Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Antidepressants surveillance in wastewater: Overview extraction and detection

Elda M. Melchor-Martínez, Mildred G. Jiménez-Rodríguez, Manuel Martínez-Ruiz, Samantha Ayde Peña-Benavides, Hafiz M.N. Iqbal, Roberto Parra-Saldívar **, Juan Eduardo Sosa- Hernández *

Tecnologico de Monterrey, School of Engineering and Sciences, Ave. Eugenio Garza Sada 2501, CP 64849, Monterrey, NL, Mexico

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ABSTRACT

The COVID-19 pandemic has been one of the biggest challenges worldwide. The psychological disorders associated with the pandemic causing depression, insomnia, post-traumatic stress disorder (PTSD) and anxiety reduce emotional stability. Different antidepressant drugs with several mechanisms of action are used with a prescription. The excretion of the compounds and their metabolites reach municipal wastewaters and enter sewage treatment plants with a low rate of remotion of pharmaceutical compounds and the releasing on the environment. Several effects on aquatic species exposed to antidepressants have been reported as the impact in gene transcription, reproduction cycles, predator defense, and motility. The aim of this work is to resume the common antidepressants detected in wastewater around the world and show the increment of its use during SARS-CoV-2 crisis.

1. Introduction

Depression is one of the most costly and burdensome mental illnesses globally; it represents one of the main leading causes of disability worldwide and can lead to suicide. It has been reported that 50% of individuals who have committed suicide were previously diagnosed with depression [1]. Effects of depression are associated with more impairment in occupational and interpersonal functioning in comparison to several common medical illnesses, the cost of depression is greater than others common medical illnesses, as more than 264 million people suffer from depression worldwide and, together with anxiety disorders, it costs the global economy US$1 trillion a year in lost productivity [2,3]. As an epidemiological phenomenon, it is paramount to get as much information as possible and make sure it is reliable. During the present review, it is explored wastewater-based epidemiology as a tool to be used for stakeholders to deliver the corresponding policy to current problems. The process includes the antidepressant drug, metabolites detected, detection method, accuracy and some current studies that successfully track the epidemic.

It is important to know that different treatments for moderate and severe depression are available; overall, antidepressant drugs are commonly used. These pharmaceuticals target different neurotransmitters involved in mood regulation which are categorized according to their chemical properties or action mechanisms and presented in Table 1; some examples include selective serotonin reuptake inhibitors (SSRIs); tricyclic antidepressants (TCA); monoamine oxidase inhibitors (MAO-I); serotonin and noradrenaline reuptake inhibitors (SNRIs); selective noradrenaline reuptake inhibitors (NARI); serotonin antagonists and reuptake inhibitors (SARI); noradrenergic and specific serotonergic antidepressants (NaSSA); selective serotonin reuptake enhancers (SSRE), dopamine reuptake inhibitors (DRI) and antidepressants with a direct effect on neuroreceptors [4,5].

Recently, the effects of the COVID-19 pandemic on mental health have been investigated and reported in several studies, concluding that the shifts in lifestyle behaviour, physical activity reduction, self-isolation, population-wide confinements, stress, uncertainty, unemployment or increased workload, and work adaptation have provoked a rise on acute psychological distress, anxiety, insomnia, depression, and post-traumatic stress disorder (PTSD) among healthcare workers and the general population [6–12]. There are also precedents regarding the negative mental health effects of quarantine and isolation measures that were put in place across different countries due to the severe acute respiratory syndrome

* Corresponding author.
** Corresponding author.
E-mail addresses: r.parra@tec.mx (R. Parra-Saldívar), eduardo.sosa@tec.mx (J.E. Sosa- Hernández).

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Table 1
Antidepressant drugs categorized by action mechanism.

