RESEARCH ARTICLE

Occurrence and removal of psychiatric pharmaceuticals in the Tehran South Municipal Wastewater Treatment Plant

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Abstract
Psychiatric drugs released by humans in wastewater have received more attention because of their potential risks for aquatic organisms. In this study, the occurrence of the two most common groups of psychiatric drugs (sedatives-hypnotics-antxiolytics and antidepressants) were evaluated in the Tehran South Municipal Wastewater Treatment Plant. All the target sedatives-hypnotics-antxiolytics (alprazolam, phenobarbital, and thioridazine) and antidepressants (fluoxetine, citalopram, sertraline, and venlafaxine) were observed in influent and secondary clarification (SC) effluent. Thioridazine (164.25 ± 218.74 ng/L) and citalopram (672.53 ± 938.56 ng/L) had the highest mean concentrations in the influent, while alprazolam (5.09 ± 2.33 ng/L) and citalopram (776.97 ± 1088.01 ng/L) had the highest concentrations in the SC effluent. The higher concentrations of the psychiatric drugs, except thioridazine, were detected in the SC effluent compared to the concentrations in the influent. The increased drugs concentrations, with negative removal efficiencies, were more distinctive in the cold season samples. Psychiatric drugs processed in the chlorination unit followed a completely different pattern compared to the drugs in the biological treatment unit. All the drugs’ concentrations, except thioridazine, decreased in the chlorination unit, ranging between 27 ± 14% for alprazolam and 75 ± 10% for citalopram. However, the mean concentrations of the detected drugs were as follows: sertraline (11.96 ± 11.62 ng/L) and venlafaxine (184.94 ± 219.74 ng/L) which could cause environmental and ecological concerns.

Keywords Psychiatric drugs · Wastewater samples · Seasonal variation · Biological treatment · Chlorine disinfection

Introduction
There are increasing concerns about the presence of pharmaceutically active compounds in municipal wastewaters and the environment (Yuan et al. 2013). Psychiatric drugs such as sedatives-hypnotics-antxiolytics (including benzodiazepines (e.g., alprazolam), barbiturates (e.g., phenobarbital), antipsychotics (e.g., thioridazine)), and antidepressants are among the most frequently prescribed for tranquility and relaxation, reducing anxiety, and inducing sedation through central nervous system suppression (Peschka et al. 2006; Yuan et al. 2013). Depression as a common psychiatric disorder in Iran is typically treated with antidepressants (Naghavi et al. 2008) that act either as selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, citalopram, and sertraline, or serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine. From 2006 to 2013, the sale of antidepressants increased by over 50% in Iran (Soleymani et al. 2018) and their prescriptions were of high prevalence (3 defined daily doses (DDD)/1000 inhabitants/day in 2006 to 6 DDD/1000 inhabitants/day in 2013). The most frequently prescribed antidepressants were fluoxetine (22.7%), citalopram (18.3%), venlafaxine (4.5%), and sertraline (0.1%) (Soleymani et al. 2018). In addition, data from the Food and Drug Administration showed an increase in

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antidepressant prescriptions and sales in subsequent years until 2019. Total prescription of fluoxetine increased from 45,500,000 pills in 2013 to 214,179,830 in 2019 (Iranian Ministry of Health and Medical Education 2019, Soleymani et al. 2018), resulting in increased concentrations of this drug in aqueous environments.

Very few studies have addressed the occurrence of psychiatric drugs in aqueous environments. With the improvements in analytical techniques, antidepressants have been detected in wastewater, surface water, groundwater, and even drinking water (Lajeunesse et al. 2012; Metcalfe et al. 2010). Antidepressants are not completely metabolized in the human body and are disposed through urine and feces. Their main components, metabolites, or conjugates are ultimately delivered to wastewater treatment plants (WWTPs). WWTPs are not particularly designed to remove them as their main function is to eliminate biodegradable carbon, phosphorus, nitrogen, and pathogens from aqueous environments (Huang et al. 2018). Therefore, psychotropic drugs are probably removed partially in WWTPs (Lajeunesse et al. 2012) and the residuals enter the environment through the effluent or sludge. By maintaining their medicinal properties, residual psychotropic drugs can inhibit serotonin reuptake (Sheng et al. 2014). Accumulation of these drugs in the tissues of aquatic organisms like fish can cause physiological and behavioral changes (Berg et al. 2013; Lajeunesse et al. 2011). Therefore, an awareness of the occurrence of psychotropic drugs in the environment leads to a better understanding of their potential health and environmental risks.

The occurrence of psychotropic drugs depends on their consumption patterns in different weather conditions. Tehran is a quickly developing and densely populated metropolitan in the north of Iran. The prevalence of depression in Tehran has been reported to be as high as 22.5% (Nazari et al. 2002), which may explain a marked increase in psychotropic compounds, especially antidepressants, in wastewater treatment systems of the city. However, there are not sufficient data on the occurrence and outcomes of sedatives-hypnotics-anxiolytics and antidepressants in Tehran WWTPs. In addition, the use of the chlorination process for the disinfection of biologically treated wastewater can induce the transformation of drugs (Sharma 2008). It is important to understand whether chlorination processes are effective in removing these drugs from the wastewater. Therefore, the present study evaluated the effect of chlorine disinfection on the removal of psychiatric drugs in the Tehran South Wastewater Treatment Plant (Tehran South WWTP). Given that the treated effluent is mostly used to irrigate the downstream agricultural fields, it is very important to investigate the fate of the selected psychiatric drugs in the largest WWTP in Iran. Hence, the occurrence of the high-risk psychiatric drugs, specifically sedatives-hypnotics-anxiolytics and antidepressants, were surveyed in July (as a warm season) and November (as a cold season) in the Tehran South WWTP. Additionally, the removal efficiency of each compound was evaluated to determine the efficiency of biological and chlorine disinfection processes.

