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# The fate and risk assessment of psychiatric pharmaceuticals from psychiatric hospital effluent

Jiajia Xiang[a], Minghong Wu[b], Jianqiu Lei[c], Chao Fu[a], Jianzhong Gu[a], Gang Xu[a,*]

[a] School of Environmental and Chemical Engineering, Shanghai University, 99 Shangda Road, Shanghai 200444, China
[b] Shanghai Applied Radiation Institute, Shanghai University, 99 Shangda Road, Shanghai 200444, China
[c] Shanghai Institute of Optics and Fine Mechanics, the Chinese Academy of Sciences, 390 Qinghe Road, Shanghai 201800, China

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ABSTRACT

Psychiatric pharmaceuticals are gaining public attention because of increasing reports of their occurrence in environment and their potential impact on ecosystems and human health. This work studied the occurrence and fate of 15 selected psychiatric pharmaceuticals from 3 psychiatric hospitals effluent in Shanghai and investigated the effect of hospitals effluent on surface water, groundwater, soil and plant. Amitriptyline (83.57 ng $L^{-1}$) and lorazepam (22.26 ng $L^{-1}$) showed the highest concentration and were found frequently in hospital effluent. Lorazepam (8.27 ng $L^{-1}$), carbamazepine (83.80 ng $L^{-1}$) and diazepam (79.33 ng $L^{-1}$) showed higher values in surface water. The concentration of lorazepam (46.83 ng $L^{-1}$) in groundwater was higher than other reports. Only six target compounds were detected in all three soil points in accordance with very low concentration. Alkaline pharmaceuticals were more easily adsorbed by soil. Carbamazepine (1.29 ng $g^{-1}$) and lorazepam (2.95 ng $g^{-1}$) were frequently determined in plant tissues. The correlation analyses (Spearman correlations > 0.5) showed the main source of psychiatric pharmaceuticals pollutants might be hospital effluents (from effluent to surface water; from surface water to groundwater). However, hospital effluents were not the only pollution sources from the perspective of the dilution factor analysis. Although the risk assessment indicated that the risk was low to aquatic organism, the continuous discharge of pollution might cause potential environment problem.

## 1. Introduction

Pharmaceutical and personal care products (PPCPs) have gained growing attention since these compounds have been found to negatively affect ecosystems and environment (Batt et al., 2008; Kolpin et al., 2002; Kosma et al., 2014; Lajeunesse et al., 2012; Mendoza et al., 2014; Schultz et al., 2010) throughout the world. Furthermore, PPCPs are defined as 'pseudo persistent' (Flint et al., 2012) due to the continuous recharge of PPCPs into the aquatic environment via wastewater and thus could cause adverse effects on human beings. Psychiatric compounds as one important class of pharmaceuticals have drawn great attention. These pharmaceuticals commonly include anxiolytics, sedatives, hypnotics, antiepileptic, antidepressants and others (Schultzt and Furlong, 2008). Some researchers (Bebianno et al., 2016; Brooks et al., 2003; Jarvis et al., 2014; Sanchez-Arguello et al., 2009) have found that these compounds cause potential negative effects on non-target aquatic organisms even at very low concentrations. Fluoxetine, carbamazepine and diazepam are representative among such drugs. Similarly to other groups of drugs, psychiatric pharmaceuticals may be not completely metabolized by the human body and thus released to aquatic environment (the excretion of carbamazepine, diazepam and fluoxetine are 1–61%, 10% and 17–25% (Carballa et al., 2008)). As regards metabolites, the human metabolites of diazepam are temazepam, nordiazepam and oxazepam. 5-chloro-2-benzophenone (metabolin-1) and 2-Amino-5-chorobenzophenone (metabolin-2) are main aqueous degradation products of diazepam, nordiazepam and temazepam under visible light (West and Rowland, 2012).