SSRIs	TCA	MAO-I	SNRIs	NARI	SARI	NaSSA	SSRE	DRI
Citalopram	Amitriptyline	Isocarboxazid	Desvenlafaxine	Amedalin	Etoperidone	Aptazapine	Tianeptine	Amineptine
Escitalopram	Amoxapine	Phenelzine	Duloxetine	Atomoxetine	Lorpiprazole	Esmirtazapine		Phenmetrazine
Fluoxetine	Desipramine	Selegiline	Levomilnacipran	Daledalin	Mepiprazole	Mianserin		Vanoxerine
Paroxetine	Doxepin	Tranylcypromine	Venlafaxine	Edivoxetine	Nefazodone	Mirtazapine		Modafinil
Sertraline	Imipramine			Esreboxetine	Trazodone	Setiptiline		
vortioxetine	Nortriptyline			Lortalamine		Teciptiline		
vilazodone	Protriptyline			Nisoxetine				
	Trimipramine			Reboxetine				
				Talopram				
				Talsupram				
				Tandamine				
				Viloxazine				

Abbreviations: **SSRIs** Selective serotonin reuptake inhibitors, **TCA** Tricyclic antidepressants, **MAO-I** Monoamine oxidase inhibitors, **SNRIs** Serotonin and noradrenaline reuptake inhibitors, **NARI** Selective noradrenaline reuptake inhibitors, **SARI** Serotonin antagonists and reuptake inhibitors, **NaSSA** Noradrenergic and specific serotonergic antidepressants, **SSRE** Selective serotonin reuptake enhancers, **DRI** Dopamine reuptake inhibitors.

(SARS) (2003), Ebola (2014), and H1N1 influenza (2009) outbreaks [13]. This review focuses on the antidepressants risks to society and, environment, its extraction and quantification methods in wastewater to understand wastewater based epidemiology potential to protect from aggressive consumption due the pandemic.

1.1. Risks of antidepressants abuse to society and environment

The study of the presence of pharmaceutically active compounds (PhACs) in urban wastewaters has gained importance due to their environmental deleterious effects. After their use, the active pharmaceutical ingredients (APIs) and metabolites are excreted, reaching municipal wastewaters and entering sewage treatment plants (WWTPs and STPs respectively). Since WWTPs and STPs are not designed to remove such substances, some residues remain in the effluents and end up in the environment, causing adverse biological effects to the wildlife [5,14]. It has been reported that fluoxetine can alter the courtship behavior of *Sturnus vulgaris*, which can affect the population dynamics, and also show a frequency reduction in food consumption [15,16]. In a lab test with group settings of *Gambusia Holbrooki* fluoxetine disrupted the frequency of aggressive interactions and food consumption.

Particularly, antidepressants have received high attention due to the risks they represent for aquatic wildlife and their potential to be abused by consumers [17]. Although they often degrade during treatment at WWTPs and STPs, levels ranging from nanograms to micrograms per liter can still be found in effluents, leading to different negative effects on aquatic species. Several reports have shown that even low levels of SSRIs or SNRIs can alter different biological processes of fish [5]; exposure to fluoxetine and TCAs amitriptyline and mianserin, has been proven to significantly impact gene transcription in zebrafish [18]; fluoxetine has also been shown to compromise the antipredator behaviour of mosquitofish, activating its locomotor activity regardless of the presence or absence of a predator [19] and it has been recorded that even low doses of this pharmaceutical affect the behaviour of the freshwater invertebrate *Gammarus pulex* [20]; tissue-specific bioaccumulation of citalopram, sertraline and venlafaxine was reported in rainbow trout (*Oncorhynchus mykiss*) exposed to the effluent of a Swedish municipal STP, where these compounds were found in the livers and brains of most fish. In addition, fish in the wild are constantly simultaneously exposed to several types of antidepressants, which can pose a higher risk [5]. Therefore, effective and sensitive methods are needed to determine the presence and quantify the environmental levels of antidepressants to evaluate and prevent their potential effects in the environment.