Materials and methods

Chemicals and reagents

Three sedatives-hypnotics-anxiolytics including alprazolam, phenobarbital, and thioridazine, and four antidepressants including fluoxetine, citalopram, sertraline, and venlafaxine were assessed in this study (Table 1). Drug standards, materials, reagents, and solvents are presented in the supplementary material section (Text S.1).

Sampling sites and sample collection

A municipal wastewater treatment plant in the south of Tehran was selected for monitoring the psychiatric drugs. The ultimate design includes eight modules with modules 1 to 4 being currently in operation. The average capacity of the plant is 450,000 m$^3$/day and serves a population of 2.1 million people (with an average per capita wastewater production of 214 L/person/day). The wastewater treatment process is a combined conventional activated sludge and trickling filter. The secondary clarifier (SC) effluent before discharge was disinfected with chlorine. The mean dosing and residual concentrations of chlorine used for disinfection of the SC effluent were 7.7 ± 0.5 and 0.2 ± 0.1 mg/L in the cold season and 9 ± 0.5 and 0.4 ± 0.4 mg/L in the warm season, respectively. A flow diagram of the Tehran South WWTP processes is shown in Fig. 1.

Composite wastewater samples were obtained after the grit chamber (inlet), secondary clarifier (SC) effluent, and the plant outlet (after chlorination) (Fig. 1). The composite sampling was a time-based method and considering the hydraulic retention time of the secondary clarifier (2 h), the auto-sampler took a certain volume every 2 h. In total, 12 samples were taken and mixed at the end of the day to represent the concentration fluctuations and system performance over the entire day. Time composite wastewater samples were collected in 4 days (at the beginning (Saturday), middle (Monday and Tuesday), and end of the week (Friday)) in a cold (November 2019) and a warm season (July 2020) to assess drug variations on different days and seasons. The mean wastewater temperature during sampling days was 11 ± 2 °C in the cold season and 31 ± 6 °C in the warm season. After sampling, sodium azide (NaN$_3$) was used for microbial growth inhibition (Phonsiri et al. 2019). Moreover, sodium thiosulfate (Na$_2$S$_2$O$_3$) 20% was used to remove the residual chlorine after the chlorination process. Then, the
| Therapeutic class/ Generic name/CAS number | Structure/ Chemical formula/Molecular weight | Reactive functional group | Water solubility | Log Koc | pKa | Log Kd* | Excretion rates** |
|-------------------------------------------|---------------------------------------------|---------------------------|-----------------|---------|-----|--------|-----------------|
| **Sedatives-hypnotics-anxiolytics**       |                                             |                           |                 |         |     |        |                 |
| Phenobarbital/50-06-6                      | ![Phenobarbital structure](image)           | Secondary amine           | 1644            | 1.8     | 7.3 | --     | 25% (6-39%) is excreted in urine as unchanged drug. |
|                                           | C₁₂H₁₂N₂O₃                                 |                           |                 |         |     |        |                 |
| Thioridazine/50-52-2                       | ![Thioridazine structure](image)           | Tertiary amine            | 0.03            | 5.9     | 9.5 | --     | 0.5-4% is excreted in urine as unchanged drug and 50% is excreted in the feces. |
|                                           | C₂₁H₂₆N₂S₂                                 |                           |                 |         |     |        |                 |
| Alprazolam/28981-97-7                      | ![Alprazolam structure](image)             | Tertiary amine            | 13              | 2.8     | 5.1 | 18.3   | 10-20% is excreted in urine as unchanged drug. |
|                                           | C₁₇H₁₃ClN₄                                 |                           |                 |         |     |        |                 |
| **Antidepressants**                        |                                             |                           |                 |         |     |        |                 |
| Sertraline/79617-96-2                       | ![Sertraline structure](image)             | Secondary amine           | 3.5             | 4.2     | 9.5 | 4.5    | <1% is excreted in urine as unchanged drug. After biotransformation, 40-45% is excreted in feces. |
|                                           | C₁₇H₁₇Cl₂N                                 |                           |                 |         |     |        |                 |
| Citalopram/59729-33-8                       | ![Citalopram structure](image)             | Tertiary amine            | 31              | 5.5     | 9.6 | 3.6    | About 26-29% of a daily dose is excreted in urine as unchanged drug. |
|                                           | C₂₀H₂₁FN₂O                                 |                           |                 |         |     |        |                 |
| Fluoxetine/54910-89-3                       | ![Fluoxetine structure](image)             | Secondary amine           | 60              | 4.7     | 10.1| 3.9    | <10% (2-5%) is excreted in urine as unchanged drug and 12% is excreted in feces. |
|                                           | C₁₇H₁₈F₂NO                                 |                           |                 |         |     |        |                 |
| Venlafaxine/93413-69-5                      | ![Venlafaxine structure](image)            | Tertiary amine            | 267             | 2.3     | 10.1| 2.5    | 1-10% is excreted in urine as unchanged drug and 2% is excreted in feces. |
|                                           | C₁₇H₂₂NO₂                                 |                           |                 |         |     |        |                 |

*Log Kd, solid-water distribution coefficients, and Log Koc, organic-carbon based sorption coefficients. These information was derived from Lajeunesse et al. (2012), Pereira et al. (2020), Silva et al. (2012), Wilde et al. (2017), and https://pubchem.ncbi.nlm.nih.gov

**Excretion rates data and metabolites were derived from Ahlford (2012), Calisto and Esteves (2009), and Metcalfe et al. (2010)
collected samples were kept at 4 °C in a cold box on the way to the laboratory. The physicochemical parameters of the samples were determined according to standard methods (APHA & AWWA 2012) as summarized in Table S1.

