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In-Stream Attenuation of Neuro-Active Pharmaceuticals and Their Metabolites

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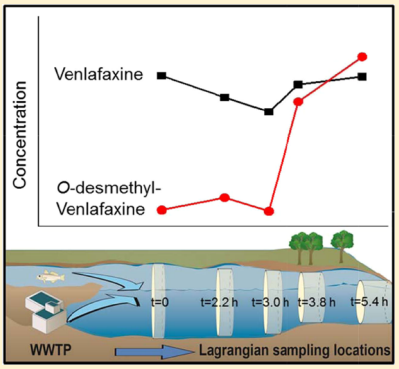
Supporting Information

ABSTRACT: In-stream attenuation was determined for 14 neuro-active pharmaceuticals and associated metabolites. Lagrangian sampling, which follows a parcel of water as it moves downstream, was used to link hydrological and chemical transformation processes. Wastewater loading of neuro-active compounds varied considerably over a span of several hours, and thus a sampling regime was used to verify that the Lagrangian parcel was being sampled and a mechanism was developed to correct measured concentrations if it was not. In-stream attenuation over the 5.4-km evaluated reach could be modeled as pseudo-first-order decay for 11 of the 14 evaluated neuro-active pharmaceutical compounds, illustrating the capacity of streams to reduce conveyance of neuro-active compounds downstream. Fluoxetine and *N*-desmethyl citalopram were the most rapidly attenuated compounds ($t_{1/2}$ = 3.6 ± 0.3 h, 4.0 ± 0.2 h, respectively). Lamotrigine, 10,11,-dihydro-10,11,-dihydroxy-carbamazepine, and carbamazepine were the most persistent ($t_{1/2}$ = 12 ± 2.0 h, 12 ± 2.6 h, 21 ± 4.5 h, respectively). Parent compounds (e.g., buproprion, carbamazepine, lamotrigine) generally were more persistent relative to their metabolites. Several compounds (citalopram, venlafaxine, *O*-desmethyl-venlafaxine) were not attenuated. It was postulated that the primary mechanism of removal for these compounds was interaction with bed sediments and stream biofilms, based on measured concentrations in stream biofilms and a column experiment using stream sediments.



INTRODUCTION

Maintaining the quality of water resources depends upon essential ecosystem services that include decomposition and detoxification of contaminants and reduced conveyance into downstream drinking water sources. Neuro-active pharmaceuticals (e.g., carbamazepine, fluoxetine, venlafaxine) are used by roughly 8% of the United States population[1] and are frequently detected in surface waters downstream from wastewater treatment plants.[2−5] The widespread detection of neuro-active compounds in drinking water supplies[6−8] implies multiple sources and long-range transport of these compounds, but because most of the earlier studies have focused upon detection and/or attenuation mechanisms in controlled laboratory settings, we have only limited understanding of the hydrologic and chemical transformation processes controlling in-stream attenuation.[9]

Laboratory studies have shown that the concentrations of neuro-active pharmaceuticals necessary to elicit a physiological response are generally much higher than what is observed in effluent-impacted streams.[9−12] However, some caution is warranted when interpreting these results as development of relevant biological endpoints is still in the early stages[13] and behavioral responses in aquatic organisms (i.e decreased predator avoidance[14]) have been documented at environmentally relevant exposure concentrations to neuro-active pharmaceuticals (e.g., bupropion, citalopram, fluoxetine, and venlafaxine).[15−17] Additionally, neuro-active pharmaceuticals have been shown to concentrate in liver and brain tissue of fish collected downstream from wastewater treatment plant effluents.[4,13,17,18] Predicting the risk that these compounds pose to aquatic ecosystems and water resources relies not only on increased understanding of potential biological effects but also on quantifying environmental fate and transport.

Concentrations of neuro-active pharmaceuticals and associated metabolites in surface waters are a function of wastewater loading, physical (dilution, advection, and dispersion), and chemical processes (sorption, biodegradation, photolysis), that can alter environmental concentrations as they are transported downstream.[19] The majority of research on possible attenuation processes controlling the fate of neuro-active pharmaceutical compounds has used controlled laboratory studies.[20−28] Although these studies help explain the observed persistence and widespread detection in surface waters, they are difficult to translate into stream attenuation rates.[29] To our knowledge, there have been very few studies that have evaluated in-stream attenuation of neuro-active pharmaceuticals. A study on the Grand River in Ontario, Canada, showed concentrations

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decreased downstream from effluent outfalls,[30] and studies conducted in 2005 and 2006 on Fourmile Creek, Iowa, and Boulder Creek, Colorado,[4,31] determined that the loading of several of neuro-active compounds (bupropion, fluoxetine, norfluoxetine, venlafaxine) decreased downstream from the effluent outfall. Quantification of in-stream attenuation of neuro-active compounds was limited to carbamazepine in all of these studies.