Hospitals may consume large quantities of pharmaceutical active ingredients per day (Perrodin et al., 2013) due to the extensive use of different therapeutic classes and psychiatric hospitals which focus on treating mental illness may consume and discharge a large amount of psychiatric pharmaceuticals (Herrmann et al., 2015). The types (multitudinous and persistence) of pharmaceuticals applied in hospitals are different from that used in other places. We could conjecture that hospital effluents may present high environmental risks. Some studies (Santos et al., 2013a; Oliveira et al., 2015; Rozman et al., 2015; Verlicchi et al., 2012a; Verlicchi and Zambello, 2016) have investigated the occurrence, fate and risk of pharmaceuticals from hospital effluents

* Corresponding author.
*E-mail addresses:* jiazi831@163.com (J. Xiang), mhwu@staff.shu.edu.cn (M. Wu), ljqlei@163.com (J. Lei), 1944141890@qq.com (C. Fu), jzhgu@staff.shu.edu.cn (J. Gu), xugang@shu.edu.cn (G. Xu).

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all over the world. Hospital wastewaters have been evaluated as more toxic than that from classical municipal sewage treatment plants (Emmanuel et al., 2009) and effluents from psychiatric hospitals might cause major environmental problems (Azuma et al., 2016; Helwig et al., 2016; Al Aukidy et al., 2014; Santos et al., 2013b; Verlicchi et al., 2012b).

Some researchers have measured a variety of pharmaceuticals in hospital effluent (Perrodin et al., 2016). Psychiatric pharmaceuticals may not be completely removed (removal efficiencies of 42–57%) in psychiatric hospital and municipal wastewater treatment plants (WWTPs). Furthermore, lorazepam, carbamazepine, citalopram and oxazepam showed negative removal efficiency (Yuan et al., 2013). These compounds have the potential to accumulate in soil or be taken up by plants when the wastewater or reclaimed water is used to irrigation (Miller et al., 2016). PPCPs have been detected in the vegetables tissues irrigated with treated wastewater (Wu et al., 2013a, 2014). Furthermore, the hospital pharmaceuticals may enter groundwater system via permeation or recharge (K'Oreje et al., 2016; Rozman et al., 2015; Swartz et al., 2006).

China is one of the largest producer and consumer of psychiatric pharmaceuticals in the world, the data from some major Chinese cities (which includes Shanghai) show that the total annual cost of the psychiatric pharmaceuticals in 2015 (20.965 billion RMB) increased by 6.7% compared to the year 2014 (http://www.chyxx.com). Shanghai is one of the most heavily populated cities in Asia with 23.8 million people. The large population might make Shanghai a large pharmaceutical consumption area. It is necessary to evaluate the contributions of psychiatric hospitals on the environmental burden. This work will help psychiatric hospital managers to identify the psychiatric pharmaceuticals which might cause negative effects on surface water ecosystems and/or groundwater systems and do their best to decrease these compounds releasing into the environment. In addition, systematic study on the environmental impact of psychiatric pharmaceuticals from Shanghai psychiatric hospital wastewater was limited, with no considerations on the comprehensive risk assessment so far.

The aims of this study were to: (i) analyze the occurrence and fate of 15 selected psychiatric pharmaceuticals in wastewater from 3 psychiatric hospitals in Shanghai; (ii) study the impacts of wastewater on surface water and groundwater around psychiatric hospital; (iii) investigate enrichment of these compounds in soil and plant which use receiving water as irrigation and make comprehensive risk assessment.

## 2. Materials and methods

### 2.1. Reagents and standards

Pharmaceutical names, CAS number, molecular formula are shown in Appendix Table S1. Standards of alprazolam, oxazepam, diazepam, lorazepam, estazolam, doxepin, nordiazepam, fluoxetine, bromazepam, mianserin and amitriptyline were provided by Cerilliant (USA). Temazepam was purchased from o2si smart solutions corporation (USA) and carbamazepine was provided by Sigma-Aldrich (USA). Photodegradation products metabolin-1 and metabolin-2 were obtained from Toronto Research Chemicals (Canada). Internal standards lorazepam-$d_4$, diazepam-$d_5$ and oxazepam-$d_5$ obtained from Cerilliant (USA) were chosen for the quantification of samples. All solvents were of HPLC grade. Acetonitrile, methanol and MTBE (methyl tertiary butyl ether) were obtained from Merk China and other solvents & chemicals were purchased from CNW (China). Ultrapure water with resistance > 18.2 MΩ*cm (the highest standard for ultrapure water) was provided by an ultrapure water polishing system (USA).