Currently, monitoring the use of antidepressants is predominantly based on general population surveys (GPS) and on prescriptions and sales data as reported in NHS for the UK health system [21]. These approaches provide relevant information about well-being patterns and medicinal use in a general population, however, they have important limitations; bias is commonly encountered in self-report surveys, data recording is not performed periodically, sales data does not provide accurate information on the actual amounts of pharmaceuticals that are being consumed, and figures do not deliver information regarding the amount of medicine used in hospital settings [4].

Wastewater-based epidemiology (WBE) is a novel approach that studies community-wide exposure or consumption of specific xenobiotics by analysing their metabolic excretion products (biomarkers) [4,17,21,22]. Since excreted biomarkers are collected by the urban sewage system, this approach provides valuable information regarding the amount and type of substances being consumed by a certain population. WBE has proved its potential in estimating close to real-time illicit drug consumption [22–25]; alcohol and tobacco use [22,26,27]; exposure to different contaminants, such as pesticides [22,28,29]; or as a tool to monitor infectious disease outbreaks [30,31].

The positive outcome of depression can be significantly improved by early detection and proper treatment by the implementation of public policy based on reliable data. WBE applications for pharmaceuticals, such as antidepressants, can provide a deeper understanding of the consumption trends of an area's population, which can be useful to estimate disease prevalence, and can also serve as an indicator of potential misuse [4,21]. Knowing this information could help health institutions to take action to prevent and reduce the use of antidepressants. It would also be useful for water treatment plants to improve their process and avoid the prevalence of these molecules in their effluents to reduce the impact on the environment. The increase in symptoms of depression, anxiety, and insomnia might be indicative of a potential increase in the use of antidepressants and other drugs i.e. the current COVID-19 pandemic as promoter of such population stress and the use of different drugs to aid to mitigate negative impact of restrictions [6–12]. Several groups have reported side-effects of antidepressants than can include damage to the central nervous system, ventricular tachycardia, also behavioral effects like anxiety, agitation, irritability, insomnia, panic attacks, aggressiveness, impulsivity, psychomotor restlessness and mania which non only represent a problem for the health systems, but also for the environment, due to the exposure of some species to the consumers' excreted residues [32,33]. This must be monitored since these drugs can be abused by consumers and because their excreted residues are harmful to the environment [34].

2. Wastewater matrix extraction methods

Although there are highly sensitive, reliable analytical methods available for the quantification of different biomarkers, samples often have to be subjected to pretreatment in order to eliminate possible matrix interferences caused by endogenous compounds, such as proteins, lipids, and other organic or inorganic molecules. Preconcentration of the analytes is also important to enhance their sensitivity [35,36]. Solid-phase

extraction (SPE) is one of the most commonly used techniques for compound extraction. SPE method is used for the isolation and concentration of specific analytes in fluids. The primary retention mechanism of the compound is based mainly on the electrostatic attraction of the charged functional group in the compound to the charged group that is bonded to the silica surface, according to that, Ion exchange SPE can be used for compounds in a solution, anionic and cationic compounds can be isolated on an aliphatic quaternary amine group or aliphatic sulfonic acid groups that is bonded to the silica surface, respectively, this is important to consider for SPE cartridge selection. The analytes have an affinity for the solid phase as they are partitioned between a solid and a liquid (instead of two immiscible liquids such as in liquid-liquid extraction or LLE). Commonly, higher affinity solvents for the analytes are used to remove the compounds retained on the solid phase [37–39]. Several reports show the use of SPE for analyte extraction from wastewater samples, as shown in Table 2.