Wastewater discharge fluctuates in response to water use in the collection system, causing contaminant loading to receiving waters to vary substantially over short time periods.[32] Therefore, to compare downstream concentrations and quantify in-stream attenuation, sampling must be performed to account for variable wastewater loading and stream discharge. In this study, a tracer study and Lagrangian sampling, which follows the same parcel of water as it is transported downstream, were used to link hydrological and chemical transformation processes. In-stream attenuation was quantitatively determined for 14 neuro-active compounds and associated metabolites: bupropion, erythro-hydrobupropion, threo-hydrobupropion, carbamazepine, 10-hydroxy-carbamazepine (10-OH-CBZ), 10,11,-dihydro-10,11,-dihydroxy-carbamazepine (DiOH-CBZ), citalopram, *N*-desmethyl-citalopram (DMCit), fluoxetine, lamotrigine, 2-*N*-glucoronide-lamotrigine (Gluc-LMG), venlafaxine, and *O*-desmethyl-venlafaxine (DMV) in a stream downstream from a wastewater treatment plant. Additionally, results from a column experiment were used to evaluate the relative importance of bed sediment and associated biofilm interactions to bolster interpretation of the results from the tracer study. Sampling of effluent from the same wastewater plant over a two-year period was also done to assess inherent variability in neuro-active pharmaceutical concentrations being discharged into surface water.

METHODS

Site Description and Tracer Study. A 5.4-km reach of Boulder Creek downstream from the City of Boulder (COB) wastewater treatment plant (WWTP) in Boulder, Colorado, was selected as the study site as it has been well characterized in previous studies.[33,34] Seven locations (Figure SI1, Supporting Information) were sampled during the tracer study: (1) Boulder Creek 50 m upstream from the WWTP effluent outfall (BC-US), (2) WWTP effluent outfall (EFF), (3) Boulder Creek at White Rocks (BC1, 2.29 km downstream), (4) Boulder Creek at Leggett Ditch (BC2, 3.28 km downstream), (5) Boulder Creek above Dry Creek (BC3, 4.05 km downstream), (5) Dry Creek, and (7) Boulder Creek at 95th Street (BC4, 5.43 km downstream).

A preliminary tracer test was conducted the day before the sampling to estimate hydrologic transit times using fluorescent dye (Rhodamine WT). A comprehensive tracer study and sampling was performed on May 4, 2011, at 9:00 h using 4.78 kg of the conservative tracer sodium bromide in 20 L of deionized water. The tracer mixture was introduced into the effluent outfall over a 1 min period. Stream discharge measurements were made according to US Geological Survey standard protocols.

Sample Collection. Grab water samples were collected from the wastewater effluent over a two-year period from November 2010–April 2012 (Table SI1, Supporting Information) and analyzed for neuro-active pharmaceuticals. Stream biofilm samples were collected upstream and downstream from the effluent outfall (April 2012) using methods outlined by Barbour.[35] During the tracer study (May 4, 2011), bromide, chloride, and gadolinium concentrations were determined in grab samples from Boulder Creek collected mid-channel using autosamplers (Teledyne Isco model 6712, Lincoln, NE) at 8–10 min intervals. Lagrangian sampling (composite depth- and width-integrated, 9–13 equal width verticals collecting a total of 6–7 L) was performed to determine neuro-active pharmaceuticals concentrations at each location over a time interval (1.0–2.25 h) bracketing the estimated hydraulic transit time of the bromide slug (Figure 1). Additionally, bromide,

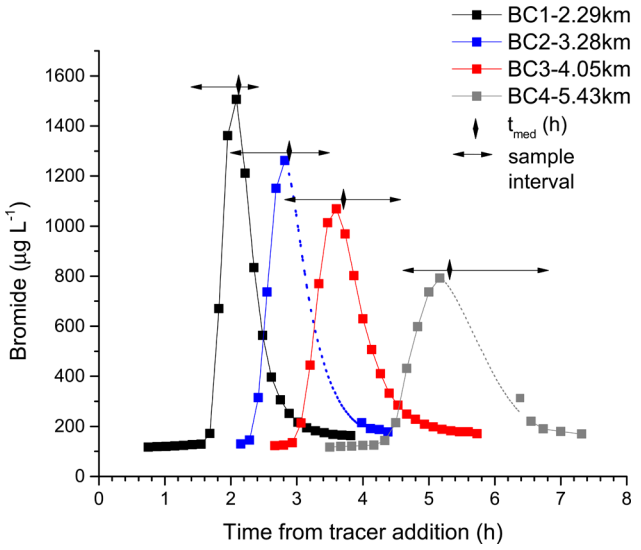

Figure 1. Bromide tracer concentrations, t_{med} (defined as the time necessary for 50% of the mass of bromide to pass the monitoring locations), and relation to time interval over which composite samples were collected; dotted lines estimated due to automatic sampler error.

