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Potential trends in Attention Deficit Hyperactivity Disorder (ADHD) drug use on a college campus: Wastewater analysis of amphetamine and ritalinic acid

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HIGHLIGHTS

- First evidence-based approach to look for non-prescription abuse of ADHD medication
- Usage data from nine weeks over two semesters on a college campus
- Trend found between increased amphetamine use and academically stressful periods

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) medication use is on the rise in the United States. The most widely used ADHD medications are the amphetamine-type compounds Adderall (mixed amphetamine salts) and Ritalin (methylphenidate). According to survey data ADHD medications are used as a study drug or "Smart Drug" by students without a prescription on college campuses. Survey data of non-prescribed drug use has limitations with accurate reporting and no empirical data of usage exists in the literature. This study looks for trends in the use of these drugs on a college campus among low-stress and high stress periods. The metabolites of these two drugs, amphetamine and ritalinic acid, are quantified in campus wastewater using solid phase extraction (SPE) and liquid chromatography–tandem mass spectrometry (LC–MS/MS). Trends show a possible increase in amphetamine levels during periods of high stress such as midterms, the last week of classes and finals week over levels from the baseline low stress weeks such as the first week of classes. Both semesters from the 2011–12 academic year were studied and the highest increase over baseline (760%) occurred during finals week of the second semester. Ritalinic acid levels gradually climbed first semester but had no obvious periodic trend second semester.

1. Introduction

The detection, measurement, and fate of pharmaceuticals and personal care products (PPCPs) in aquatic environments such as surface and wastewater have been the focus of rapidly increasing study over the past two decades (Daughton and Ternes, 1999; Daughton and Ruhoy, 2009). More recently the measure of illicit drugs and their metabolites has also gained focus in aquatic environments (Castiglioni et al., 2011; van Nuijs et al., 2011). Unlike pharmaceuticals whose quantities released into the environment can be better estimated with sales data, illicit drug consumption has, until recently, been estimated with surveys, interviews, medical records, and crime statistics. These general indicators have been shown to significantly under report usage (Zuccato et al., 2005). The vast majority of these PPCP and illicit drug studies have included sampling at wastewater treatment plants (WWTPs) involving measurements of either influent or effluent water or often both (Jones-Lepp et al., 2004; Castiglioni et al., 2006a,b; Batt et al., 2008; Gros et al., 2009; Thomas et al., 2012). The monitoring of illicit drugs and their metabolites can be studied to answer human toxicological questions about abuse levels for populations (Van Nuijs et al., 2011). Thus far mostly large populations such as cities and regions have been surveyed with these data. One study moved upstream from a WWTP and sampled wastewater from smaller populations at fitness centers taken directly at their building outlets before entering the municipal sewer system (Schröder et al., 2010). It has been hypothesized that moving sampling even further upstream could detect illegal drug use in Olympic villages; however, this application has been debated (Katsoyiannis and Jones, 2011; Harman et al., 2011). The debate comes because as this field of sewer epidemiology evolves, merely finding a metabolite of detectable concentration is not sufficient. Reliable and proper sampling and the associated sampling uncertainty

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have recently become as much of an issue as the detected drug levels (Ort et al., 2010a,b; Mathieu et al., 2011; van Nuijs et al., 2012; Castiglioni et al., 2013).

While many papers report levels of pharmaceuticals or illicit drugs in the environment, there has been less mention of pharmaceutical overuse and/or non-prescription use. One such non-prescription concern is the use of Attention Deficit Hyperactivity Disorder (ADHD) medication as a "Smart Drug" (Talbot, 2009). These medications come in two general forms, amphetamine containing salts and methylphenidate. The most popular amphetamine type drug is Adderall and to a lesser extent Vyvanse. Methylphenidate is best known as Ritalin but other formulations include Concerta and Focalin. Use of these compounds as "Smart Drugs" (and to a lesser extent for pleasure) has been documented with surveys in the toxicology and drug abuse literature as well as the popular US media (Babcock and Byrne, 2000; Kaye and Darke, 2012; Williams et al., 2004; Trudeau, 2009).

Adderall and Ritalin are used as study aids to enhance executive functions which allow students to focus for long periods of time (Farah et al., 2004). This neurocognitive enhancement has a potential benefit during academically stressful periods such as midterms or final exams. These drugs are reportedly easy to find for college students, either obtaining extra drugs from friends prescribed the drugs (5% of the entering class of 2011 nationwide were diagnosed with the disorder) or by falsely listing ADHD symptoms to a medical provider and obtaining a prescription (Johnson, 2011; Talbot, 2009). A study that used the 2001 College Alcohol Study survey of 119 American 4-year colleges and universities reported that approximately 6.9% of the students had non-medical use of either methylphenidate or amphetamine in their lifetime and 2.1% in the past month (McCabe et al., 2005). Survey data of college students found the prevalence rate of non-prescriptive Ritalin and/or Adderall use to range from 0% to 25% for the past year use and 0% to 13% for the past month use (Shillington et al., 2006). A 2012 review paper by Kaye reported that earlier studies had shown that Ritalin was the stimulant of choice on college campuses but the report continues by citing college students now misuse amphetamine salts at a higher rate and more than their non-student peers (7.9% versus 5.4%) with the trend reversed for methylphenidate (1.7% versus 2.7%) (Kaye and Darke, 2012).