**Sample preparation: extraction and cleanup**

All samples were vacuum filtered using a 1-μm glass fiber filter followed by a 0.45-μm nylon membrane filter (Merck, Darmstadt, Germany) to eliminate total suspended solids (TSS) and bacteria. The pH of the filtered samples was adjusted to 7 (Sheng-Liu et al. 2013), and a cleating reagent (5% Na₂EDTA) was added to the samples. Then, the solid-phase extraction (SPE) was conducted with 200 mg/6 mL Oasis HLB cartridges reversed phase (Waters Corp, Milford, USA) (see Text S.2 for extraction details). The final analyte extracts were evaporated to dryness under a moderate nitrogen stream at 30 °C and were reconstituted with 1000 μL methanol. Five microliters of the reconstituted solution was injected into a high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) system.

**HPLC–MS/MS analysis**

Chromatographic analysis of the samples was done using HPLC (Alliance 2695 Waters system, Milford, USA). HPLC separation was done using an Atlantis T3-C18 reversed phase column (Waters Corp, Milford, USA) with a 3 μm, 150 mm×2.1 mm inner diameter. The column temperature was kept at 40 °C. The sample injection volume was 5 μL, and the flow rate was 0.15 ml/min. The HPLC mobile phases were solvents (A) and (B). Solvents (A) and (B) were acetonitrile containing 0.1% (v/v) formic acid and water containing 0.1% (v/v) formic acid, respectively. HPLC conditions and gradient elution of mobile phase are summarized in Table S2. Detection was performed using a triple quadrupole mass spectrometer from Micromass Quattro micro API (Waters, Manchester, UK) equipped with an electrospray ion (ESI) source interface. Mass spectrometry analysis (MS) conditions are summarized in Table S2. Mass spectrometry analysis was done in a multiple reaction monitoring (MRM) mode. An overlay of extracted MRM chromatograms for all seven target psychiatric drugs is shown in Fig. S1. Thioridazine, alprazolam, sertraline, citalopram, fluoxetine, and venlafaxine were analyzed in a positive electrospray ionization mode (ESI⁺), while phenobarbital were analyzed separately in a negative electrospray ionization mode (ESI⁻). Optimized LC–MS/MS parameters (such as retention time and selected ion masses) are shown in Table S3.

**Method validation**

Quantification was based on linear regression calibration curves using a matrix match calibration approach. For method validation, sensitivity parameters (LOD and LOQ), linearity, recovery, and repeatability were determined for three different matrices (influent, SC effluent, and after chlorination effluent). The lowest concentration level that could provide a signal-to-noise ratio of 3 for LOD and 10 for LOQ was used to estimate the limits of detection (LOD) and quantification (LOQ) (Table S4). For setting up matrix-matched calibrations, the samples (i.e., influent, SC effluent, and after chlorination effluent) were cleaned up using an SPE technique (Xu et al. 2005, Zhou and Kang 2013) to remove interfering matrix components. The matrix-matched calibration curves were built by spiking 7 different amounts of analyte standards, which were 2.5–500 ng/L for sedatives and fluoxetine and...
5–3000 ng/L for the other three antidepressants (citalopram, sertraline, and venlafaxine), to the SPE cleaned up sample extracts. Moreover, blank samples (i.e., without analytes) were also analyzed (“Sample preparation: extraction and cleanup” section) to subtract the area of any peak that could be detected at quantifying levels (Ofrydopoulou et al. 2021). Precision was calculated as the relative standard deviation (RSD) of a triplicate analysis of waste-water samples which were spiked by a mixture of each of the target sedative and antidepressant drugs (200 ng/L). To test the accuracy, recovery experiments were done for two concentration levels in triplicates for each of the matrices. All samples were filtered as described above, extracted using HLB cartridges, and the target drugs analyzed according to the proposed methodology (Tables S2 and S3). A summary of method validation results is shown in Table S4. The coefficient of determinations ($r^2$) was greater than 0.985 for all seven target psychiatric drugs. The RSD values were less than 5%, showing high repeatability of the applied method. In addition, mean recoveries of the selected sedatives-hypnotics-anxiolytics and antidepressants ranged from 59.6 ± 13.2% to 66.5 ± 10.5% and 50.1 ± 10.7 to 59.1 ± 15.9 for influent, 80.8 ± 12.7% to 97.2 ± 18.9% and 61.2 ± 7.8 to 93.6 ± 5.1 for SC effluent, and 89.9 ± 8.6% to 98.3 ± 1.8% and 60.2 ± 1.3 to 97.3 ± 5.2 for chlorinated effluent, respectively (Table S4). Finally, the recovery correction factors were used to determine the actual concentration values of any drugs.

**Data analysis**

For data analysis, the concentration values, which were not detected, were set to half of LOD and half of the LOQ if they were between LOD and LOQ (Kosma et al. 2020). The Wilcoxon test (the nonparametric test) was done to examine the concentration differences the target psychiatric drugs in two different seasons.

The pattern and concentrations of the target psychiatric drugs during the sampling days in the Tehran South WWTP were evaluated using heat map analysis that indicates minimum (dark green) and maximum (dark red) concentrations of drugs. The heat map analysis was built for two seasons by using the daily measured concentrations obtained during 1 week in each season.

The overall aqueous phase removal percentage was calculated using the aqueous phase concentrations of a target drug in the inlet ($C_{\text{Inlet}}$) and outlet ($C_{\text{Outlet}}$) of the treatment units: \[
\text{Removal efficiency during the secondary treatment} = \left( \frac{C_{\text{Inlet}} - C_{\text{Secondary effluent}}}{C_{\text{Inlet}}} \right) \times 100
\]

\[
\text{Removal efficiency during disinfection} = \left[ \frac{C_{\text{Secondary effluent}} - C_{\text{Outlet}}}{C_{\text{Secondary effluent}}} \right] \times 100
\]

In order to calculate the aqueous removal percentages, the concentration values of the target drugs in the inlet, secondary clarifier (SC), and outlet of the Tehran South WWTP were used (Eqs. 1 and 2). However, it should be noted that if the target drug was not detected at each of the locations, the LOD concentration was set with fixed values (i.e., half of LOD), and the aqueous removal percentages were calculated (Table S5). Moreover, when the measured concentrations of the target drugs were < LOD (below the limits of detection), the removal percentage of the target drug was not calculated and presented with “NA.”