chloride, gadolinium, and neuro-active pharmaceutical concentrations were determined in a composite depth- and width-integrated sample collected from Boulder Creek upstream from the effluent outfall (collected at 8:30 h), effluent grab samples (collected at 5:00, 9:00, and 13:00 h) and a grab sample from Dry Creek (collected at 12.50). Median travel times (t_{med}) were defined as the time necessary for 50% of the mass of bromide to pass the monitoring locations.[36] Water samples for inorganic element analysis were filtered through 0.45 μm membranes and collected in acid-rinsed polyethylene bottles. Water samples for the neuro-active pharmaceutical compounds were collected in cleaned amber glass bottles, filtered through 0.7 μm glass fiber filters, and stored at 4 °C prior to extraction. Samples for the tracer and column studies were processed and analyzed 1 d later; holding times for other samples were less than 7 d. Stream biofilm samples were frozen (−20 °C) and analyzed 25 d after collection.

Analytical Procedures. Chloride and boron were determined by inductively coupled atomic emission spectrometry; other inorganic elements in stream samples were determined by inductively coupled plasma-mass spectrometry.[37,38] Bromide concentrations for the column study experiment were measured by ion chromatography (Dionex DX500, Sunnyvale, CA).

The neuro-active compounds (bupropion, hydroxy-bupropion, carbamazepine, fluoxetine, lamotrigine, and venlafaxine) were initially targeted using high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) quantified

Table 1. In-Stream Attenuation Parameters and Results of Column Experiment

	tracer study			column experiment	
compound	k (h^{-1})[a]	$t_{1/2}$ (h)[b]	r^2 (p value)[c]	maximum C/C_0[d]	R_f[e]
bupropion	0.12 ± 0.087	6.0 ± 0.3	0.98 (6×10^{-5})	0.55	15
erythro-hydrobupropion	0.087 ± 0.019	7.9 ± 1.4	0.81 (0.009)	1.01	5.5
threo-hydrobupropion	0.097 ± 0.031	7.1 ± 1.7	0.64 (0.03)	0.61	10
carbamazepine	0.033 ± 0.009	21.0 ± 4.5	0.71 (0.02)	0.94	2.5
10-hydroxy-carbamazepine	0.074 ± 0.005	9.3 ± 0.6	0.98 (1×10^{-4})	1.00	1.4
DiOH-CBZ[f]	0.056 ± 0.015	12.4 ± 2.6	0.76 (0.03)	0.70	3.1
oxcarbazepine	0.106 ± 0.010	6.5 ± 0.6	0.96 (5×10^{-4})	0.75	2.4
citalopram	**-0.08 ± −0.02**	**NA**	**0.62(0.04)**	no breakthrough	>20
N-desmethyl citalopram	0.17 ± 0.008	4.0 ± 0.2	0.99 (3×10^{-5})	no breakthrough	>20
fluoxetine	0.19 ± 0.019	3.6 ± 0.3	0.95 (6×10^{-4})	no breakthrough	>20
lamotrigine	0.059 ± 0.012	11.7 ± 2.0	0.82 (0.008)	0.59	15
2-*N*-glucuronide lamotrigine	0.12 ± 0.024	5.9 ± 1.0	0.82 (0.008)	0.52	16
venlafaxine	**NA**	**NA**	**0.17(0.22)**	0.09	>20
***O*-desmethyl venlafaxine**	**-0.21 ± −0.05**	**NA**	**0.75(0.02)**	0.14	>20

[a]In-stream attenuation coefficient ± standard error. [b]In-stream half-life ± standard error. [c]Correlation coefficient and p value relative to linear fit of first-order decay process. [d]Maximum measured concentration after passing through the column divided by initial effluent concentration. [e]R_f = Retardation factor computed as the ratio between target compound velocity (V/V_0) relative to bromide (based on the center of mass of the breakthrough curves). [f]DiOH-CBZ = 10,11,dihydro-10,11,dihydroxy-carbamazepine, first-order decay modeled without initial theoretical mixing concentration; attenuation not observed for compounds in bold font; NA = not applicable.