There has been an effort from several research groups to conduct green methods to avoid the use of hazardous substances, which have traditionally been used, such as common solvents with known toxicity (e.g. acetonitrile, methanol or dichloromethane). A green analytical method was developed to extract and quantify 37 micropollutants in wastewater samples from a WWTP in Portugal, including SNRI Venlafaxine, SSRI Fluoxetine and the Norfluoxetine metabolite [40]. The method was based on solid phase extraction (SPE) in combination with an ultra-high performance liquid chromatography with tandem mass spectrometry (UHPLC-MS/MS). Ribeiro et al. evaluated the concentration of the pollutants after secondary biological and tertiary UV treatments, and successfully employed ethanol as the conditioning and eluting solvent, using an OASIS® HLB cartridge. The use of ethanol in the SPE process showed similar overall recoveries than those obtained with methanol. From the different pollutants mentioned earlier, Venlafaxine showed the highest recovery (97.2–104%), followed by Fluoxetine (42.8–53.2%). Norfluoxetine showed a lower recovery of 11.9–15.3%.

Other techniques for analyte extraction have also been studied. For instance, a method that combines gel electromembrane extraction (GEL-EME) and switchable hydrophilicity solvent-based homogeneous liquid-liquid microextraction (SHS-HLLME) was recently developed. The procedure was followed by gas chromatography flame ionization detector (GC-FID) and was used to successfully extract and quantify TCA Desipramine and SSRI Citalopram from human serum, breast milk and wastewater samples [41]. Common electromembrane extraction (EME) allows the extraction of ionic analytes from aqueous solutions into a small volume of an acceptor solution by using an organic solvent immobilized in a propylene hollow fiber as a supported liquid membrane (SLM). In this study, a green agarose-based membrane was used to substitute this SLM in order to avoid the use of toxic organic solvents. Moreover, agarose is a cheap and convenient material, which can be used for several membrane thicknesses. Platinum electrodes were set in the sample and acceptor solutions, both of which were connected to a power supply that was used to extract the ionic compounds [41,42]. The resulting acceptor solution was then used as the sample solution in the SHS-HLLME, and dipropylamine (DPA) was selected as the optimal SHS. In order to evaluate the performance of the method, the biological and wastewater samples were spiked with the target analytes at concentrations of 25.0, 50.0, and 250.0 ng/ml. The obtained RDS and relative recovery values were within 5.7–13.0% and 65.6–93.7%, respectively. The combination of both extraction methods results suitable for the analysis of real samples in complex matrices [41].

2.1. Quantification of metabolites by analytical methods

Sewage is a complex matrix and WBE samples contain scarce concentrations of the target biomarkers, therefore, their determination and quantification represent critical steps in WBE; up to now, mass spectrometry represents the most frequently used analytical method due to its high sensitivity and selectivity. Liquid chromatography - mass spectrometry (LC-MS) (both conventional LC and ultra high performance LC) is the most common technique used for this purpose [35]. Currently, most published methods for the quantification of antidepressants in wastewater focus on analysing the compounds after extraction through reverse-phase liquid chromatography coupled to tandem mass-spectrometry (RPLC-MS/MS) via multiple reaction monitoring (MRM). Efforts towards developing broader-range bioanalytical methods that can simultaneously measure several antidepressants and their metabolites from wastewater samples, in low concentrations, and in short periods of time, have been made [4,22].

A LC-MS/MS based analytical method for the analysis of 14 antidepressants and their *N*-desmethyl metabolites was presented by Ref. [14]. Raw influent and final effluent samples were obtained from 5 Canadian STPs. The LC system was coupled to a triple quadrupole mass spectrometer (QqQMS) with a positive electrospray ionization (ESI) source. A total run time of 20.0 min was achieved and the limits of detection (LOD) values ranged from 0.1 to 0.2 ng/L for the effluent samples and from 0.03 to 0.4 ng/L for those from the influent. The limits of quantification (LOQ) of the final effluent samples ranged from 0.04 to 0.7 ng/L and those from the raw influent varied from 0.1 to 0.7 ng/L (Lajeunesse et al., 2012).