**Results and discussion**

**Occurrence of the target psychiatric drugs in influent**

**Sedatives-hypnotics-anxiolytics**

The mean concentrations of the sedatives-hypnotics-anxiolytics detected in the influent samples were < LOQ for phenobarbital and alprazolam, and 164.25 ± 218.74 ng/L for thioridazine (Table 2). Thioridazine had the highest...
### Table 2

Mean concentration, range (i.e., min and max), and detection frequency (%) for each drug in the Tehran South WWTP inlet, secondary clarifier (SC), and outlet samples

| Therapeutic class/ generic name | WWTP inlet (ng/L) | SC effluent (ng/L) | WWTP outlet (ng/L) |
|---------------------------------|-------------------|-------------------|-------------------|
|                                 | (n=8)             | (n=8)             | (n=8)             |
|                                 | Mean * (range)    | Detection frequency (%) | Mean (range) | Detection frequency (%) | Mean (range) | Detection frequency (%) |
| Sedatives-hypnotics-anxiolytics |                   |                   |                  |                   |                  |                  |
| Phenobarbital                   | 1.93 ± 0.0 (1.23–174.68) | 25.0 | 3.51 ± 1.76 (1.55–4.95) | 37.5 | ND**** (ND) | 0.0 |
|                                 | (LOQ)**           |                   |                  |                   |                  |                  |
| Thioridazine                    | 164.25 ± 215.74 (2.10–485.31) | 50.0 | 6.54 ± 4.98 (1.29–11.20) | 37.5 | 28.22 ± 21.94 (9.08–52.17) | 37.5 |
| Alprazolam                      | 1.88 ± 0.0 (< LOQ) | 37.5 | 5.09 ± 2.33 (3.65–7.78) | 37.5 | 3.86 ± 2.28 (2.21–6.46) | 37.5 |
| Antidepressants                 |                   |                   |                  |                   |                  |                  |
| Sertraline                      | 183.42 ± 174.68 (2.33–417.57) | 75.0 | 18.41 ± 29.08 (1.34–76.47) | 75.0 | 11.96 ± 11.62 (4.00–29.04) | 50.0 |
|                                 | (LOQ)**           |                   |                  |                   |                  |                  |
| Citalopram                      | 672.53 ± 938.56 (4.66–2006.27) | 62.5 | 776.97 ± 1088.01 (3.50–2364.35) | 62.5 | 435.41 ± 474.49 (7.60–945.74) | 37.5 |
| Fluoxetine                      | 2.50 ± 0.0 (< LOQ) | 25.0 | 4.40 ± 2.91 (2.04–7.65) | 37.5 | ND (< LOQ) | 0.0 |
|                                 |                   |                   |                  |                  |                  |                  |
| Venlafaxine                     | 206.98 ± 255.18 (22.28–566.93) | 50.0 | 303.59 ± 325.38 (105.49–785.78) | 50.0 | 184.91 ± 219.74 (2.50–429.15) | 37.5 |

*n: the number of samples

**Mean refers to the mean of concentration values detected in samples

*** < LOQ: below the limit of quantification

**** ND refers to not detected, meaning the concentration is below LOD (limit of detection)

### Table 3

Seasonal range and mean concentrations expressed in ng/L in the Tehran South WWTP inlet, secondary clarifier (SC), and outlet samples

| Therapeutic class/ generic name | WWTP inlet (ng/L) | SC effluent (ng/L) | WWTP outlet (ng/L) |
|---------------------------------|-------------------|-------------------|-------------------|
|                                 | (n=8)             | (n=8)             | (n=8)             |
|                                 | Mean (range)*     | Detection frequency (%) | Mean (range) | Detection frequency (%) | Mean (range) | Detection frequency (%) |
| Sedatives-hypnotics-anxiolytics |                   |                   |                  |                   |                  |                  |
| Phenobarbital                   | 1.93 ± 0.0 (1.23–174.68) | ND***             | 3.51 ± 1.76 (1.55–4.95) | ND               | ND               |
|                                 | (< LOQ)**         |                   |                  |                   |                   |                  |
| Thioridazine                    | ND                | 164.25 ± 215.74 (2.10–485.31) | ND              | 6.54 ± 4.98 (1.29–11.20) | ND               | 28.22 ± 21.94 (9.08–52.17) |
| Alprazolam                      | 1.88 ± 0.0 (< LOQ) | ND              | 5.09 ± 2.33 (3.65–7.78) | ND               | ND               |
| Antidepressants                 |                   |                   |                  |                   |                  |                  |
| Sertraline                      | 2.33 ± 0.0 (< LOQ) | 273.97 ± 134.39 (114.71–417.57) | 6.82 ± 1.87 (5.50–8.14) | 24.20 ± 35.69 (1.34–76.47) | 4.67 ± 0.95 (4.01–5.34) | 19.25 ± 13.85 (9.46–29.04) |
|                                 | (< LOQ)**         |                   |                  |                  |                  |                  |
| Citalopram                      | 839.50 ± 994.32 (4.66–2006.27) | 4.66 | 970.32 ± 1152.89 (9.07–2364.35) | 3.59 | 435.41 ± 474.49 (7.60–945.74) | ND               |
| Fluoxetine                      | 2.50 ± 0.0 (< LOQ) | ND              | 4.40 ± 2.91 (2.04–7.65) | ND               | ND               |
|                                 | (< LOQ)**         |                   |                  |                  |                  |                  |
| Venlafaxine                     | 25.66 ± 4.78 (22.28–29.04) | 388.31 ± 252.61 (209.69–566.93) | 107.28 ± 2.53 (105.49–109.07) | 499.90 ± 404.30 (214.01–785.78) | 2.81 | 276.01 ± 216.37 (123.01–429.15) |