### 2.2. Sampling and sites description

Sampling sites and sampling design are shown in Fig. 1. Hospital effluent samples were collected from the effluent of 3 medium-size psychiatric hospitals located in Shanghai, China at the end of November 2015 (sampling points are georeferenced in Table S5). Hospital H1 (Area 21,300 $m^2$) has a wide range of mental medical specialties and has 800 beds. Hospital H2 is tertiary mental health specialist hospital in Shanghai has 1878 beds and Hospital H3 is 650 bedded hospital. The psychiatric hospitals have their own small wastewater treatment plants and the treated wastewater is discharged into receiving waters. The daily waste water flow rates of H1, H2 and H3 are 1056 t, 2478 t and 858 t. Appropriate sampling method will help to determine the value of measured data for the experimental assessment of the occurrence and fate of PPCPs as well as for the formulation and validation of mathematical models (Ort et al., 2010a). At the effluent of each hospital sampling point, the four times (at 8 a.m., 12 a.m., 4 p.m. and 8 p.m.) wastewater samples were combined to obtain a 12-h composite sample (there is no significant change in wastewater flowrates throughout sampling). To obtain representative samples, hospital effluent samples were typically collected multiple times along consecutive days in each sampling point (Olalla et al., 2018; Rodriguez-Mozaz et al., 2015; Verlicchi et al., 2012c). Some researchers collected a mixed water sample for each hospital (Boillot et al., 2008; Kummerer et al., 1997). Considering there was no significant change in wastewater flowrates and water samples were collected in dry season (avoiding dilution effects), the quantity or quality of hospital effluent had no obvious change in the short term. We collected a 12-h composite water sample from each hospital point and prepared three copies (Table S8). Hospital effluent samples (2 L) were collected in clean amber glass bottles. Before sample collection, all the sampling bottles were rinsed with sample wastewater. The effluent samples were preserved in dark place at 4 °C and were analyzed as soon as possible.

The Huangpu River (average flow rate is 319 $m^3$/s) near psychiatric hospital H1 flows into the Yangtze River. The Suzhou River (average flow rate is 10 $m^3$/s) near psychiatric hospital H2 flows into the Huangpu River and the Dianpu River (average flow rate is 3.2 $m^3$/s) near psychiatric hospital H3 flows into the Huangpu River. The flow direction of studied river is showed in Fig. 1. There are several municipal WWTPs in the upstream of studied rivers and the sampling points have certain distance from WWTPs. The weather was sunny during sampling and the river samples (4 L) were collected at 0.5 m depth using sampling equipment from the upstream, adjacent waters and downstream (Fig. 1) of psychiatric hospital respectively. Three surface water samples were also collected at 8 a.m., 12 a.m., 4 p.m. and 8 p.m. at each sampling side to obtain a 12-h composite sample. In addition, groundwater (aquifers) that might be affected by receiving water was sampled from sampling wells. The flow direction of groundwater was from G1 to G2 (Fig. 1). Groundwater sampling sites should be not too far from psychiatric hospital and be close to surface water sampling points.

Soil samples (irrigation by surface water generally) near the surface water sampling points were collected using hand-held shovel. The samples were wrapped with foil paper tightly, freeze-dried, ground into a powder, griddled and stored at − 20 °C. For plants (*Zoysia matrella*) grown on the sampling soil, 3 whole plants were taken from each sampling point and combined as one single sample. Plant samples were washed using tap water and then rinsed with ultrapure water to remove the adhering soil and flag. Plant tissues were then cut into small pieces, freeze-dried, crushed and stored at − 20 °C until analysis.

### 2.3. Data analyses

For aqueous samples, the SPE procedure was derived from Ferrer and Thurman (Ferrer and Thurman, 2010) with modifications. Briefly, 400 mL of filtered groundwater and surface water, 200 mL of effluent were mixed with methanol (1%, v/v), then adjusted to pH = 8 and added internal standards mixture as recovery surrogates. SPE operation was performed with 200 mg/6 mL HLB extraction cartridges (CNW, China). 6 mL methanol following 6 mL ultrapure water was added into