliminate a significant percentage of SSRIs in the laboratory, due to their physicochemical characteristics and their behavior in complex mixtures in the environment, they have not yet been eradicated, showing a persistence in the soil, subsoil and surface waters of the entire planet that may represent a future risk.

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1. Introduction

Depression, which is considered as a psychiatric condition, is characterized by an imbalance in mood, affect, and behavior regulators and is recognized in high-income countries as one of the most common causes of disability. This condition is associated with high health costs, medical expenses, and social costs, reflected in reduced work productivity (Bucciarelli et al., 2021). In addition, the increasing prevalence of depression poses a new challenge for health workers and researchers. In 2004, the World Health Organization had predicted that by 2030 depression would be the mental disorder with the highest level of disability worldwide (Sindu, 2020; WHO, 2008).

The first generation of antidepressants corresponds to the monoamine oxidase inhibitors (MAOIs), generated during the 1950s, while in the 1970s, the so-called atypical, heterocyclic, or second-generation antidepressants appeared (Galan, 2015). From the mid-1980s, new classes of pharmaceuticals were developed for use in the treatment of depression. It was the first class of psychotropic drugs designed that targeted a specific site of action using in vitro receptor binding affinity technology to avoid serious adverse effects (commonly reported with the above generations). The result was selective serotonin reuptake inhibitors (SSRIs) that were created to be safer and more tolerable than antidepressants used in previous decades. Fluoxetine was the first SSRIs released on the market, introduced in 1987. Since then, this class of antidepressant pharmaceuticals has become the most prescribed psychotropics in different countries (Chavez, 2008; Lochmann and Richardson, 2019).

SSRIs are used in first line for the treatment of moderate to severe depression, it have high therapeutic efficacy and are safer and more tolerable compared to other antidepressants (e.g. serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs)) (Gołyszny and Obuchowicz, 2019; Hieronymus et al., 2016). Six SSRIs are commercially available: citalopram and its enantiomer escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline; despite their similar mechanism of action, SSRIs have different molecular structures, as shown in Fig. 1 (Vadodaria et al., 2021). These drugs do not have identical secondary pharmacological characteristics even though they share the primary mechanism of action, modulation of monoaminergic transmission, mainly in which somatodendritic 5-HT1A auto receptors play an essential role in 5-HT autoregulation (Gołyszny and Obuchowicz, 2019; Sanchez et al., 2014).

They are called selective since they do not affect other sodium receptors or channels, as do TCAs, a mechanism to which most of the adverse effects associated with these are attributed (Fig. 2) (Preskorn et al., 2004). The serotonergic hypothesis postulates that, in depression, serotonin activity is decreased due to genetic or environmental causes. The characteristic therapeutic effects of SSRIs can be attributed to delayed neurochemical adaptations, that is, desensitization of somatodendritic serotonin 1A auto receptors in the midbrain raphe nucleus. Blocking the reuptake of monoamine at the level of the presynaptic receptors 5HT-1A, 5HT-2C, and

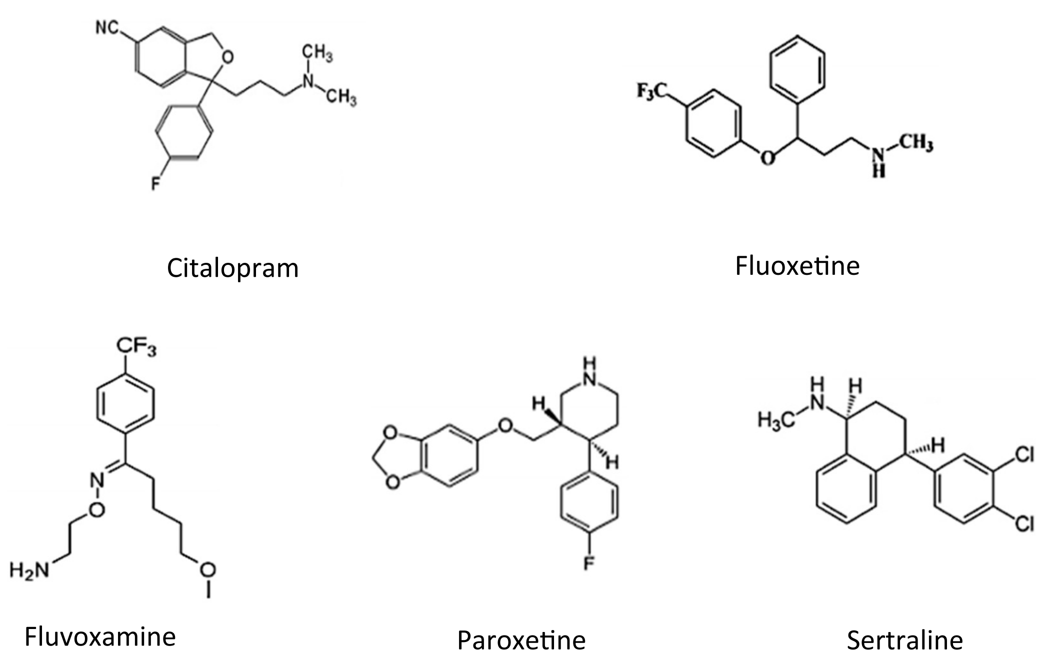

Fig. 1. Molecular structure of SSRIs.

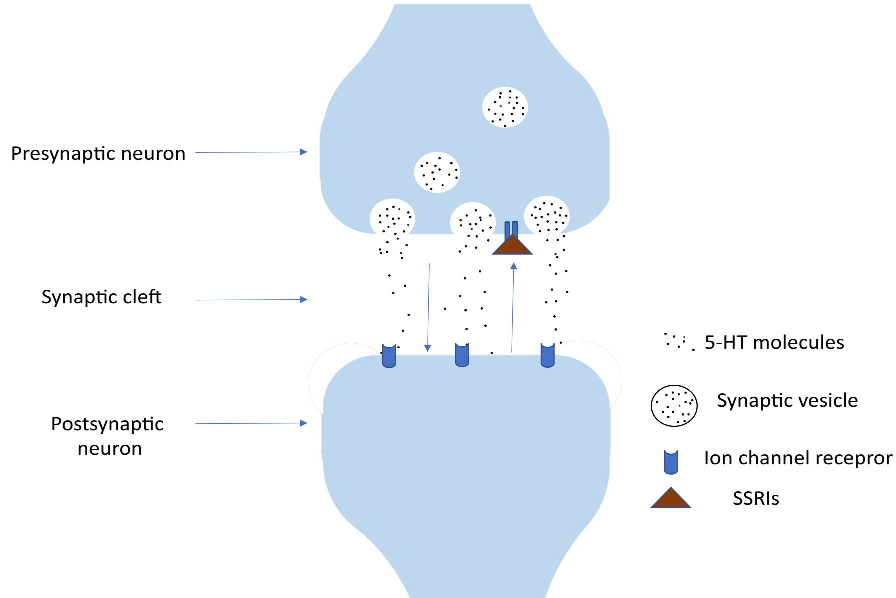

Fig. 2. General mechanism of action of SSRIs.

5HT-3C increases the neurotransmission of this system, which results in the antidepressant effect (Chavez, 2008). On the other hand, the main hypothesis to explain the immediate side effects is that serotonin increases in specific subtypes of serotonin receptors in regions of the body where relevant physiological processes are regulated. Desensitization of postsynaptic receptors in these same discrete brain regions may explain the development of tolerance to these same side effects (Lochmann and Richardson, 2019).