by a seven point calibration curve using authentic standards and the internal standard d_{10}-carbamazepine.[39] Briefly, water samples were spiked with the labeled internal standard d_{10}-carbamazepine (Cambridge Isotope Laboratories, Andover, MA), concentrated using solid-phase extraction (C-18 SPE), neuro-active compounds eluted with methanol, evaporated to 0.5 mL, and injected (20 μL) onto a high performance liquid chromatography system (HPLC). The stream biofilm was homogenized, a subsample spiked with the labeled internal standard d_{10}-carbamazepine, extraction solvent added (4:1 methanol:water mixture containing 0.1% formic acid), and the entire mixture sonicated for 20 min, centrifuged at 3500 rpm for 5 min, and the eluent applied to the SPE column and eluted in a similar manner as the water samples. Environmental mass spectrometry traditionally relies on the use of known standards for targeted analyses, but information on which compounds and metabolites warrant further investigation is often limited. To circumvent this limitation and expand the number of neuro-active compounds and metabolites evaluated, extracts previously analyzed by LC/MS/MS were subsequently injected (within 1 d) onto an HPLC system connected to a time-of-flight mass (TOF) spectrometer model 6520 Agilent (Agilent Technologies, Santa Clara, CA). The following neuro-active compounds and metabolites were present at concentrations similar to the initially targeted compounds: erythro-bupropion, threo-hydrobupropion, 10,11,-dihydro-10,11,-dihydroxycarbamazepine (DiOH-CBZ), 10-hydroxy-carbamazepine (10-OH-CBZ), citalopram, *N*-desmethylcitalapram (DMCit), 2-*N*-glucuronide-lamotrigine (Gluc-LMG), oxcarbazepine, and *O*-desmethyl-venlafaxine (DMV). Quantification of these compounds was performed by evaluation of the accurate mass (±0.0030 m/z) of prominent peaks, diagnostic ions (Figure S12), extracted from the full scan LC-TOF-MS chromatogram, and fragment ions indicative of neuro-active metabolites using previously described techniques[39,40] and described in detail in the Supporting Information (SI). Matrix effects on ion response will be similar between water samples due to Lagrangian sampling. Following identification of possible metabolites, authentic standards were used to verify retention times and mass spectra. The method detection limit was defined as the lowest concentration of the chemical that yielded minimum ion signal-to-noise ratios of 3:1 for both the quantitation and confirmatory ions. Spike and recovery studies were performed on water (n = 2, concentration equivalent to 40 ng L^{-1}) and biofilm matrices (n = 1, concentration equivalent to 7800 ng kg^{-1}). Recoveries ranged from 71−108%, mean 96% in water, and 46−170%, mean 92%, fluoxetine recovery <2% in biofilm. None of the target compounds were detected in sample blanks. Method reproducibility for neuro-active compounds determined by LC/MS/MS (bupropion, carbamazepine, fluoxetine, lamotrigine, and venlafaxine) was evaluated by analyses of field replicates (two sets of replicate water samples), and an average relative percent difference between replicate samples (avgRPD) computed (3%, Table SI1, Supporting Information). Method reproducibility for compounds analyzed by LC-TOF-MS (erythro-hydrobuprion, threo-hydrobupropion, 10-OH-CBZ, oxcarbazepine, citalopram, DMCit, Gluc-LMG, DMV) was evaluated by analyses of field replicate samples (one set of replicate water samples, avgRPD was 16%, Table SI1, Supporting Information). Method reproducibility for the biofilm analyses was evaluated by analyses of field replicate samples (one set of replicate biofilm samples, avgRPD for detected compounds was 6%).

Column Studies. To explore the potential attenuation via sorption and/or biodegradation due to interactions with stream bed surfaces, a flow-through column study was performed. Bed sediment material collected from Boulder Creek upstream from the WWTP effluent on November 1, 2011, was wet sieved so that the particle size ranged from 0.25 to 5.6 mm and was subsequently added to a stainless steel column (5 cm diameter ×14 cm length). This was then pre-treated with Boulder Creek water collected upstream from the WWTP effluent by passing the water in an up-through mode for 2 h to remove air bubbles, and the column was sealed for ∼18 h. The following day WWTP effluent containing neuro-active compounds (also collected at 1300 h, November 1, 2011) and sodium bromide (concentration 1 mg L^{-1}) was applied to the base of the column at a flow rate of 1.9 ± 0.056 mL min^{-1}; samples were