Another bioanalytical method was developed by Ref. [4] in order to assess spatio-temporal trends in the use of antidepressants throughout different areas in Belgium. The aim of the study was to propose a methodology that could ultimately be used as a preventive information system that could help to rapidly identify pattern changes in the use of these pharmaceuticals. Samples were taken from influent wastewater of four different Belgian WWTPs that covered an approximate of 1.2 million inhabitants. The authors used a sensitive Ultra High Performance LC (UHPLC) coupled to a triple quadrupole mass spectrometer with an electrospray interface (ESI) in positive ionization mode. Dynamic multiple reaction monitoring (dMRM) was also used. The presence of 18 out of 27 studied biomarkers was confirmed in the WWTPs' samples. The total run time of the process was 20.0 min and the lower limits of quantification (LLOQ) for all 27 compounds ranged between 1 and 25 ng/L [4].

One of the most recent improvements for the extraction and quantification of metabolites from a low volume sample is presented by Ref. [22]. In this study, the authors describe an ultra-fast high-throughput method for the quantification of 135 contaminants of emerging concern (CECs), including several common antidepressants. This direct injection liquid chromatography-tandem mass spectrometry LC-MS/MS technique is able to run a complete test of filtered wastewater in 5.0 min using only 10 μL of sample on a short biphenyl cartridge. Up to 76 analytes were processed simultaneously during the gradient, an average of <30 ng/L limits of detection (LOD) were obtained, and matrix effects were reported as <11% [22]. Table 2 summarised some quantification methods that have been proposed and probed for the analysis of CECs in wastewater.

3. Conclusions and remarks

Up until now the impact of the COVID-19 pandemic on antidepressant consumption on a global scale has not been calculated [45]. Great efforts on wastewater sampling during SARS-CoV-2 spread to detect substances are representing an epidemiological strategy to provide scientific data of the mental health pandemic, countries in Asia, Europe, and USA are recording values of the use of antidepressants, the majority based on analytical methods such as LC-MS [46]. Also, applying the methodology of wastewater based epidemiology provides a significant global public health tool to detect SARS-Cov-2. Challenges in the use of complex matrices as wastewater and preconcentration methods have led to proposed methods that offer advantages over conventional sample preparation techniques as the generation of smaller volumes of biodegradable solvents makes this method eco-friendly. The mixed-bed multilayer trap

Table 2
Analytical Detection of antidepressants drugs in wastewater.

Antidepressant (Metabolite)	Drug Group	Extraction	Recovery (%)	Detection Method	Matrix	LoD	LoQ	Detected Range	Place Collection	Reference
Amitriptyline (AMI, nortriptyline)	TCA	SPE StrataX-C Cartridges	87 ± 3 88 ± 2 98 ± 14	LC-QqQMS	Raw influent Final effluent Sludge	0.03 ng/L 0.01 ng/L 0.04 ng/L	0.1 ng/L 0.04 ng/L 0.1 ng/L	46–283 ng/L	5 STPs in Canada	[14]
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	MCX ~ 80–110 HLB ~ 40-70	RPLC-MS/MS	Raw Influent	NR	91.50%	15–750 ng/L	4 WTPs in Belgium	[4]
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	58 ± 3 90 ± 3	UHPLC-MS	Raw Influent Sludge	NR	NR	126–167 g/day	WWTP England, UK	[43] [21]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	72–95 ng/L	WWTP London, UK	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	ND	WWTP Monterrey, Mexico	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	72–87 ng/L	WWTP Southwestern, USA	[22]
Bupropion (Bupropion-d9, BUP)	SSRI	NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	ND	WWTP London, UK	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	ND	WWTP Monterrey, Mexico	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	23–162 ng/L	WWTP Southwestern, USA	[22]
Dosulepin (Northiaden, dothiepin sulfoxide, northiaden sulfoxide)	SNRI	SPE Oasis® HLB cartridges Oasis® MCX cartridges	82 ± 1 90 ± 6	UHPLC-MS	Raw Influent	NR	NR	32.5–49 g/day	WWTP England, UK	[43] [21]
Fluoxetine (Norfluoxetine, desmethylfluoxetine)	SSRI	SPE StrataX-C Cartridges	85 ± 6 93 ± 1 97 ± 10	LC-QqQMS	Raw influent Final effluent Sludge	0.3 ng/L 0.2 ng/L 0.1 ng/L	0.7 ng/L 0.7 ng/L 0.4 ng/L	9–26 ng/L	5 STPs in Canada	[14]
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	MCX ~ 40–80 HLB ~ 50-70	RPLC-MS/MS	Raw Influent	NR	102.70%	7.5–750 ng/L	4 WTPs in Belgium	[4]
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	71 ± 2 82 ± 7	UHPLC-MS	Raw Influent	NR	NR	30.4–42.3 g/day	WWTP England, UK	[43] [21]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	50–58 ng/L	WWTP London, UK	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	ND	WWTP Monterrey, Mexico	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	ND	WWTP Southwestern, USA	[22]
Imipramine (Desipramine)	TCA	SPE Oasis® HLB cartridges Oasis® MCX cartridges	MCX ~ 80–100 HLB ~ 40-50	RPLC-MS/MS	Raw Influent	NR	90.00%	NR	4 WTPs in Belgium	[4]
Mianserin (Mianserin)	NaSSA	SPE Oasis® HLB cartridges	MCX ~ 60–100 HLB ~ 50-60	RPLC-MS/MS	Raw Influent	NR	96.3%.	NR	4 WTPs in Belgium	[4]