Currently, SSRIs' exact pharmacokinetics and pharmacodynamics have not been determined, only hypotheses can be suggested. The hepatic metabolism of these drugs is highly influenced by genetic and pathophysiological factors and interactions with other drugs. The relationship between drug concentrations and active metabolites present individual variations, which contributes to the therapeutic effects and complicates predicting the response and dose adjustment. From the clinical point of view, it must be considered that its metabolites can have two types of activity for this pharmacological group: starting with the serotonin reuptake inhibitor objective from which the antidepressant effect derives and, secondly, the inhibitory activity of different isoenzymes of cytochrome P450 responsible for the production of interactions with other drugs (Otero et al., 1996). It is essential to mention that the effects on CYP450 enzymes, which mediate most of the oxidative metabolism of human drugs, vary in each SSRIs despite the similarity in the mechanism of action, efficacy, and side effect profiles (Uriarte, 2011). Significant inhibition of CYP enzymes means that a co-administration of these SSRIs produces a several-fold increase in co-prescribed drugs, the clearance of which depends on the CYP enzyme inhibited by the administered SSRIs. Increased levels of the involved drug can cause various detrimental effects, including decreased tolerability, withdrawal syndromes, or increased adverse effects and toxicity (Table 1) (Preskorn et al., 2004).

Most SSRIs have similar half-lives, close to 24 h, however, fluoxetine has a half-life of 24 to 48 h. Furthermore, its active metabolite, norfluoxetine, has a mean half-life of 7 to 15 days in a regular adult patient and three weeks in a healthy patient over 65 years of age (Lochmann and Richardson, 2019). In general, these pharmaceuticals have high fat-soluble characteristics, so they present good absorption after oral administration. Its absorption rate is slow and longer than other antidepressants, reaching maximum plasma concentrations usually between four and 8 h after administration. The fraction of the absorbed dose in the gastrointestinal tract is high; however, the systemic bioavailability of SSRIs is markedly reduced by the extensive first-pass effect they experience (Otero et al., 1996).

Regarding the distribution of SSRIs in the body, the lipid solubility of these antidepressants determines that they are rapidly and widely distributed in the body, finally diffusing through the blood-brain barrier. Only a fraction less than 4% of the total drug in the body is present in the systemic circulation. The degree of binding to plasma proteins is greater than 90% for all SSRIs, except fluvoxamine, a binding percentage of 77%. These drugs are excreted in breast milk, reaching concentrations similar to those in plasma, such as paroxetine or lower, as in the case of fluvoxamine, fluoxetine, and their active metabolite norfluoxetine (Otero et al., 1996; Uriarte, 2011).

In general, most of the adverse effects of SSRIs are dose-dependent and are therefore consistent with those expected with excess serotonin. The most common adverse effects include nausea, vomiting, diarrhea, headache, lightheadedness, drowsiness or insomnia, sweating, trembling, dry mouth, anxiety. Less commonly occurring adverse effects include bruxism, paresthesia, weight gain, sexual dysfunction, and myoclonus (Lochmann and Richardson, 2019). Certain SSRIs are more likely to cause withdrawal symptoms when discontinued than others, such as fluvoxamine and

Table 1
SSRIs that participate as inhibitors or substrates of some enzymes of the CYP450 family (Uriarte, 2011; Preskorn et al., 2004).

SSRIs	CYP1A2		CYP2C		CYP2D6		CYP3A	
	Inhibitor	Substratum	Inhibitor	Substratum	Inhibitor	Substratum	Inhibitor	Substratum
Citalopram					X	X		
Fluoxetine			X		X	X	X	
Fluvoxamine	X	X	X		X		X	
Paroxetine	X				X	X	X	
Sertraline			X		X	X	X	X

paroxetine. Fluoxetine and vortioxetine are the least likely to cause withdrawal symptoms due to the half-life of both the parent drug and its active metabolite in the case of fluoxetine, norfluoxetine (Uriarte, 2011). Studies have also been carried out on teratogenicity, and the use of SSRIs during pregnancy has been associated with an increase in the incidence of three or more minor structural anomalies, the incidence of premature births, and low newborn weight (Chavez, 2008; Lochmann and Richardson, 2019). SSRIs have also been associated with increased hostility, suicidal ideation, and psychomotor agitation in clinical trials with children, adolescents, and young adults up to 24 years of age. However, these effects did not occur in people aged 24 to 65 years. For this reason, monitoring patients for worsening depression and suicidal thoughts is recommended (Lorman, 2018, Sheldon H. Preskorn, 1997).

As mentioned, due to its effectiveness and lower incidence of adverse effects, from 1991 to 2018, the total consumption of SSRIs (reflected in the total prescription) increased by 3001% in the United States (Medicaid) going from US$64.5 million to US$2 billion in 2004, decreasing to US $755 million in 2018 (Alrasheed et al., 2020). On the other hand, although it is known that the consumption and prescription of SSRIs have risen dramatically in the last 30 years, in March and April 2020, higher levels of anxiety and depression were recorded in most countries compared to previous years attributed to the COVID-19 pandemic, increasing symptoms related to this disease such as confusion, memory impairment, post-traumatic stress disorder, insomnia as well as depressive and anxious episodes (Mouffak et al., 2021), and according to some authors, it also led to an increase in the consumption of SSRIs, among other antidepressants in several countries (Farina et al., 2021; Armitage, 2021), although some others consider that this increase is not representative (Walker et al., 2021), so it is important to make critical reviews of consumption and sales in order to clarify this hypothesis.

On the other hand, after administration, SSRIs can undergo metabolic biotransformation, leading to the excretion of the unchanged compound or metabolites, then these can arrive into water bodies mainly through discharges of industrial, domestic, and hospital effluents, which can be confirmed with detection reports in various aquatic matrices worldwide (Azzi et al., 2021; de Souza et al., 2021; Gornik et al., 2020b; Miller et al., 2021). In addition, most wastewater treatment plants do not have the necessary removal methods to eliminate these pharmaceuticals (Gornik et al., 2021; Rejek and Grzechulska-Damszel, 2018), which can represent a future risk, so the scientific community is increasingly concerned about the possible toxic effects on aquatic organisms and human health. Therefore, it is essential to research these pharmaceuticals in various aquatic matrices.

Due to all of the above, the main objective of the present article was to provide an update on consumption (pre- and post-COVID-19 pandemic), fate, occurrence in environment, toxicological effects on organisms, and current treatment technologies used to remove SSRIs from wastewater.

2. Methodology

A systematic search of published articles and documents was carried out, to identify relevant, a bibliographic search was carried out from September until December 2021 in databases such as Pub-Med, Scopus, Science Direct, Springer, Wiley and Google Scholar. The search was performed using the terms: “antidepressants”, “SSRI” OR “SSRIs” AND “COVID-19”; accompanied by the following words, “prescriptions”, OR “consumption”, OR “sales”, OR “toxic effects” AND “environment”, OR “removal methods”. Unpublished studies (e.g. conference proceedings) were not included. From the results obtained (740 documents), we selected a total of 131 publications, which were further classified into subtopics (i.e. physicochemical characteristics, prescription, sales, occurrence, distribution, ecotoxicology and removing methods).

Due to the fact that there are several reviews available, and that a debate was also generated on the increase in the consumption of antidepressants during the COVID-19 pandemic, in this article we focus on comparing data published pre-pandemic (2015–2019) and post-pandemic (2020-current), in order to provide useful information that allows analyzing the consumption of these pharmaceuticals, sales, environmental occurrence, as well as their possible effects on the environment; in addition to the review of updated removal methods and their effectiveness.

3. Results and discussion

3.1. Prescribing and consumption of SSRIs after and post-COVID-19 pandemic

Good mental health is considered vital for human beings to lead healthy and productive lives and to preserve it, the most prescribed antidepressant drugs globally are SSRIs due to their safety profile and the consideration that there are no significant differences in terms of efficacy between the different antidepressants available on the market (Arnáiz et al., 2006; Blüml et al., 2017; Halonen et al., 2018). However, data on national consumption and sales are scarce in some countries, such as Latin America, while in others annual statistics can be found. Below quote the data found pre-COVID-19 pandemic.

Chen et al. (2008) evaluated the US Medicaid Program from 1991 to 2005, and found that the total number of antidepressant prescriptions increased substantially from 1991 to 2004 (from 6.8 million to 35.0 million scripts, over a 400% increase), but then fell in 2005 to 32.7 million prescriptions. SSRIs gradually came to dominate the market over the last 15 years.