*Mean refers to the mean of concentration values detected in samples

** < LOQ: below the limit of quantification

*** ND refers to not detected, meaning the concentration is below LOD (limit of detection)
concentration in the warm season and lowest concentration in the cold season in the influent samples (Table 3) and showed a significant difference between the warm and cold seasons (W = 0.0, p value < 0.05) (Table S6). To our knowledge, it is the first time that thioridazine was detected in the influent stream of a WWTP. Thioridazine is a phenothiazine antipsychotic drug used to treat generalized anxiety disorder and schizophrenia. Considering the high consumption rate and the excretion percentage of this drug (0.5–4%) (Wilde et al. 2016), its concentrations are expected to range from 26 to 35 ng/L in the influent. However, the detected concentration of thioridazine ranged from 2.10 to 485.31 ng/L in the present study, indicating that a much higher concentration of this drug finds its way into the Tehran South WWTP. It seems that the concentrations for thioridazine estimated based only on excretion and consumption data are not realistic because excreted drugs are distributed depending on demographic information of the population served by a WWTP and it may considerably vary in different geographic zones. Moreover, thioridazine was found at higher detection frequency and concentrations compared to the other target sedatives-hypnotics-antianxietytics, while its excretion percentage as a parent compound was low (Wilde et al. 2016). This may be attributed to the higher persistence of thioridazine than the other two compounds (Golbaz et al. 2021). Hence, field monitoring of these drugs can increase our understanding of their distributions in wastewater and help develop better estimation models.

Alprazolam and phenobarbital were only detected in 37.5% and 25% of the influent samples, respectively. The differences between the concentration and detection frequency of the drugs found in this study compared to other studies can be attributed to the different local rates of consumption (Table S7). Our results showed good agreement with the previous studies that reported alprazolam and phenobarbital at very low concentrations (around or below the LOQ level) in influent samples. Alprazolam concentrations measured in the influent samples in this study (Table 2) were within the range reported elsewhere ((Yuan et al. 2013) (<LOD), (Subedi et al. 2017) (<LOQ), (Wu et al. 2015) 7.6 ng/L), and (Subedi and Kannan 2015) 6.0 ng/L). Phenobarbital concentrations were not detectable in the influent samples (Hass 2012). The low concentration and detection frequency of these drugs reported in different studies might be due to the transformation/metabolism of drugs which can be excreted mainly as a metabolite, adsorption to wastewater particles, or due to the parent compound transformation in the sewer system (Gracia-Lor et al. 2012).

Antidepressants

In the antidepressant group, citalopram had the highest concentration (ranging from 4.66 and 2006.27 ng/L) in the influent samples (Table 2). Similarly, previous studies reported citalopram at higher concentrations compared to the other antidepressants. For instance, in Norway, citalopram concentration in the influent samples ranged between 13 and 612 ng/L, whereas fluoxetine ranged from 0.4 to 2.4 ng/L (Vasskog et al. 2006). Moreover, citalopram was detected in the influent samples in Canada at a mean level of 23.6 ng/L, whereas sertraline and fluoxetine concentrations were 20 and 18 ng/L, respectively (Lajeunesse et al. 2012). Citalopram is excreted in urine as 26% of the daily dose, so this compound is found at relatively high concentrations in wastewater influents. For the other three antidepressants (fluoxetine, sertraline, and venlafaxine), the conjugated metabolites predominate in urine and the unconjugated forms of these drugs are present in low proportions in urine (Calisto and Esteves 2009, Lajeunesse et al. 2012). This can explain why these drugs found in lower concentrations compared to citalopram. For example, the lower detection frequency and concentrations of venlafaxine in the influent samples compared to those of citalopram may be due to the conversion of this drug to its metabolites, such as desmethylvenlafaxine and O-desmethylvenlafaxine. Lajeunesse et al. (2012) found a much higher concentration of desmethylvenlafaxine (as high as 4.3 mg/L) in the influent samples compared to its parent compound (Lajeunesse et al. 2012). Rúa-Gómez and Püttermann (2012) also reported higher concentrations of metabolite of this drug (Rúa-Gómez and Püttermann 2012). In fact, O-desmethylvenlafaxine is the dominant metabolite in human urine, which is excreted at a rate of 29–30% of the daily dose.

Furthermore, the concentrations of citalopram in the influent samples showed a noticeable seasonal pattern, with mean concentrations being lowest during the warm season (4.66 ± 0.0 ng/L) and peaking in the cold season (839.50 ± 994.32 ng/L) (W = 15.5, p value < 0.05) (Table 3). This finding confirmed the expected usage patterns for citalopram as an example of typical concentrations for most antidepressants during the year (Iranian Ministry of Health and Medical Education 2019). Golovko et al. 2014 reported that higher consumption and consequently higher concentrations of these drugs in WWTP influent caused by depression and low mood in the colder and darker months (Golovko et al. 2014). The concentration pattern of sertraline was completely different from citalopram. Sertraline concentration in the influent was lower in the cold season (2.33 ± 0.0 ng/L) than in the warm season (273.97 ± 134.39 ng/L) (W = 0.0, p value < 0.05). As the excretion by patients is considered to be the main pathway for the entrance of drugs into wastewater (Calisto and Esteves 2009), the measurement of human metabolism and excretion rates of antidepressants can help to understand the differences in antidepressant concentrations in wastewater in different seasons. Since sertraline is mainly excreted as an un-metabolized parent in the feces (40–45%), unlike citalopram, its high concentration in the
influent samples in a season with higher flow rates was probably due to the desorption from feces. The sewage flow rates in the Tehran South WWTP varied from 365,688 m$^3$/day in November to 401,276 m$^3$/day in July. The sewage flow rates could be increased in July 2020 mainly due to the ambient temperature rise (from 7.7 ± 3.3°C in November 2019 to 31.9 ± 2.3°C in July 2020), COVID-19 outbreak, and higher water consumption in Iran (Rezaeitavabe et al. 2021). Therefore, large quantities of sertraline settled and accumulated in sewer networks can be re-suspended during July, leading to pulses of drugs discharged to the plant. Desorption of drugs bound to particulates was demonstrated in laboratory studies by simulating storm scenario impact on desorption of pharmaceuticals (Hajj-Mohamad et al. 2017). Increased aqueous phase concentrations were detected even when diluted with storm water.