collected at 75 mL intervals (approximate column pore volume). The column experiment was conducted at ambient room temperature (water and air temperature ~21 °C). The column influent pH was 7.2 ± 0.2, and effluent pH was 7.2 ± 0.3. Dissolved oxygen concentrations were not measured. The organic matter fraction of the bed sediment was determined by loss on ignition (4 h at 450 °C) to be f_{om} = 0.0029 (n = 3). The bulk density was 1.52 g cm^{-3}, the bed sediment density was 2.51 g cm^{-3}, the volumetric water content was 0.39 (dimensionless), and the column pore volume was 84 mL, determined by the mass of water lost from material in packed saturated columns emptied onto an open pan and dried (T = 105 °C) for 2 wks (n = 3).

Attenuation of the target compounds was evaluated by comparing concentrations going in and coming out of the column (C/C_0) after seven pore volumes had passed through the column (time period of 5.3 h). A retardation factor (R_f) was computed as the ratio between target compound velocity (V/V_0) relative to bromide based on the center of mass for the breakthrough curves (Table 1, Figure SI4, Supporting Information).

RESULTS AND DISCUSSION

Neuro-active pharmaceuticals and associated metabolite concentrations were well above the method detection limits (<5 to <100 ng L^{-1}) in both wastewater effluent and downstream samples. Lamotrigine was identified at the detection limit in samples collected upstream of the effluent outfall; all other neuro-active compounds were below the detection limits in upstream samples (Table SI1, Supporting Information). Lamotrigine (1760−5700 ng L^{-1}), its primary metabolite Gluc-LMG (200−35000 ng L^{-1}), and 10-OH-CBZ (640−4400 ng L^{-1}) were consistently found at the highest concentrations. Concentrations of neuro-active pharmaceuticals and associated metabolites in the City of Boulder's wastewater effluent varied in samples collected at different times of the year and over the course of the day during the tracer study (Table SI1, Supporting Information). The observed range of concentrations greatly exceeded analytical variability (Table SI1, Supporting Information). For example, citalopram, DMCit, and DMV concentrations in the effluent varied considerably during the tracer study (May 4, 2011; samples collected at 5:00, 9:00, and 13:00), and the percentage change between the maximum and minimum concentration was 480%, 55%, 390%, respectively. Daily and seasonal effects on wastewater volume influence concentrations, and metabolite to parent ratios were used to evaluate changes during different samplings. As shown in Figure 2, metabolite to parent compound ratios were variable, both at different times of the year and in effluent samples collected the day of the tracer study (labeled 5AM, 9AM, and 1PM in Figure 2). In general, metabolites were found at concentrations that exceeded or were comparable to concentrations of the parent compounds. Seasonal differences may be related to changes in pharmaceutical use and the influence of seasonal temperature on metabolism and biodegradation in the wastewater plant. Hourly differences related to dose/time changes in the profile of excreted pharmaceuticals[41,42] may also play a role in the shifting metabolite/parent compound ratios. The primary purpose of this study was not to evaluate seasonal or daily variation in neuro-active compound concentrations, but results are provided to emphasize the importance of a carefully designed sampling regime to account for this variability. The limited

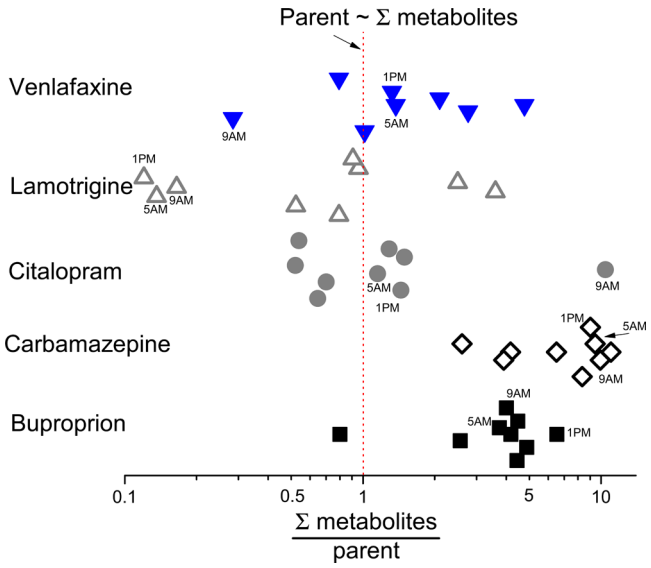

Figure 2. Ratio of metabolites to parent compound in City of Boulder wastewater effluent for neuro-active pharmaceuticals based on samples collected from 2010 to 2012 (n = 8); 5AM, 9AM, and 1PM samples all collected May 4, 2011.