On the other hand, Serna Amáiz et al. (2006) carried out a cross-sectional observational study of the dispensing of antidepressant medications made by prescription of the National Health System of the Region of Lleida (Spain), during the years 2002 to 2004, finding an increase of 9.4% in the number of patients with antidepressant treatment in 2004 compared to 2002. When studying the groups of antidepressants, they observed that the ones that are prescribed in a higher percentage are SSRIs (65.6%), followed by tricyclics and heterocyclics (22.7%), venlafaxine (8.6%), mirtazapine (1.4%), reboxetine (1%) and monoamine oxidase inhibitors (0.1%).

Another study carried out over 11 years (2000 – 2010) in Valencia (Spain) obtained results that are consistent with this trend, since they found that the prescription of SSRIs increased significantly (63.9%), which represented 681.7 million euros for the Valencian community (Verdú et al., 2014).

Lewer et al. (2015) conducted a study in 27 countries during the years 2014 and 2015, finding a prevalence of antidepressant use of 7.2% in 2010, the double of a previous estimate (3.7% in 2000) which reflects a increase in prescription rates over the same period.

Meanwhile, Blüml et al. (2017), evaluated 402 German districts in the years 2010 to 2013, finding that the mean number of antidepressant pills sold per 100,000 persons across the German districts is 120.4 (SD = 29.3).

A study by Haloen et al. (2018) in Finland during the years 1995 to 2014, reports that the prevalence of SSRIs use was the highest in the capital area and lowest in the Northern/Eastern area, in terms of its use it increased from 15,179–21,674 people (1996–1999) to 20,167–31,887 people (2011 to 2014).

Gomez-Lumbreras et al. (2019) carried out a study in Denmark, Norway, Sweden, Catalonia (Spain) and Veneto (Italy) during the years 2007 to 2011, finding that the SSRIs group represented half of the antidepressants consumption, with a maximum increase over time of the study of 14.75%. In addition, over these period they observed an increase of use, in both Northern and Southern European locations. Veneto was the region that showed the lowest consumption, but differences among the Nordic and Southern settings were not found.

During the COVID-19 pandemic, the whole world experienced significant changes in the way it learns, works and lives, and as a result, has seen a significant impact on mental health (Rajkumar, 2020). In March and April 2020, higher levels of anxiety and depression were recorded in most countries compared to previous years. Higher rates of anxiety and depression were recorded in unemployed people and economic hardship than the rest of the population. In addition, young people's mental health deteriorated sharply, with a marked accentuation in late 2020 and early 2021, with a dramatic increase in symptoms of anxiety and depression (Niederkrotenthaler et al., 2022; Robinson et al., 2022). So that, several studies confirm that the COVID-19 pandemic, in addition to raising the mortality rate from viral infection, triggered a sharp increase in mental health problems (Korkmaz and Güloğlu, 2021), therefore, an increase in the consumption of antidepressants is expected in the coming years., supported by this being used as first-line therapy for these disorders (Khan et al., 2020).

To confirm this theory, several authors have reported interesting data, for example, in China, a study was carried out at the beginning of the pandemic to determine people's psychological distress; the results showed that the pandemic had consequences on mental health, reflecting an increase in anxiety, depression, and panic disorders (Qiu et al., 2020). Similarly, a study was conducted in Germany early in the pandemic, with more than 50% of participants experiencing psychological distress and anxiety (Eichenberg et al., 2021). Mazza et al. (2020) conducted a study in Italy at the beginning of the pandemic; the results showed that 7.2% of the participants had severe anxiety, 11.5% had very severe anxiety, 14.6% had severe stress symptoms, and 12.6% had very severe stress symptoms, 17% had severe depression, and 15.4% had very severe depression. In addition, in the United States, the prevalence of depressive symptomatology tripled during the COVID-19 pandemic compared to pre-crisis data; the study was conducted using data obtained in early April 2020 (Ettman et al., 2020). Recently, a study of 3904 individuals investigated whether the symptomatology produced by COVID-19 could be associated with the subsequent development of depressive symptoms. The results showed that 52.4% of the participants showed symptoms of major depression, people with a more severe COVID-19 health status, men and young individuals showed more pronounced symptoms of depression (Perlis et al., 2021).

Although it has been recognized that mental health problems have increased, treatment for the various disorders remains scarce. As a consequence of the increase in mental disorders, some authors believe that prescriptions and consumption of psychoactive drugs, particularly antidepressants, will increase dramatically (Amendola et al., 2021; Hedna et al., 2021; Hernández-Rodríguez et al., 2021).

A study in England found that by March 2020, the dispensing of antidepressant drugs peaked, in line with the official declaration of the pandemic by the World Health Organization's COVID-19. An increase in the number of antidepressant dispensing was found, with an additional 92 million units dispensed from January 2020 to August 2020; while in the quarter of the same year there was a statistical increase of 5.78% in antidepressants prescribed and dispensed, compared to the same quarter of the year 2019. On the other hand, the use of antidepressant medications increased steadily since July 2015, with 4.46 million medicines prescribed and dispensed per quarter, maintaining similar figures until the third quarter of 2020 (observing an increase of 27.9%) (National Health Service, 2021).

Furthermore, the cost associated with the sale of antidepressants was significantly higher in 2020 compared to 2019. There was an increase of more than double the cost recorded in 2019, with figures for April 2020 of £35 million. As a result, total antidepressant prescriptions from January 2020 to September 2020 cost more than £96 million, which is more than the cost in the same period in 2019. Compared to pre-pandemic years (in 2016) 5 million antidepressants were dispensed per month, costing £21 million (Rabeea et al., 2021). Also, noted that the cost of SSRIs prescriptions tripled from £41.14 million in 2019 to £128.87 million in 2020, representing 6% more units dispensed in 2020. Of the SSRIs, sertraline was the most prescribed drug with 1.79 million more units dispensed than in 2019 (an increase in the cost of 113 million pounds more); the increase in cost was attributed to a shortage of the active ingredient and an increase in the cost of generic drugs during the pandemic (Rabeea et al., 2021).

This increase in the number of SSRI prescriptions has been observed worldwide, with a 2- to 3-fold increase reported in France, the UK, the US, Asia, and Australia (Bauer et al., 2008; Gualano et al., 2014; Martín Arias et al., 2010; Soleymani et al., 2018). In the United States, a 21% increase in the number of antidepressant prescriptions was observed in February and March 2020, the highest point since the declaration of the COVID-19 pandemic (Gavidia, 2020).

Armitage (2021) studied the number of antidepressant prescriptions made in general practice between April 1, 2020 to September 30, 2020, it was 38′609,032, 3.94% higher than the corresponding period in 2019 (i.e. 37′144,303), and attributes this change to the COVID-19 pandemic. However, these data were refuted by Walker et al. (2021) who say that the 2019 to 2020 increase of 3.9% is actually smaller than previous years, since the same comparison between 2018 and 2019 yields a 6.1% increase in prescribing, so they consider it is therefore highly misleading to attribute this increase to the pandemic.

On the other hand, Farina et al. (2021) report a general slight increase in psychotropic medications sales during the whole pandemic period compared with the previous year. The percentage of sales seems to vary according to the pandemic phases and related lockdowns in Rome (Italy). They observed a general increase in SSRIs sales (2.63%) during the COVID-19 year (March 2020 to February 2021) compared with the previous year, this growth varies according to the restriction phases with an initial decrease in March to May 2019 and an upsurge in June to September 2019 and October 2019 to February 2020. These data are important, since they suggest that the consumption of SSRIs may vary depending on the confinement and opening dates established during the COVID-19 pandemic, in addition to the fact that they may affect other factors such as age and gender, since previous studies have also showed that women and middle-aged people are more likely to consume (Gomez-Lumbreras et al., 2019; Arnáiz et al., 2006; Lewer et al., 2015).