(*continued on next page*)

Table 2 (*continued*)

Antidepressant (Metabolite)	Drug Group	Extraction	Recovery (%)	Detection Method	Matrix	LoD	LoQ	Detected Range	Place Collection	Reference
		Oasis® MCX cartridges								
Mirtazapine (Desmethylmirtazapine)	NaSSA	Hypersil Gold column	NR	LC–MS/MS	Raw influent Final effluent	NR	0.002 μg/L	0.023–0.17 μg/L	WWTP in the Czech Republic	[44]
		Cogent Bidentate C18 column						0.013–0.068 μg/L		
Norfluoxetine (Norfluoxetine)	SSRI	SPE Oasis® HLB cartridges Oasis® MCX cartridges	72 ± 4 74 ± 5	UHPLC-MS	Raw Influent	NR	NR	9.8–17.0 g/day	WWTP England, UK	[43] [21]
Nortriptyline (10-E-Hydroxynortriptyline)	TCA	SPE StrataX-C Cartridges	89 ± 1 92 ± 1 45 ± 5	LC-QqQMS	Raw influent Final effluent Sludge	0.05 ng/L 0.03 ng/L 0.2 ng/L	0.2 ng/L 0.1 ng/L 0.8 ng/L	4.7–27 ng/L	5 STPs in Canada	[14]
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	MCX ~ 30–80 HLB ~ 50-70	RPLC-MS/MS	Raw Influent	NR	103.60%	10–750 ng/L	4 WTPs in Belgium	[4]
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	83 ± 2 79 ± 4	UHPLC-MS	Raw Influent	NR	NR	7.4–12.3 g/day	WWTP England, UK	[43] [21]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	64–67 ng/L	WWTP London, UK	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	ND	WWTP Monterrey, Mexico	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	ND	WWTP Southwestern, USA	[22]
Paroxetine (Paroxetine)	SSRI	SPE StrataX-C Cartridges	73 ± 4 72 ± 4 63 ± 10	LC-QqQMS	Raw influent Final effluent Sludge	0.1 ng/L 0.1 ng/L 0.04 ng/L	0.3 ng/L 0.3 ng/L 0.1 ng/L	1.8–16 ng/L	5 STPs in Canada	[14]
Sertraline (Norsertraline)	SSRI	SPE StrataX-C Cartridges	86 ± 5 90 ± 1 60 ± 6	LC-QqQMS	Raw influent Final effluent Sludge	0.1 ng/L 0.01 ng/L 0.2 ng/L	0.4 ng/L 0.04 ng/L 0.8 ng/L	7.7–34 ng/L	5 STPs in Canada	[14]
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	MCX ~ 90–100 HLB ~ 40-80	RPLC-MS/MS	Raw Influent	NR	97.60%	15–750 ng/L	4 WTPs in Belgium	[4]
		Hypersil Gold column	NR	LC–MS/MS	Raw influent Final effluent	NR	0.003 μg/L	0.007–0.027 μg/L	WWTP in the Czech Republic	[44]
		Cogent Bidentate C18 column						0.003–0.006 μg/L		
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	74–93 ng/L	WWTP London, UK	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	67–93 ng/L	WWTP Monterrey, Mexico	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	ND	WWTP southwestern, USA	[22]
Venlafaxine (Venlafaxine)	SNRI	SPE StrataX-C Cartridges	98 ± 2 97 ± 2 101 ± 6	LC-QqQMS	Raw influent Final effluent Sludge	0.1 ng/L 0.04 ng/L 0.04 ng/L	0.4 ng/L 0.04 ng/L 0.5 ng/L	788–2982 ng/L	5 STPs in Canada	[14]