stream biofilm sampling showed that bupropion (4200 ng kg^{-1}), carbamazepine (590 ng kg^{-1}), DiOH-CBZ (3100 ng kg^{-1}), 10-OH-CBZ (1800 ng kg^{-1}), oxcarbazepine (630 ng kg^{-1}), fluoxetine (290 ng kg^{-1}), lamotrigine (10000 ng kg^{-1}), venlafaxine (3800 ng kg^{-1}), and DMV (8200 ng kg^{-1}) were detected above 100 ng kg^{-1} in the sample collected downstream from the WWTP (Table SI1, Supporting Information). Neuro-active compounds were not detected in the upstream biofilm sample.

Tracer Study. Wastewater effluent discharge was observed to change on a regular diel cycle corresponding to water-use activities of the community;[43] in a 4 h time period before and after addition of the tracer mixture, effluent discharge varied by 300%. Over this same time period, stream discharge varied by 3.2%.[44] The City of Lafayette removed 0.057 m^3 s^{-1} from just above the effluent outfall during the tracer study. The amount of water being diverted from or discharging into Boulder Creek from two irrigation ditches was negligible, and precipitation did not occur during the tracer study. Dry Creek contributed 5% of the flow to Boulder Creek. At the time of the introduction of the tracer mixture, effluent discharge was 0.60 m^3 s^{-1}, and upstream of the effluent discharge streamflow was 0.47 m^{3}s^{-1}, and thus at the theoretical downstream mixing point effluent discharge represented 56% of the total discharge in Boulder Creek. Stream discharge measurements at the sampling locations BC1, BC2, and BC3 were consistent with expected discharge obtained from summing effluent and upstream discharge less the water removed by the City of Lafayette and indicated no substantive losses or gains from the mixing point to BC3 (Table SI1, Supporting Information). The thalweg depth averaged 0.23 m, and stream velocity averaged 0.29 m s^{-1}. The discharge measured at BC4 was 24% lower, although this was likely due to sampling errors associated with making a discharge measurement at very low velocities (<0.1 m/s) caused by pooling behind a water diversion structure located 150 m downstream. There were no observations of gains or losses from water supply ditches or tributaries during the day of the tracer study. Although Dry Creek contributed an