The studies described agree with the report made in the Organization for Economic Cooperation and Development (OECD) countries, in which was found that the consumption of antidepressant medication doubled from 2000 to 2019, making European countries the largest consumers of antidepressants in the world. Also, there was a significant difference in the consumption of these drugs between countries; for example, Iceland reported the highest consumption of antidepressant drugs in 2020 with a rate of 153.4 defined daily doses (DDD) per 1000 people while for Latvia it's 19.8, being a rate eight times higher (Fig. 3) (OECD, 2021).

Prescription for 2019 in the United States are not included in this OECD study; however, as mentioned earlier, these drugs are among the top 200 most prescribed drugs for this year (Table 2) (Kane, 2021).

As can be seen, there is evidence of an increase in the case of pathologies such as depression and anxiety derived from the COVID-19 pandemic, which also suggests an increase in the consumption of antidepressant medications (with SSRIs being the most prescribed in the world); and that it may not only represent an economic problem in the future (since the total cost of depression and anxiety disorders globally is approximately US$1 trillion annually) (Lin et al., 2021), but also that the increase in antidepressant use worldwide raises concerns about the safety, efficacy, and environmental impact of long-term use. Therefore, research, specifically in the context of the current pandemic, on consumption and prescriptions worldwide will provide relevant information for individuals, scientists, and policymakers to make decisions that lead to better management of antidepressants (Rabeea et al., 2021).

3.2. Occurrence of SSRIs in the environment after and post-COVID-19 pandemic

Although there are few studies that report the environmental changes that caused the lock-down during the COVID-19 pandemic, the existing ones refer to a positive effect on the conditions of most countries in the world (Rupani et al., 2020). For example, a decrease in heavy metal concentrations as well as an improvement in surface water quality was demonstrated in Africa, Brazil, China, India, Nepal, Turkey, Italy, the United States and Peru (Molekoa et al., 2021; Khan et al., 2021; Shen et al., 2021; Tokatlı and Varol, 2021; Pant et al., 2021; Bhat et al., 2021; Alcantara et al., 2021; Custodio et al., 2021; Hamidi et al., 2021); In addition, it has been found that the contamination of groundwater, coastal water and in general of water bodies in most regions of the world were mitigated (Yang et al., 2021). However, it is also reported that there may be indirect harmful environmental effects of the pandemic, as in Argentina, where Ardusso et al. (2021) report that a significant increase in the

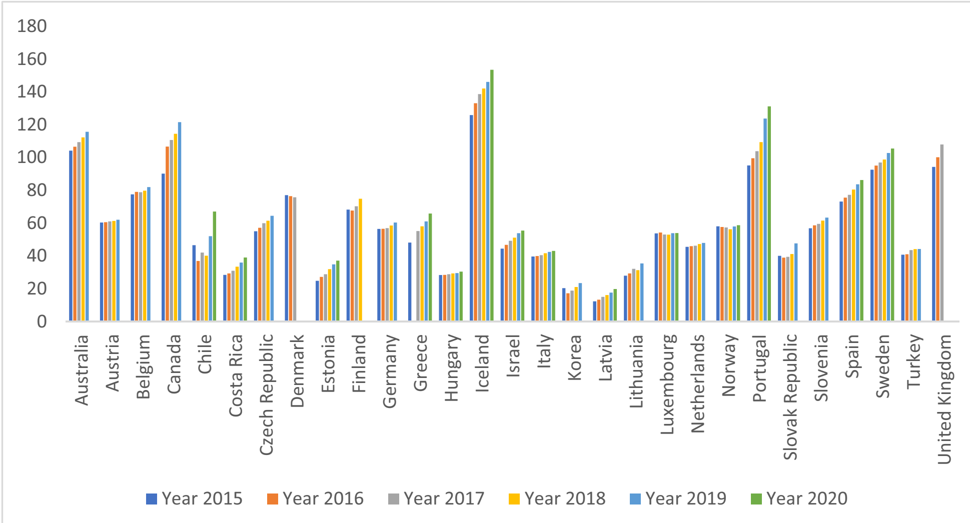

Fig. 3. Antidepressants consumption between 2015 and 2020 (OECD, 2021).

production of masks and other products made of polymeric materials such as gloves and protective clothing (with not properly disposed of), contribute to plastic pollution in marine environments and coastal waters.

Another of these indirect negative effect of the pandemic, is the increase in the consumption of pharmaceuticals, and their concentrations found in the environment compared to pre-COVID periods. SSRIs enter water bodies through effluents, mainly domestic and hospital, after their use and excretion; of industrial effluents during their manufacture and also, as a consequence of poor disposal of unused or expired drugs (Schultz et al., 2010).

In a 2007 report issued by the United States Environmental Protection Agency (EPA), SSRIs' physicochemical characteristics were analyzed to use these data to predict their environmental persistence and fate. Values such as the octanol: water partition coefficient (Kow) and the normalized sorption coefficient of organic carbon (Koc) were measured, finding that SSRIs have high Koc and Kow values, conditions that indicate their strong tendency to get incorporated into sediments, sludge, soils and organic particles in suspension and to remain adsorbed in said matrices (Table 3) (Drug-Bank, 2021; Black and Ambrust, 2007).

Kwon and Armbrust (2005) pointed out that more than 70% of fluoxetine was found in biosolids samples as a result of its adsorption to humic acids and particulate organic material present in the collected samples and indicated that, in general, the SSRIs have an adsorption capacity greater than 91% except for fluvoxamine, whose capacity is approximately 73% (Black and Ambrust, 2007; Kwon and Armbrust, 2004, 2005). These indicate that they have a high affinity for soils and sediments, which in the absence of other degradation processes could increase the active half-life of each of these in aquatic environments due to uptake in sediments. The constant presence of these pharmaceuticals, as well as their metabolites, in environmental matrices, which include wastewater, surface, underground and drinking water, soils, sediments, bio-solids, and tissues, together with their high percentage of persistence and their toxicity in non-target organisms, is the reason why there is current concern about these drugs as emerging pollutants of aquatic environments both in their unchanged form, as well as their metabolites (Brooks et al., 2005; Calisto and Esteves, 2009; B. Ma et al., 2018a; Pivetta et al., 2020).

Some psychiatric drugs are characterized by not being fully metabolized by the body; therefore, they are excreted without altering their original structure. However, even when drugs are entirely metabolized, their products can be biologically active, as is the case with fluoxetine and norfluoxetine, so they can harm the environment or can be transformed into the original compound in environmental conditions due to bacterial actions (Silva et al., 2012; Tejada et al., 2014). Following their release from wastewater treatment plants (WWTPs), antidepressants are widely distributed in surface waters around the world, (Table 4).

And as mentioned above, as the consumption of SSRIs increases, there is also an increase in its occurrence in the environment, especially after the COVID-19 pandemic, as can be seen in Fig. 4 (This figure shows us the only calculated average of the concentration data for each type of SSRI in Table 4, in order to compare the data between pre-COVID-19 (2015–2019) and post-COVID-19 (2020 – 2021).

In terms of SSRIs distribution, the articles reported in this review mainly cover Europe, with 50% of the studies belonging to that continent, followed by North America with 38% and Asia with 10% (Fig. 5).

However, data from developing regions (e.g. México, Latin America, Africa and South America) are very scarce or non-existent. Nevertheless, the absence of information is not an indicator that SSRIs are not present in those regions. Regarding probabilistic distributions of environmental exposure, the 5th and 95th percentiles for the SSRIs, covering all the global geographic regions studied by Mole and Brooks (2019) were 2.31 and 3022.1 ng/L for the tributary, 5.3 and 841.6 ng/L for the effluent, 0.8 and 127.7 ng/L for fresh water and 0.5 and 22.3 ng/L for the coast, respectively.

3.3. Toxic effects of SSRIs

To understand the possible effects of SSRIs on different organisms, it is necessary to mention the importance of serotonin, the 5-HT transporter, and its evolutionary conservation since it is the therapeutic target of these

Table 2
SSRI prescriptions for 2019 in the US.

SSRI	Year	Prescriptions per year	Reference
Citalopram	2019	21,546,700	(Kane, 2021)
Escitalopram		27,510,958	
Fluoxetine		27,110,302	
Paroxetine		9,783,755	
Sertraline		37,157,933	

Table 3
Water partition coefficient and normalized sorption coefficient of organic carbon of SSRIs.