Fluoxetine and venlafaxine concentrations in influent did not show a significant difference between the warm and cold seasons ($p$ value > 0.05) (Table S6). These drugs are extensively metabolized in the body and very little quantities are excreted un-metabolized in the urine or feces. Similar venlafaxine concentrations in raw wastewater were reported as 116 ng/L (Rúa-Gómez and Püttmann 2012), 260 ng/L (Schlüsener et al. 2015), and 119 ng/L (Loos et al. 2013). Table S7 gives an overview of antidepressants concentrations in aquatic environments.

It seems that there are equal or higher concentrations and detection frequency of antidepressants in influent samples compared to sedatives-hypnotics-anxiolytics drugs (Table 2).

**Secondary biological treatment**

**Sedatives-hypnotics-anxiolytics**

The mean concentrations of phenobarbital and alprazolam in the SC effluent samples were 3.51 ± 1.76 and 5.09 ± 2.33 ng/L, respectively (Table 2). Phenobarbital and alprazolam were quantified in WWTP effluents by several authors (Table S7). For example, Heberer (2002) observed comparable phenobarbital concentrations (30 ng/L, on average) in effluents of biological treatment units in Germany (Heberer 2002). Similar concentrations of alprazolam were detected in effluents of secondary biological treatment units (Subedi and Kannan 2015, Yuan et al. 2013). Santos et al. (2013) reported that the alprazolam concentration in effluents of primary and secondary treatment units operating with trickling filters was between 11.3 and 33.5 ng/L (Santos et al. 2013). Pereira et al. (2020) concluded that the mean concentrations of alprazolam in the effluent were 9.2 ng/L (Pereira et al. 2020). In the present study, higher phenobarbital and alprazolam concentrations were detected in the SC effluent in comparison with the influent samples during the cold season (November), indicating their negative removal efficiencies in the cold months (Table 3). Considering their SC effluent concentrations, the removal efficiencies of phenobarbital and alprazolam ranged from –34 to −156% and –94 to −314%, respectively (Figs. 2a and 3a). Therefore, phenobarbital and alprazolam did not degrade during the biological process. This result can imply their high persistence in the environment. The resistance of phenobarbital to degradation in the aquatic environment under aerobic conditions was also reported previously (Peschka et al. 2006). Low or negative removal of other drugs belonging to the same psychiatric class such as carbamazepine (−12%), oxazepam (−17%), and memantine (1%) was reported by Golovko et al. (2014). Moreover, they reported a higher carbamazepine concentration in the effluent was higher than in the influent during the cold season (Golovko et al. 2014). The negative removal of phenobarbital and alprazolam was probably related to the conversion of their glucuronide and conjugated metabolites into the parent compound through enzymatic processes during the treatment (Golovko et al. 2014; Verlicchi et al. 2012). Furthermore, some forms of these drugs such as phenobarbital and alprazolam, which are not soluble, are excreted with the feces from body. Hence, they were not detected in the influent samples (aqueous phase). However, during the biological process in the aeration basin, they are released due to hydrolysis reactions.

The thioridazine concentrations in the SC effluent samples were below the 11.20 ng/L, although its concentrations were recorded as high as 485.31 ng/L in the influent (Table 2). This indicated that thioridazine was considerably removed during the biological process (51 to 98% in the warm season) (Figs. 2a and 3a). The pKa of thioridazine is 9.5, indicating that it almost entirely exists in the environment as a cation. Cations are usually removed by adsorption on particles containing organic carbon. Hence, thioridazine was removed mostly through adsorption to the suspended solids. While phenobarbital and alprazolam have low pKa, organic-carbon sorption coefficients and high water solubility (Table 1). Hence, phenobarbital and alprazolam have limited sorption, leading to minimal removal of these drugs in the aeration basin.

**Antidepressants**

In the antidepressant group, citalopram was detected in a higher concentration in the SC effluent samples compared to the other antidepressant (Table 2). Similar concentrations of the target antidepressants in effluent samples were also reported. The concentration of citalopram was 430 ng/L in India (Fick et al. 2009). Santos et al. (2013) reported that the mean concentration of venlafaxine and fluoxetine in effluents of primary and secondary treatment units operating during the cold season (November), indicating their negative removal efficiencies in the cold months (Table 3). Considering their SC effluent concentrations, the removal efficiencies of phenobarbital and alprazolam ranged from –34 to −156% and −94 to −314%, respectively (Figs. 2a and 3a). Therefore, phenobarbital and alprazolam did not degrade during the biological process. This result can imply their high persistence in the environment. The resistance of phenobarbital to degradation in the aquatic environment under aerobic conditions was also reported previously (Peschka et al. 2006). Low or negative removal of other drugs belonging to the same psychiatric class such as carbamazepine (−12%), oxazepam (−17%), and memantine (1%) was reported by Golovko et al. (2014). Moreover, they reported a higher carbamazepine concentration in the effluent was higher than in the influent during the cold season (Golovko et al. 2014). The negative removal of phenobarbital and alprazolam was probably related to the conversion of their glucuronide and conjugated metabolites into the parent compound through enzymatic processes during the treatment (Golovko et al. 2014; Verlicchi et al. 2012). Furthermore, some forms of these drugs such as phenobarbital and alprazolam, which are not soluble, are excreted with the feces from body. Hence, they were not detected in the influent samples (aqueous phase). However, during the biological process in the aeration basin, they are released due to hydrolysis reactions.