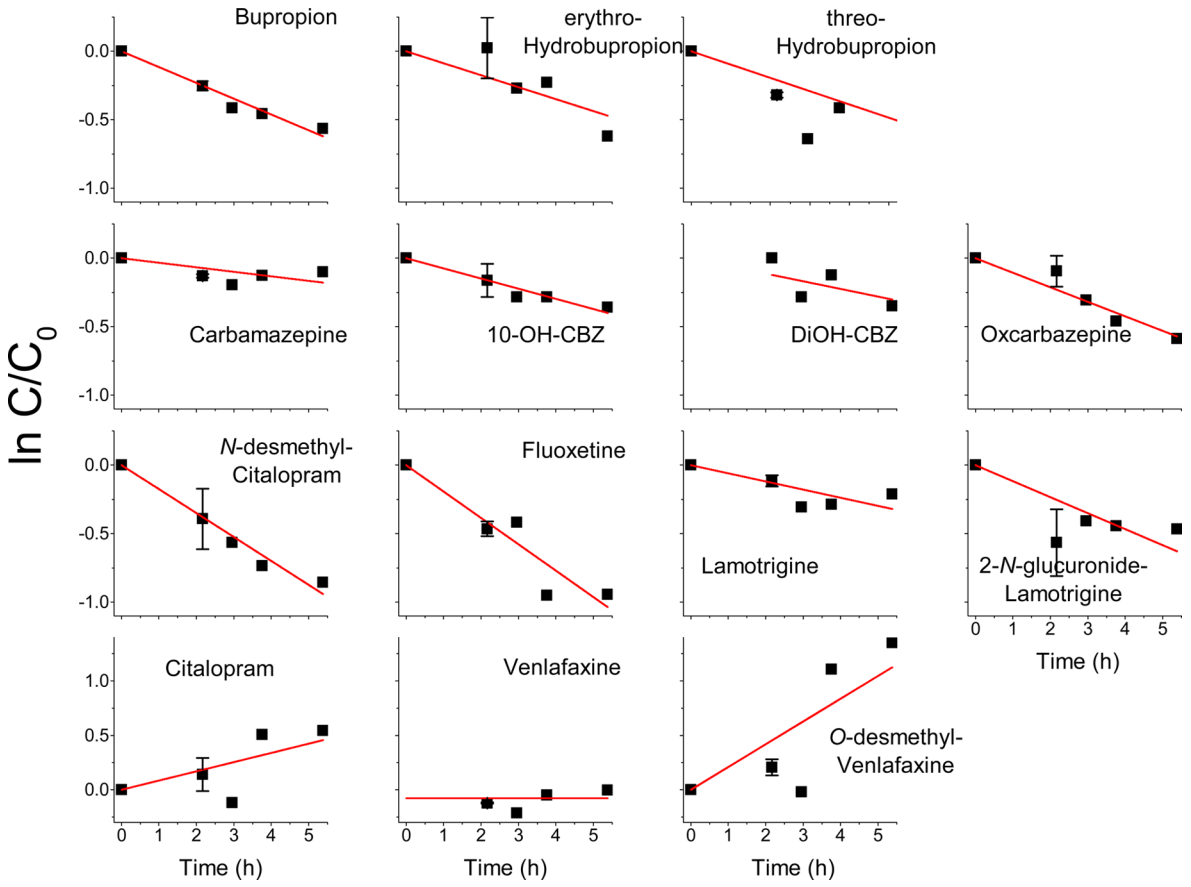

Figure 3. In-stream attenuation of target compounds modeled by linear first-order processes; ln C/C_0 corresponds to the concentration of the Lagrangian parcel normalized to the concentration at the theoretical mixing point. Error bars representing standard error for parent compounds based on triplicate analyses at BC2 not visible at this scale. Error bars for metabolites and citalopram correspond to analytical variability relative to concentration at BC2.

additional 0.037 $m^3\ s^{-1}$ of flow, neuro-active compounds were not detected in this sample. On the basis of analyses of the nonreactive inorganic constituents chlorine and gadolinium (data not shown), there was no evidence of additional inflow from groundwater, water supply ditches, or tributaries. Mass recovery of the bromide tracer determined by integrating the area underneath the tracer curve and multiplying this value by the idealized discharge at the theoretical mixing site corrected for background bromide concentrations, was as follows: BC1 (92.7%), BC2 (95.6%), BC3 (94.9%), and BC4 (92.2%). Transient storage in the studied reach was evaluated using bromide data and the mathematical model one-dimensional transport with inflow and storage (OTIS).[45] The nonlinear least-squares optimization by the model provided the following parameters: dispersion (D), 2.43 ± 0.262 $m^2\ s^{-1}$; cross-sectional area (A), 3.10 ± 0.206 m^2; transient storage zone cross-sectional area (A_s), 0.298 ± 0.192 m^2; and storage zone exchange coefficient (α) $1.0 \times 10^{-4} \pm 1.5 \times 10^{-5}\ s^{-1}$ (all reported as the value ±2 standard deviations). Using these OTIS-defined parameters, the fraction of median travel time (F_{med}) due to transient storage was 0.036, defined by the following equation[36]

$$F_{\text{med}} \cong (1 - e^{-L(\alpha/u)})\left(\frac{A_s}{A + A_s}\right) \quad (1)$$

where L is the reach length (m) and u is the average stream velocity ($m\ s^{-1}$). These results indicate that only a minimal amount of transient storage occurred at the time of the study.

In order to quantitatively evaluate in-stream attenuation of the targeted compounds, the same parcel of water should be sampled as it moves downstream (Lagrangian sampling). As shown in Figure 1, advection and dispersion will cause this parcel to disperse over time, and consequently, composite samples were collected over a time period varying from 1.00 to 2.25 h. In contrast, automatic sampler data represent discrete points in time. As indicated by the automatic sampler data (data not shown), concentrations of the conservative elements chloride and gadolinium at each downstream sampling location changed over time due to the influence of variable effluent loading to the stream. Consequently, automatic sample concentrations of chloride and gadolinium at the each downstream sampling location were compared to their concentrations at the theoretical mixing site and used to determine whether the "center time" of the composite sample was collected ahead or behind the Lagrangian parcel (as determined by the bromide tracer; Figure 1 and Table SI1, Supporting Information). Removal from the aqueous phase due to bed−sediment interactions will reduce concentrations of the target compounds, but over the time frame evaluated (<6 h), it will not result in measurable differences between travel times of the conservative tracers (bromide, chloride, and gadolinium) and the targeted compounds, as demonstrated for pharmaceuticals attenuated by sorption.[46]