SSRIs	*Log Kow*	*Log Koc*	pKa
Citalopram	3.58	5.63	9.78
Fluoxetine	4.1	4.65	9.8
Fluvoxamine	2.8	3.82	8.86
Paroxetine	3.15	4.47	9.77
Sertraline	5.15	4.17	9.85

Table 4
Occurrence of SSRIs in the environment before- and post- COVID-19 pandemic.

SSRIs	Environmental matrix	Country	Sample source	Detection method	Average concentration reported (ng/L)	Reference
pre-COVID-19						
Citalopram	Influent of WWTP	Germany	Municipal region	LC-MS	180 ± 4	(Schlüsener et al., 2015)
		Portugal	River in urban area	LC-MS	23.7	(Paíga et al., 2016)
		Shanghai	River in urban area	HPLC	7.14	(L. dan Ma et al., 2018b)
	WWTP effluent	Germany	Municipal region	LC-MS	120 ± 22	(Schlüsener et al., 2015)
		Portugal	River in urban area	LC-MS	26.9	(Paíga et al., 2016)
		Shanghai	River in urban area	HPLC	14.26	(L. dan Ma et al., 2018b)
	Surface water	Portugal	River in urban area	LC-MS	0.86	(Paíga et al., 2016)
Fluoxetine	Influent of WWTP	Germany	Municipal region	LC-MS	24 ± 1	(Schlüsener et al., 2015)
		Portugal	River in urban area	LC-MS	9.22	(Paíga et al., 2016)
		Shanghai	River in urban area	HPLC	2.19	(L. dan Ma et al., 2018b)
	WWTP effluent	Germany	Municipal region	LC-MS	8 ± 1	(Schlüsener et al., 2015)
		Portugal	River in urban area	LC-MS	16.4	(Paíga et al., 2016)
		Mexico	Municipal region	HPLC	4.41–6.93	(Estrada-Arriaga et al., 2016)
		Shanghai	River in urban area	HPLC	4.11	(L. dan Ma et al., 2018b)
	Surface water	Portugal	River in urban area	LC-MS	2.01–19.5	(Paíga et al., 2016)
Fluvoxamine	Influent of WWTP	Portugal	River in urban area	LC-MS	5.21–17.8	(Paíga et al., 2016)
	WWTP effluent	Portugal	River in urban area	LC-MS	11.3–34	(Paíga et al., 2016)
Paroxetine	Influent of WWTP	Germany	Municipal region	LC-MS	9.1 ± 0.2	(Schlüsener et al., 2015)
		Portugal	River	LC-MS	23.6	(Paíga et al., 2016)
	WWTP effluent	Germany	Municipal region	LC-MS	2.3 ± 0.2	(Schlüsener et al., 2015)
		Portugal	River in urban area	LC-MS	26.5	(Paíga et al., 2016)
	Surface water	Portugal	River in urban area	LC-MS	25.5	(Paíga et al., 2016)
Sertraline	Influent of WWTP	Germany	Municipal	LC-MS	49 ± 1	(Schlüsener et al., 2015)
		USA	River in urban area	HPLC	31.6–114	Subedi and Kannan, 2015
		Mexico	Municipal region	HPLC	0.77–3.11	Estrada-Arriaga et al., 2016
		Shanghai	River in urban area	HPLC	6.36	(L. dan Ma et al., 2018b)
	WWTP effluent	Germany	Municipal region	LC-MS	9 ± 1.1	(Schlüsener et al., 2015)
		USA	River in urban area	HPLC	15.7–88.3	Subedi and Kannan, 2015
		Mexico	Municipal region	HPLC	5.9–7.38	Estrada-Arriaga et al., 2016
post-COVID-19						
Citalopram	Influent of WWTP	Greece	Hospital	UHPLC-Orbitrap-MS	211.9	(Kosma et al., 2020)
	WWTP effluent	Greece	Hospital	UHPLC-Orbitrap-MS	83.1	(Kosma et al., 2020)
Fluoxetine	Influent of WWTP	Greece	Hospital	UHPLC-Orbitrap-MS	212.5	(Kosma et al., 2020)
		Tunisia	Hospital	LC-MS	1200	(Afsa et al., 2020)
		USA	Municipal region	LC-MS	ND-159	(Bishop et al., 2020)
		Greece	Municipal region	LC-MS	20.9–124.4	(Christophoridis et al., 2021)
	WWTP effluent	Brazil	Municipal region	LC-MS	85	(Pivetta et al., 2020)
		Greece	Hospital	UHPLC-Orbitrap-MS	552.5	(Kosma et al., 2020)
		Tunisia	Hospital	LC-MS	120	(Afsa et al., 2020)
	Surface water	Brazil	Municipal region	LC-MS	3.5	(de Souza et al., 2021)
		China	River in urban area	HPLC	2.0	(R. Ma et al., 2020)
		USA	Lake	HPLC	~ 2.0	(Sharma and Hanigan, 2021)
		Tunisia	Costal zone	LC-MS	41	(Afsa et al., 2020)
Fluvoxamine	Influent of WWTP	Greece	Hospital	UHPLC-Orbitrap-MS	203	(Kosma et al., 2020)
	WWTP effluent	Greece	Hospital	UHPLC-Orbitrap-MS	324.9	(Kosma et al., 2020)
Paroxetine	Influent of WWTP	Greece	Hospital	UHPLC-Orbitrap-MS	89.3	(Kosma et al., 2020)
	WWTP effluent	Greece	Hospital	UHPLC-Orbitrap-MS	40.5	(Kosma et al., 2020)
Sertraline	Influent of WWTP	Greece	Hospital	UHPLC-Orbitrap-MS	79.5	(Kosma et al., 2020)
		Brazil	Municipal region	LC-MS	417	(Pivetta et al., 2020)
	WWTP effluent	Brazil	Municipal region	LC-MS	25	(Pivetta et al., 2020)
		Greece	Hospital	UHPLC-Orbitrap-MS	94.3	(Kosma et al., 2020)

LC-MS: Liquid Chromatography tandem- Mass spectrometry.
UHPLC-Orbitrap-MS: Ultra High Performance Liquid Chromatography-Orbitrap-Mass Spectrometry.
HPLC: High performance liquid chromatography.

drugs. Serotonin plays a crucial role in regulating specific neuroendocrine pathways in mammals such as rats, mice, and macaques, including pathways related to reproduction, stress, appetite regulation, water balance, and behavioral functions (Jørgensen, 2007). The 5-HT transporter, the target molecule for fluoxetine and other SSRIs, is found in all classes of vertebrates (Mennigen et al., 2011). SSRIs have been shown to affect neuroendocrine systems in mammals, apparently due to increased serotonin concentrations and altered 5-HT receptor function after chronic exposures. The changes involve affectations at the hormonal level (Jørgensen, 2007).

An example is the release of oxytocin and the expression of messenger RNA, since they are reduced in long-term treatment with fluoxetine, a situation attributable to desensitization of 5-HT1A receptor after prolonged activation of the receptor due to the increase in 5- HT at the synapse. For this reason, the different effects of SSRIs on neuropeptides, main fluoxetine, are partially produced by indirect action on 5HT receptors through elevated levels of 5-HT under long-term treatment (Raap and Van de Kar, 1999). Consequently, it is speculated that 5-HT transporters from aquatic organisms such as fish should bind to SSRIs with similar pharmacokinetics to human 5-HT transporters (Mennigen et al., 2011).

The main concern of the increase in consumption, the inefficient degradation in treatment plants, and the constant detection of SSRIs in aquatic matrices, is the unknown that arises from the possible toxic effects they may cause in aquatic biota. Therefore, efforts are needed to assess the toxicity of SSRIs and identify the best biomarkers (e.g. biochemical alterations, neurotoxicity, teratogenesis, cytotoxicity, genotoxicity, oxidative stress, behavioral alterations, among others) and bioindicators from different levels of the food chain (e.g. amphibians, birds, insects, crustaceans, fish, mammals) for toxicity assessment, (Jacob et al., 2021). Table 5 shows toxicity studies on various model aquatic organisms.