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with trickling filters were 272 ng/L and <LOQ, respectively (Santos et al. 2013). The reported concentrations of the target antidepressants vary greatly in literature. For example, the mean concentration of citalopram was 34 ng/L in Coimbra (Santos et al. 2013) which was several times lower than the concentration measured in the present study (i.e., 776.75 ng/L). The mean concentrations of citalopram and sertraline were reported in another study as 95.1 and 9.7 ng/L, respectively (Pereira et al. 2020). The maximum fluoxetine concentration reported was 99 ng/L in WWTP effluents in Canada (Metcalfe et al. 2003), while it was 7.65 ng/L in the Tehran South WWTP (see Table 2).

Fig. 2 Bee swarm plot for removal efficiencies (%) of the target psychiatric drugs in the various treatment processes regardless of the season: a and d biological process, b and e chlorine disinfection process, and c and f overall removal.
Fig. 3 Aqueous removal percentages (%) of the target psychiatric drugs in the various treatment processes (biological process (a), chlorine disinfection (b), and overall removal (c)) in two different seasons (November 2019 and July 2020). *: NA, not applicable, meaning the target drugs were not detected in the Tehran South WWTP inlet, secondary clarifier (SC), and outlet samples.
In the warm season, the SC effluent concentrations of fluoxetine, citalopram, and venlafaxine follow the influent concentration pattern, while lower sertraline concentrations were detected in the SC effluent samples than in the influent (Table 3). The relatively high removal sertraline efficiency in the summertime may be due to the higher microbial activities in the warm season (Fig. 3a). In fact, the higher wastewater temperatures in combination with long daylight periods in summertime can be important factors for the increase of biodegradation rates and photo transformation mechanisms of some drugs (Kosma et al. 2020). Moreover, as a general rule, sorption is important when the log Kd value is greater than 4 (Deegan et al. 2011). The log Kd value for sertraline is close to 4.6 and its sorption to sludge or particulate matter can be assumed to be maximum.

In contrast, the higher concentrations of all antidepressants (fluoxetine, citalopram, sertraline, and venlafaxine) found in the SC effluent samples than in the influent during the cold season, indicated a negative removal (Figs. 3a and 2d). In a similar vein, Golovko et al. (2014) reported negative removal efficiencies for venlafaxine in wintertime (Golovko et al. 2014). Negative or low removal efficiencies were also reported for antidepressants (Golovko et al. 2014; Santos et al. 2013). The negative removal might be due to their enzymatic cleavage of the conjugated metabolites and subsequent reverse metabolism of the parent compound during the treatment process (Gracia-Lor et al. 2012; Kosma et al. 2020). Moreover, the estimated pKa values of all the target antidepressants are higher than 9 (Table 1), indicating that they exist almost entirely as cations in the environment. Generally, cations are adsorbed more strongly into soil and suspended solids containing organic carbon. During the biological process, they can be released into the bulk liquid due to the biotic and abiotic reactions. These release into the bulk liquid was probably affected by operating conditions such as solids retention time (SRT). Indeed, SRT is an important factor in the adsorption of antidepressants to particles. The SRT in the Tehran South WWTP varied from 11 to 34 days in November and 2 to 6 days in July. The desorption of all the antidepressants could increase in November due to the increased SRT and MLSS (mixed liquor suspended solids). Moreover, the increased bacterial decay rates under long SRTs in the biological unit may contribute to the release of the adsorbed drugs.

**Chlorine disinfection**

**Sedatives-hypnotics-anxiolytics**

The mean thioridazine and alprazolam concentrations were 28.22 ± 21.94 and 3.86 ± 2.28 ng/L in the samples, respectively (Table 2). Phenobarbital was not detected in any chlorinated samples. The behavior of the target sedative-hypnotic-anxiolytic drugs differed significantly during the chlorination process due to the difference in their structure and reactivity against chlorine. Phenobarbital was moderately oxidized after the chlorination process (71 ± 19%). Phenobarbital has a cyclic imides structure (R-CO–NH-CO-R’) that seems to be relatively rapidly oxidized by chlorine, while alprazolam was less oxidized (27 ± 14%), suggesting poor reactivity between this drug and chlorine (Figs. 2b and 3b). The poor reactivity of alprazolam with chlorine dioxide using wastewater effluent was also reported previously (Hey et al. 2012). A similar behavior was observed for chlorine reactivity with drugs belonging to the same therapeutic class, such as carbamazepine and diazepam (Huber et al. 2005). The resistance of these poorly oxidizable antianxiety drugs (i.e., alprazolam) to oxidation by chlorine compounds could be attributed to the presence of the electron-accepting functional groups i.e., the chloro group in their structure (Hey et al. 2012). Moreover, thioridazine concentration increased in 37.5% of the samples compared to the SC samples (Table 2), probably due to the desorption from the solids escaped from the secondary clarifier. Furthermore, the thioridazine concentration increased when the amount of TSS in the same samples was higher than the standard value (TSS > 30 mg/L), due to the TSS escape from the clarifier tank. It is highly probable that thioridazine, which was adsorbed on the negatively charged suspended and colloidal particles during the biological process, desorbed back into the bulk liquid during the chlorination process due to the protonation of thioridazine under slightly acid pH (pH 6.3 to 6.8), leading to the increased concentration of thioridazine in the effluent samples of the chlorination unit.