To detect and quantify the use of these drugs in wastewater, the metabolites must be known. Adderall is excreted in the urine as 30–40% intact amphetamine (Adderall Prescribing Information) and Vyvanse (lisdexamfetamine dimesylate) is excreted as 42% amphetamine (Vyvanse Prescribing Information; Krishnan et al., 2008). Ritalin, Ritalin-SR (methylphenidate), Concerta and Focalin (dexmethylphenidate) are excreted as α-phenyl-2-piperidine acetic acid (ritalinic acid) at 86% in adults (we assume our population to be all adults 18+ years of age) (Concerta Prescribing Information, Focalin Prescribing Information, Ritalin Prescribing Information). Previous studies have found these compounds in the raw influent at WWTPs. Amphetamine levels at WWTPs in the US have been shown to range from 80 to 550 ng/L (Chiaia et al., 2008). The only reported study to measure ritalinic acid in wastewater reported "high variability" ranging from <50 to 270 ng/L in effluent samples from Germany (Letzel et al., 2010).

One small population has been sampled on a college campus for seven drugs of abuse (Panawennage et al., 2011). It was noted that the highest level of amphetamine in the wastewater came on a day during finals week but no subsequent analysis was made. To the authors' knowledge, this is the first comprehensive investigation to determine the non-prescription abuse of ADHD medication by sampling wastewater and using an evidence-based approach. This type of wastewater epidemiology requires the measurement of very specific sewer systems, upstream from WWTPs. The sampled population in the following study was made up of nearly 500, 18–22 year old men and women sampled from their dormitories at a residential college in the Pacific Northwest. Sampling occurred throughout the academic year and included periods of low and high academic stress. Although the number of individuals in the population was well known, the human marker creatinine was included in the analysis to account for variations in dilution among sampling periods and to estimate sampling uncertainty (Chiaia et al., 2008; Smith-Palmer, 2002; Barr et al., 2005).

2. Methods

2.1. Standards and reagents

(±)-Amphetamine, (±)-amphetamine-D6, (±)-methamphetamine-D9, ritalinic acid, and (±)-threo-ritalinic acid-D10 were purchased from Cerilliant (Round Rock, TX). Creatinine standard and reagent were purchased from EnzoLife Sciences (#ADI-907-030A Farmingdale, NY). SPE conditioning and mobile phase solvents used Milli-Q-purified water (Milford, MA) and HPLC grade ChromaSolv methanol and acetonitrile from Sigma-Aldrich (St. Louis, MO) and ACS grade formic acid, glacial acetic acid and hydrochloric acid were from EMD chemicals (Gibbstown, NJ). The purchased standards were diluted in 0.5% acetic acid.

2.2. Sample collection

Raw wastewater composite samples were collected for 72-hour periods at 1 hour intervals (125 mL each draw) with a Teledyne ISCO 6712 portable sampler (Lincoln, NE). An ISCO 2150 continuous wave Doppler flow meter logged instantaneous flow at 15 minute intervals and these data were used to integrate total volume over the 72 hour period. These devices were placed in a manhole in the sanitary system of the four dorms (Schematic shown in Fig. S1). This sewer line services these dorms and the sampling site is the last accessible point on campus before the sewer line connects to the municipal sewer. This sanitary line is not connected to surface water lines and is thus not susceptible to high flows from rain events. A subsequent fluorescein dye test was used to determine the length of individual toilet flushes from each of the dorms within this gravity fed system. Residence time between the point of entry and the sampler were 5–7 min and 7–30 min at typical high and low flow rates, respectively. The fluorescent dye persisted for 7–12 min at high flow rates and 14–30 min at low flow rates. Table 1 shows the dates, times, total flow volume, and time during the semester for each of the nine sampling events. Initially only four samples were planned each semester but by the spring semester, a fifth sample was included during the high stress of the last week of school. The composite samples were filtered and extracted onto SPE cartridges within 6 h of the last draw event.

Table 1
Sampling collection times and calculated total volume for each of the nine sampling periods.

Time in semester	Collection start	Collection end	Total flow volume (L)
First semester			
1st week	8/30/2011 6:00 AM	9/2/2011 5:00 AM	126,000
Midterms	10/12/2011 6:00 AM	10/15/2011 5:00 AM	313,000
Post-midterms	10/19/2011 6:00 AM	10/22/2011 5:00 AM	296,000
Finals week	12/13/2011 6:00 AM	12/16/2011 5:00 AM	223,000
Second semester			
1st week	1/17/2012 6:00 AM	1/20/2012 5:00 AM	121,000
Midterms	3/6/2012 6:00 AM	3/9/2012 5:00 AM	230,000
Post midterms	3/20/2012 6:00 AM	3/23/2012 5:00 AM	218,000
Last week	4/29/2012 9:00 AM	5/2/2012 8:00 AM	213,000
Finals week	5/7/2012 6:00 AM	5/10/2012 5:00 AM	221,000