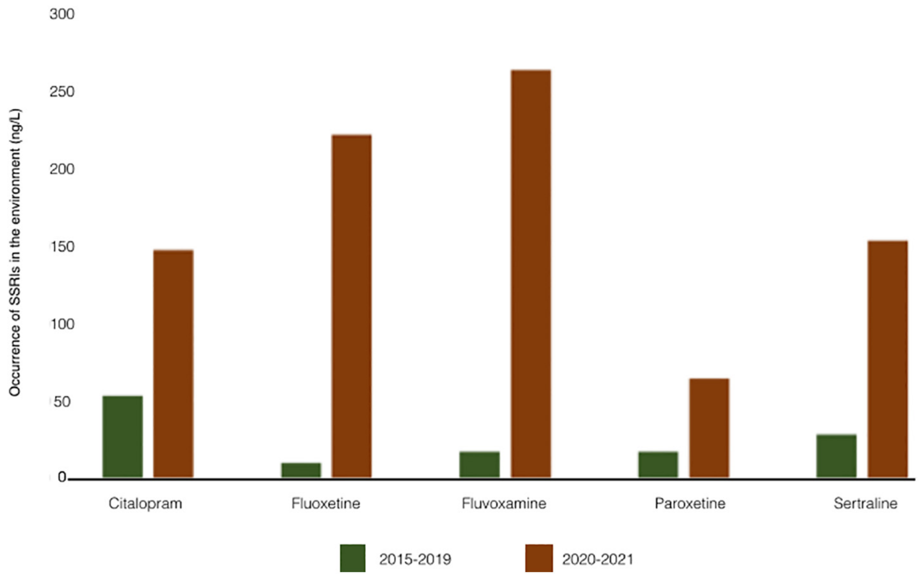

Fig. 4. Occurrence of SSRIs in the environment before and during COVID-19 pandemic.

In 2017 Tahar et al. realized a risk assessment model, introducing a concept that includes the terms source-pathway-receptor. Explaining the relationship between those factors. It takes into consideration the size of the population served by each WWTPs, as a larger population implies higher levels of drug use. It also refers to the fact that the success of drug disposal will depend on the different processes related to the treatment, operation and management of the WWTPs. The third factor to consider is the performance of WWTPs. This method of risk factor analysis is of great importance as it makes it easier for national governments to calculate risk assessment at the local, municipal, state and national levels (Tahar et al., 2017). These types of studies are scarce but extremely important to know the type of risk that different organisms may have when are exposed not only to a specific type of contaminant, but also to a mixture of these, from the smallest to the superiors, in order to know how their presence can affect the ecosystem and also the health of the human. This implies that not only the organisms located in the affected ecosystem should be considered, but it's also necessary to consider the effects on minor organisms up to the major ones connected through the trophic chain (Garvey et al., 2015).

3.4. SSRIs removal methods

As mentioned above, removal of SSRIs from wastewater is not carried out, nor is it regulated by international regulations; however, there are current studies in which effective techniques and methods are evaluated for this objective (Table 6) Among them, it can be observed that the methods of UV photolysis, activated carbon, electron beam irradiation, and molecular polymers have shown a removal greater than 99.9% in different samples.

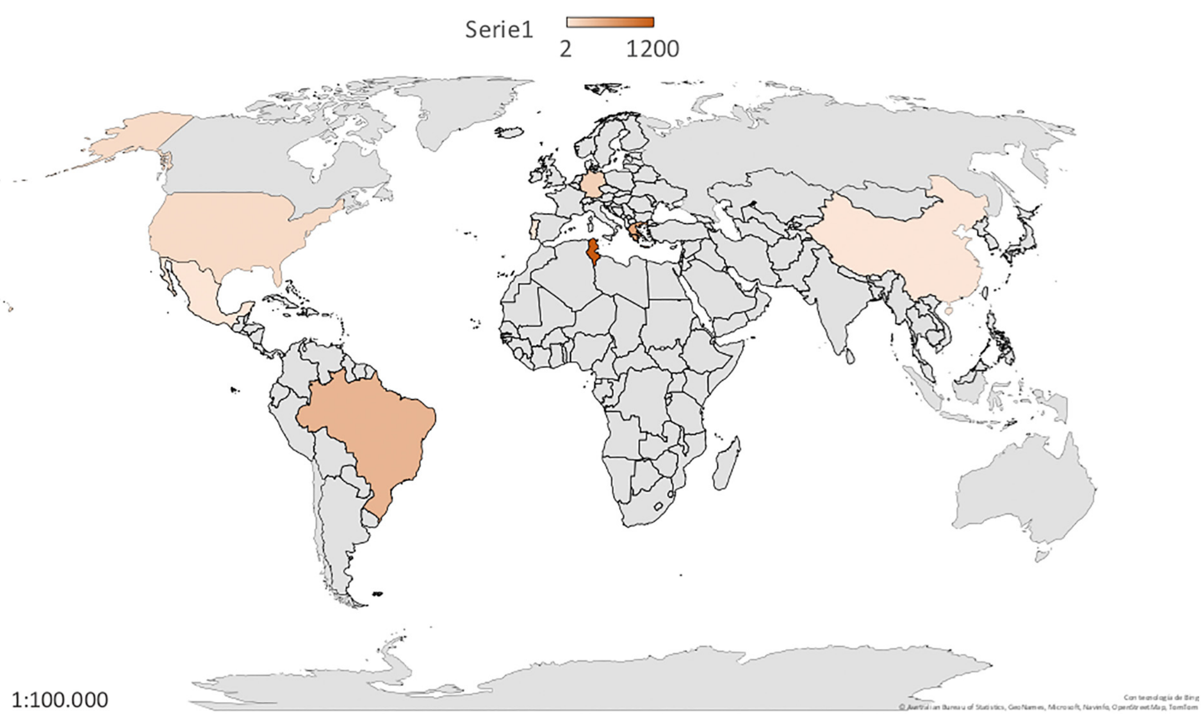

Fig. 5. SSRIs spatial distribution was reported in worldwide influents and effluents waterbodies in the last five years.

Table 5
Toxic effects of SSRIs drugs on diverse aquatic organisms.