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Table 2 (*continued*)

Antidepressant (Metabolite)	Drug Group	Extraction	Recovery (%)	Detection Method	Matrix	LoD	LoQ	Detected Range	Place Collection	Reference
						0.2 ng/L				
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	MCX ~ 90–110 HLB ~ 60-80	RPLC-MS/MS	Raw Influent	NR	99.20%	5–1500 ng/L	4 WTP in Belgium	[4]
		SPE Oasis® HLB cartridges Oasis® MCX cartridges	61 ± 4 100 ± 5	UHPLC-MS	Raw Influent	NR	NR	178–242 g/day	WWTP England, UK	[43] [21]
		Hypersil Gold column	NR	LC–MS/MS	Raw influent Final effluent	NR	0.007 µg/L	0.12–0.80 µg/L	WWTP in the Czech Republic	[44]
		Cogent Bidentate C18 column						0.12–1.11 µg/L		
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	256–289 ng/L	WWTP London, UK	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	104–1032 ng/L	WWTP Monterrey, Mexico	[22]
		NR	NR	Direct LC–MS/MS	Raw Influent	29 ± 59 ng/L	95 ± 197 ng/L	52–208 ng/L	WWTP Southwestern, USA	[22]

Abbreviations:**LC-MS/MS** Liquid chromatography-tandem mass spectrometry, **LC-QqQMS** Liquid chromatography-tandem triple quadrupole mass spectrometry, **RPLC-MS/MS** Reversed phase liquid chromatography coupled to tandem mass spectrometry mass-spectrometry, **UHPLC-MS** Ultra high performance liquid chromatography-tandem mass spectrometry, **SPE** Solid phase extraction, **SSRI** Selective serotonin reuptake inhibitor, **SNRI** Serotonin norepinephrine reuptake inhibitors, **TCA** Tricyclic antidepressants, **NaSSA** Noradrenergic and specific serotonergic antidepressants, **NR** not reported, **ND** non detection.

columns are complementary methods that could retain a wide range of polar compounds expanding the analytical scope. However, there are great opportunities in developing more efficient preconcentration and extraction methods. Several limitations have been mentioned by the research groups such as sampling plan focused in urban areas, rural communities should be included; analysis method, a reference method and reference standard could improve the limits of quantification for target compounds in pooled wastewater, and the sociodemographic characterization of the samples is important to estimate the rates of common health and lifestyle-related substances. Finally, the presence of chemicals in wastewater deposited in the effluents, end up in the environment, disturbing wildlife with changes in animal behavior. Highly prescribed antidepressant drugs during the pandemic have relevant effects in aquatic organisms with the exposition to serotonin modulators causing changes in the survival behavior against predators.

Conflict of interest

The authors declare no conflict of interest.

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.

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