**Antidepressants**

In the antidepressant group, citalopram had the highest concentration (ranging from 7.60 to 945.74 ng/L) in the chlorinated samples (Table 2). The concentrations of all the target antidepressants decreased in the chlorination effluent samples compared to the SC samples. Chlorine was able to oxidize fluoxetine 62 ± 22%, citalopram 75 ± 10%, sertraline 49 ± 15%, and venlafaxine 71 ± 31% (Fig. 2e and Table S7). In addition, sertraline had the highest detection frequency (50%) in the chlorination effluent samples, indicating its high persistence and less reactivity with chlorine, while citalopram and venlafaxine had the highest reactivity with chlorine, followed by fluoxetine. Moreover, chlorine had a greater effect on low concentrations of all the target antidepressants and increased their removal efficiency. Relatively consistent removal efficiencies for venlafaxine, fluoxetine, and sertraline by using different chlorine compounds (chlorine dioxide or sodium hypochlorite) were reported in the literature (Hey et al. 2012; Lv et al. 2021; Molé et al. 2019).
Hörsing et al. (2012) showed that the removal efficiency of citalopram by chlorine dioxide was dependent on the concentration of chlorine. For example, 40% of citalopram was removed in chlorine concentrations of 25 ng/L and it increased to 95% at concentrations of 0.11 mg/L (Hörsing et al. 2012).

Antidepressants are structurally very different due to the difference in the reactivity of the target antidepressants with chlorine. All the target antidepressants in the present study included two reactive sites: the amine moiety and the aromatic ring. Since aromatic components react independently, liquid solution pH, oxidation of the target antidepressants is described by the $pK_a$ of the amines. The $pK_a$s of amines are higher than 9; hence, all the target antidepressants should have increased the rates of the reaction above pH 8. Chlorine is expected to attack mainly the basic amine moiety of all the target antidepressants (Sharma 2008). Citalopram and venlafaxine have a tertiary amine functional group, whereas sertraline and fluoxetine have a secondary amine functional group (Table 1). Citalopram and venlafaxine could be oxidized by more than 70% with 7–9 mg/L chlorine, while sertraline and fluoxetine were moderately oxidized during chlorination to form secondary amines. The rapid degradation of the tertiary amines during chlorination than for secondary amines was reported previously (Mitch and Schreiber 2008). Another structural difference affecting the reactivity of antidepressants with chlorine is the presence of halogens, as electron acceptors, such as the chloro group in sertraline, fluoro in citalopram, and fluoxetine and the number of these groups (Table 1). As the number of halogens increases in the structure of antidepressants, their chance to be oxidized by chlorine decreases and vice versa. Our result showed that citalopram, having one fluoro in its structure, was more oxidized by chlorine than sertraline with two chloros (Fig. 3b and Table S7). These findings were consistent with the fundamental chemistry of the drugs. Although chlorine seems effective in the removal of antidepressants in the Tehran South WWTP, the byproducts of the chlorination process may still cause high health risks and should be studied in the plant.

In general, the overall removal of the target psychiatric drugs in the Tehran South WWTP is shown in Figs. 2c and f and 3c and chlorine disinfection was the most effective step for psychiatric drugs removal.

**Daily variations**

The concentration heat map shows daily variations of the target psychiatric drugs (Fig. 4). The concentrations of these drugs, except venlafaxine, in the influent samples increased until the middle of the week (Monday and Tuesday) and then decreased over the weekend (Friday) (Fig. 4a). This trend could be due to the high consumption of these drugs at the beginning of the week. In fact, as the week begins on Saturday here in Iran, people have more social activities and

![Heat map analysis of the target psychiatric drugs during the sampling days in the Tehran South WWTP; a influent and b effluent. The color of each cell represents the detected concentrations at different days (temporal variation) (ng/L).](image-url)
may be exposed more to economic and social challenges. This may increase the use of these drugs and their concentrations in the wastewater. The lower concentrations in the influent on the weekend could be due to being away from the social stress.

Figure 4b shows the concentrations of the drugs in the final effluent (after chlorination). A similar pattern was observed for the effluent, confirming the highest concentrations in the beginning and middle of the week. In the daily samples, the concentrations of some of the target psychiatric drugs like venlafaxine increased remarkably in the final effluent samples compared to the influent specimens. Several processes and even non-process-related reasons may cause this increase in the effluent concentration as discussed in the earlier sections.

Conclusions

The occurrence and removal of three sedative-hypnotic-antxiolytic drugs (alprazolam, phenobarbital, and thioridazine) and four antidepressants (fluoxetine, citalopram, sertraline, and venlafaxine) were studied in the Tehran South WWTP to evaluate the effectiveness of biological and chlorination processes. The target sedative-hypnotic-antxiolytic and antidepressant drugs were detected in the influent at mean concentrations ranging from <LOQ to 164.25 ng/L and <LOQ to 672.53 ng/L, respectively. Citalopram and sertraline in antidepressant class and thioridazine in sedative-hypnotic-antxiolytic class showed a seasonal difference. After the biological treatment unit, greater concentrations of the target psychiatric drugs, except thioridazine and sertraline, were detected in SC effluent, with higher concentrations found during November. This result confirmed that the psychiatric drugs' removals in the biological treatment units were negative and dependent on their chemical characteristics and operating conditions of the biological units such as SRT. Additionally, the results showed that the removal of the drugs, other than thioridazine, occurred mainly in the chlorine disinfection. The concentrations of all the target psychiatric drugs were low after the chlorination process, regardless of the sampling seasons. However, these low concentrations could have health effects on the ecosystem.

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