SSRI	Species group	Scientific name	Concentration and exposure time	Major findings	Reference
Citalopram	Fish	*Danio rerio*	100 and 400ngL^{-1} for 14 days	• Caused few effects on behavior in the setting • Concentrations of citalopram were too low to affect the tested non--reproductive behaviors efficiently	(Porseryd et al., 2017)
	Crustacean	*Procambarus virginalis*	1 μgL^{-1} for 21 days	• Significantly lower velocity and shorter distance moved	(Buřič et al., 2018)
	Fish	*Pimephales promelas* *Danio rerio*	9.3 and 38.4 mgL^{-1} for 96 h	• Affected behavior • Fathead minnow larvae displayed great behavioral sensitivity	(Steele et al., 2018)
	Fish	*Danio rerio*	26–5600 μgL^{-1} for 6 day	• Anxiolytic effects	(Pohl, 2019)
	Fish	*Gasterosteus aculeatus*	150ngL^{-1} and 1.5μgL^{-1} for 10 and 20 days	• A dose-dependent suppression in response to the overhead stimulus • Significant decrease in locomotor activity	(Höglund et al., 2020)
	Fish	*Danio rerio*	0.001–14.5 μM for 0 to 120 h	• Reduction of their swimming distance • The maximum velocity in the dark was equal or higher compared to the total distance moved	(Zindler et al., 2020)
	Fish	*Squalius cephalus*	1μgL^{-1} for 42 days	• Increased the fish aggression • Concentration in the brain revealed a positive linear relationship between concentration and aggression	(Hubená et al., 2021)
	Fish	*Danio rerio*	30 and 100 mgL^{-1} for 5 min	• Reduced the tendency to swim near the bottom of the tank • Affects sexes differentially • Male subjects showed increased conditioned aversion.	(Karakaya et al., 2021)
Fluoxetine	Fish	*Betta splendens*	10 μM for 3 h	• Reduced aggression and impairs learning independent of social reinforcement type • Motor inhibition of aggressive behavior	(Eisenreich et al., 2017)
	Fish	*Cichlasoma dimerus*	2 μg g^{-1} for 15 days	• No significant differences were found on serotonergic turnover • Pituitary ßLH content was significantly higher • Presence of foam cells and an acidophilic PAS positive in testes	(Dorelle et al., 2017)
	Fish	*Gambusia holbrooki*	8-226ngL^{-1} for 28 days	• Increased activity levels irrespective of the presence or absence of a predatory • Reduced mosquitofish freezing behavior • caused both non-monotonic and sex-dependent shifts in behavior	(Martin et al., 2017)
	Fish	*Gambusia holbrooki*	1, 10 and 100 μgL^{-1} for 1 week	• Adverse sub-lethal effects on a basic behavioral characteristic • No impact on diurnal activity patterns was observed	(Melvin, 2017)
	Fish	*Pseudorasbora parva*	50-200μgL^{-1} for 4 h and 42 days	• Lipid peroxidation end-points were enhanced 80% in the liver and gills. • AChE activity was increased 40% after exposure to 50 μgL-1 and 55% at 200 μgL-1 following 4 h exposure. • The activities of proteases in the intestine were inhibited at 200 μgL^{-1}	(Hongxing Chen et al., 2018)
	Freshwater planarian	*Schmidtea mediterranea*	1.638-1000μgL^{-1} for 96 h	• LC_{50} of 357.93 • Time for head regeneration in decapitated planarians was not affected • Caused concentration-dependent increase in locomotor activity and DNA damage, and decrease in feeding.	(Ofoegbu et al., 2019)
	Fish	*Pomatoschistus microps*	100ngL^{-1}-10 mgL^{-1} for 1 and 96 h	• Reduced antioxidant CAT activity with increasing concentrations but had no significant effect on SOD activity. • No significant damage (LPO and DNAd) was observed. • Inhibited AChE activity (up to 37%) • Decreased the number of both feeding and active individuals	(Duarte et al., 2019)
	Fish	*Poecilia reticulata*	40 and 400ngL^{-1} for 28 days	• Altered male mating strategy • Conducted significantly more coercive 'sneak' copulations • Reacted to the risk of predation	(Fursdon et al., 2019)
	Fish	*Gambusia holbrooki*	31 and 374ngL^{-1} for 35 days	• This resulted in males spending a more significant amount of time pursuing females • Low-exposed males were more likely to attempt copulation than unexposed males. • Produced context-specific behavioral effects	(Martin et al., 2019)
	Fish	*Danio rerio*	56, 70 and 500μgL^{-1} for 96 h	• The altered metabolites associated with toxicity at high pH included urea, glycine and D-glucose 6-phosphate • Caused significant metabolic dysregulation related to apoptosis and oxidative stress • Higher energy consumption	(Mishra et al., 2019)
	Rotifera	*Brachionus koreanus*	250ngL^{-1}-2000μgL^{-1} for 10 days	• Significant reduction • in the population growth rate • LC_{50}: 1560μgL^{-1} • Induced oxidative stress	(Byeon et al., 2020)
	Fish	*Cichlasoma dimerus*	2 and 20 μg g^{-1} for 5 days	• Exhibited a marked reduction in food intake • Decreased in total body weight and total hepatocyte area • Decreased in glycogen and lipid content and an increase in protein levels in the liver was observed	(Dorelle et al., 2020)
	Fish	*Argyrosomus regius*	0.3 and 3μgL^{-1} for 15 days	• Affected fish growth, triggering antioxidant defense responses, inhibiting detoxification mechanisms, and increasing lipid peroxidation and DNA damage in the liver. • High bioconcentration in muscle	(Duarte et al., 2020)
	Crustacean	*Daphnia magna*	5.4ngL^{-1}-5.4μgL^{-1} for 7 months	• Direct effects on heart rate and swimming behavior in the first generation • Reduced the velocity • Growth rate varied significantly across generations.	(Heyland et al., 2020)
	Fish	*Danio rerio*	100μgL^{-1} for 6 days		(Huang et al., 2020)

(continued on next page)

Table 5 (*continued*)

SSRI	Species group	Scientific name	Concentration and exposure time	Major findings	Reference
	Fish	*Danio rerio*	10μgL^{-1} for 96 h	• 170 genes were significantly differentially expressed • 60% of the responsive transcripts were downregulated, with 102 genes showing decreased expression and 68 genes with increased expression • It affected the total hatching rate • Accelerated the hatching time • Caused disturbances in the organogenesis of fish	(Nowakowska et al., 2020)
	Fish	*Carassius auratus*	100ngL^{-1} for 7 and 14 days	• Significantly bioconcentrated in the fish brain and liver and transformed mainly to norfluoxetine's active metabolite. • Serotonin and choline, and liver metabolic status were simultaneously altered.	(Yan et al., 2020)
	Fish	*Danio rerio*	0.001–14.5 μM for 0 to 120 h	• Reduction in stress-related swimming activity • Showed a concentration-dependent decrease in total distance moved	(Zindler et al., 2020)
	Mollusc	*Sepia officinalis*	5ngL^{-1} for 5 days	• Affected maturation of the predatory behavior • Changes in predatory behavior	(Chabenat et al., 2021)
	Fish	*Danio rerio*	100ngL^{-1} for 11 days	• Heart malformations including pericardial edema, circulation abnormalities, and thrombosis were observed. • Toxicity induced by S-fluoxetine was more severe than R-fluoxetine	(Chai et al., 2021)
	Fish	*Danio rerio*	5ngL^{-1}-5μgL^{-1} for 7, 14, and 28 days	• Decreased swimming speed. • Significantly increased time motionless. • The effects vary over time and also in a non-monotonic manner.	(Al Shuraiqi et al., 2021)
	Amphibian	*Bufo bufo*	5μgL^{-1} for 7 days	• Negatively affected tadpoles' growth and development • Behaviors were also impaired. • Significant increase in the frequency of cellular and nuclear abnormalities	(Aliko et al., 2021)
	Fish	*Dicentrarchus labrax*	500ngL^{-1}-50μgL^{-1} for 21 and 28 days	• 689 and 632 different significant transcripts • Energy metabolism was affected • Exocytosis and vesicle formation	(Costa et al., 2021)
	Amphibian	*Bufo bufo*	5μgL^{-1} for 7 days	• Negatively affected tadpoles' growth and development • Behaviors were also impaired. • Significant increase in the frequency of cellular and nuclear abnormalities	(Aliko et al., 2021)
	Sea urchin	*Heliocidaris crassispina*	10 and 100 ngL^{-1} for 7 and 8 days	• Caused negative physiological and behavioral responses in the early life stages • With pH 8.0 treatment, larvae exposed to low concentration had significantly more DNA damage than control and high concentrations. • The impacts of fluoxetine and pH can also be independent	(Lo et al., 2021)
	Fish	*Danio rerio*	5-40ngL^{-1} for 72 and 96 h	• The main teratogenic effects induced were pericardial edema, hatching retardation, spine alterations, and craniofacial malformations. • Demonstrated that as the concentration increased, oxidative damage biomarkers got more influence over the embryos than antioxidant enzymes	(Orozco-Hernández et al., 2021)
	Freshwater hidroid Fish	*Hydra magnipapillata* *Oryzias javanicus*	1.6–7.6 mgL^{-1} for 24 to 96 h 1–2.5 mgL^{-1} for 24 to 96 h	• Induced the contraction of the tentacles and body column • Reduced their swimming performance at a minimum concentration • Affected various physiological and metabolic processes in both species	(Yamindago et al., 2021)
	Fish	*Betta splendens*	3.4578ngL^{-1} for 25 days	• Increases in latency for the mirror and white wall and decreases in aggressive responding to the mirror	(Greene and Szalda-Petree, 2022)
Paroxetine	Fish	*Danio rerio*	1–100 μgL^{-1} for 6 days	• Hypoactivity, reducing the number of movements anywhere from 25% to 40% • Altered swimming behavior in the early transient exposure	(Huang et al., 2019)
	Fish	*Danio rerio*	100μgL^{-1} for 6 days	• Decreased the number of movements by up to 13% • 1518 genes were significantly differentially expressed • 58% were significantly downregulated, with 885 out of the 1518 genes showing decreased expression	(Huang et al., 2020)
	Fish	*Danio rerio*	10μgL^{-1} for 96 h	• Three-times lower proliferation of hepatocytes was observed • It affected the total hatching rate	(Nowakowska et al., 2020)
Sertraline	Fish	*Gambusia holbrooki*	1, 10 and 100 μgL^{-1} for 1 week	• Altered circadian rhythms. • Significantly altered diurnal activity patterns	(Melvin, 2017)
	Amphipod	*Gammarus locusta*	8-1000ngL^{-1} for 48 days	• Detected no significant changes in critical ecological endpoints • Females were potentially more susceptible to the chronic effects	(Neuparth et al., 2019)
	Fish	*Danio rerio*	1–100 μgL^{-1} for 6 days	• Significantly affected spontaneous swimming • Significant interaction between drug exposure and light change	(Huang et al., 2019)
	Crustacean	*Daphnia magna*	100ngL^{-1}-1μgL^{-1} for 7 months	• Transient increase of ephippia formation in the F1 and F2 • Reduction of the normalized heart rate • The average offspring size of *D. magna* varied significantly across the four generations.	(Heyland et al., 2020)
	Fish	*Danio rerio*	10μgL^{-1} for 96 h	• Three-times lower proliferation of hepatocytes was observed • Increased the rate of abnormal embryo and larvae development • The highest bioaccumulation factor (BCF) was obtained	(Nowakowska et al., 2020)
	Fish	*Morone saxatilis x Morone chrysops*	4.5, 35.4, and 96.8μgL^{-1} for 6 days	• Increased time to capture prey • detected in brain and plasma, though not always in a dose-dependent fashion • Decreased whole-brain serotonin levels	(Stoczynski and van den Hurk, 2020)
	Fish	*Oncorhynchus mykiss*	4.4, 42 and 400μgkg^{-1}	• Suppression of the escape reflex and increased resistance to stress • Significant increase in the number of neutrophilic bands and neutrophil/lymphocyte ratio • Significant decrease in ammonia and lactate concentrations	(Vaclavik et al., 2020)

Table 5 (*continued*)

SSRI	Species group	Scientific name	Concentration and exposure time	Major findings	Reference
	Crustacean	*Ceriodaphnia cornuta*	0.2-100μgL^{-1} for 14 days	• Interference effect on the induced morphological defense • Reduced the horns induction	(Zhu et al., 2020)
	Fish	*Squalius cephalus*	1μgL^{-1} for 42 days	• Could induce different effects depending on the concentration	(Hubená et al., 2021)

These are relatively cheap and innovative methods that could be included in WWTPs processes. The most effective methods for the removal of citalopram is by photolysis, for fluoxetine it is electron beam irradiation, for paraoxetine it is printed molecular polymers while for sertraline it is photolysis and printed molecular polymers. For fluvoxamine, based on the search performed, the only method is FeO application, so it becomes a new opportunity area (Drzewicz et al., 2019; Gornik et al., 2020a, 2020b, 2021; Osawa et al., 2019; Shao et al., 2018).

Innovative methods are constantly being designed in order to eliminate the different polluting compounds present in wastewater. But, also it is important to demonstrate that the matrices treated with these new disinfection and elimination methods are safe for the environment considering that any compound can be a pollutant depending on the concentration and the site where they are present, therefore, continuing to develop new methods is important for the future removal of various emerging contaminants, including SSRIs.

4. Conclusions and perspectives

Although SSRIs have not been included in the Watch Lists under the Water Framework Directive of the European Commission, the use of antidepressants, in general, has shown an increase in recent decades due to the increase in pathologies such as depression and anxiety, also, the COVID-19 pandemic was an important additional factor for the increase in the incidence of psychological disorders such as depression, anxiety and stress, evidenced in the increase in the consumption of SSRIs. This increase in consumption may represent a future contamination problem that may affect the environment because when these compounds and their metabolites are excreted, they can enter the water bodies due to the fact that there is a low or null rate of removal in water treatment plants, for which they are released into the environment in different concentrations, having multiple and diverse effects on terrestrial and aquatic species exposed to them such as repercussions on genetic transcription, deficiency in reproduction and motility, alterations in migration and during defense against predators. Despite the fact that some beneficial effects of the confinement due to the COVID-19 pandemic have been reported, such as the decrease in the concentration of metals or the improvement of the quality of water in many countries; Attention should also be paid in the future to the indirect harmful effects produced by the increased production and consumption of plastics and pharmaceuticals, such as SSRIs. As can be seen in this review, we can suggest that the COVID-19 pandemic produced an increase in both, the consumption of SSRIs and their occurrence in different water bodies, which could subsequently generate various effects on non-target organisms. However, since there are few reports so far, it is imperative to continue with studies in the ecotoxicological area to determine the direct influence that the pandemic could have, and if necessary, to be able to counteract the effects it could have on the environment. In addition, it is necessary to continue with the study of new techniques that allow this type of contaminant to be removed from the water efficiently, without generating compounds that can become more toxic. As a perspective, it is proposed to carry out a risk assessment study at the municipal level in Mexico since there are no similar data or studies.

CRediT authorship contribution statement

Nidya Diaz-Camal: Investigation, Formal analysis, Writing – original draft. **Jesús Daniel Cardoso-Vera:** Investigation, Formal analysis, Writing – original draft. **Hariz Islas-Flores:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision. **Leobardo Manuel Gómez-Oliván:** Resources, Writing – review & editing. **Alejandro Mejía-García:** Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 6
Removal methods and techniques.

SSRIs	METHOD / TECHNIQUE	EFFECTIVENESS	REFERENCE
Citalopram	Adsorbents generated by pyrolysis of paper mill sludge	34–58%	(Calisto et al., 2014)
	Mass coupled liquid chromatography + chiral separation	36 ± 7%	(Schlüsener et al., 2015)
	UV photolysis	100%	(Osawa et al., 2019)
	Chlorination	98%	(Osawa et al., 2019)
	Activated carbon	99.9%	(Gornik et al., 2021)
Fluoxetine	Mass coupled liquid chromatography + chiral separation	65 ± 4%	(Schlüsener et al., 2015)
	Electron beam irradiation process.	99%	(Shao et al., 2018)
	Anthracite biofilters with granular activated carbon	97.3%	(Ma et al., 2018a, 2018b)
	FeO	50%	(Drzewicz et al., 2019)
	Activated sludge adsorption	37.2	(Cao et al., 2020)
	Red Mud Magnetite Nanoparticles	92%	(Aydın et al., 2021)
Fluvoxamine	FeO	35%	(Drzewicz et al., 2019)
Paroxetine	Mass coupled liquid chromatography + chiral separation	76 ± 2%	(Schlüsener et al., 2015)
	Red mud magnetite nanoparticles.	96%	(Aydın et al., 2021)
	Biodegradation by *Phragmites australis*	90%	(Dias et al., 2021)
	Biodegradation by *Phragmites australis* + *Cu*	95%	(Dias et al., 2021)
	Printed molecular polymers	99.99%	(Gornik et al., 2021)
Sertraline	Printed molecular polymers	99.99%	(Gornik et al., 2021)
	Mass coupled liquid chromatography + chiral separation	82 ± 2%	(Schlüsener et al., 2015)
	Through TiO_2 photocatalyst supported on glass cloth	94%	(Rejek and Grzechulska-Damszel, 2018)
	Photolysis (direct sunlight).	99.99%	(Gornik et al., 2020b)
	Biodegradation with activated sludge	90%	(Gornik et al., 2020a)

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