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To correct for biases induced by not sampling the Lagrangian parcel, concentrations of nonconservative elements (e.g., neuro-active pharmaceuticals) measured in the composite samples were modified as follows. The load at a theoretical mixing zone (W_{mix}) downstream from the effluent outfall is equivalent to the sum of the effluent load (effluent discharge, Q_{Eff} × effluent concentration, C_{Eff}) and the upstream load (upstream discharge, less the flow diverted to the City of Lafayette water supply ditch, Q_{US}, × C_{US}),

$$W_{mix} = Q_{Eff}C_{Eff} + Q_{US}C_{US} \quad (2)$$

Upstream discharge during the tracer study varied by less than ±3.2%[44] and was assumed to be constant. Because neuro-active compounds were not detected at the upstream sampling location (C_{US} ~0), the concentration of the targeted neuro-active compounds at the mixing zone (C_{mix}) is defined

$$C_{mix} = \frac{Q_{Eff}C_{Eff}}{Q_{US} + Q_{Eff}} = \frac{Q_{Eff}C_{Eff}}{Q_{mix}} \quad (3)$$

The time difference between the composite sample and the Lagrangian parcel at each sampling location can be assumed to be offset by an equivalent time at the effluent channel. Therefore, the load at the theoretical mixing point coinciding with the sampled composite parcel (W^*_{mix}) is defined similarly as $W^*_{mix} = Q^*_{Eff}C^*_{Eff}$; C^*_{Eff} estimated by linear interpolation between the three measured values (5:00, 9:00, and 13:00). At each downstream sampling location, the load (W_i) is dependent upon in-stream reactions, approximated as being first-order decay processes occurring over the hydraulic travel time interval from the mixing zone to the sampled location (t), such that

$$W_i = W_{mix}e^{-kt} \quad (4)$$

and the fractional difference in loads as a result of being off the Langrangian parcel can be defined as

$$\frac{W_i}{W^*_i} = \frac{W_{mix}e^{-kt}}{W^*_{mix}e^{-kt}} \approx \frac{W_{mix}}{W^*_{mix}} \quad (5)$$

approximated by assuming that the hydraulic travel times for the sampled parcel and the idealized parcel are similar. The expected load of the Lagrangian parcel (W_i) relative to the measured load of the composite sample (W^*_i) is as follows

$$\frac{W_i}{W^*_i} = \frac{C_iQ_i}{C^*_iQ^*_i} \sim \frac{W_{mix}}{W^*_{mix}} \quad (6)$$

which can be solved for the Langrangian concentrations (C_i) relative to the measured concentration (C^*_i), the fractional difference in loads, and assuming that Q_i and Q^*_i are equal to Q_{mix} and Q^*_{mix} if there are negligible sources between the mixing zone and the sample site (as observed in this study)

$$C_i = C^*_i\frac{W_{mix}}{W^*_{mix}}\frac{Q^*_{mix}}{Q_{mix}} \quad (7)$$

Measured concentrations (Table SI1, Supporting Information) were modified as discussed above to give the ideal Lagrangian parcel concentrations at each of the downstream sample locations. Figure 3 plots time versus the natural logarithm of normalized Lagrangian concentrations (ln C/C_0). The slope of the line represents the pseudo-first-order in-stream attenuation rate for each compound, and a corresponding in-stream half-life ($t_{1/2}$) was determined. Results are presented in Table 1 as the values ± standard error. Figure 3 shows that the majority of compounds were attenuated over the 5.4-km stream reach (corresponding to a negative slope), although citalopram, venlafaxine, DMV are exceptions. For compounds in which in-stream attenuation could be reasonably modeled as a first-order decay process ($r^2 > 0.7$, $p < 0.05$), in-stream attenuation rates were ranked as follows: fluoxetine > DMCit > Gluc-LMG ~ bupropion ~ oxcarbazepine > erythro-hydrobupropion > 10-OH-CBZ > lamotrigine ~ DiOH-CBZ ≫ carbamazepine. In-stream attenuations of threo-hydrobupropion and venlafaxine were not well predicted by first-order decay ($r^2 < 0.7$). Citalopram, venflaxine, and DMV were not attenuated from the water column over the 5.4-km evaluated reach, indicating environmental processes controlling the fate of these compounds differ from the other evaluated neuro-active compounds.

In-stream attenuation rates determined in Boulder Creek provide environmentally relevant information for evaluating mechanisms controlling the fate of neuro-active pharmaceuticals in different systems. Additionally, these in-stream attenuation rates can be used to predict expected concentrations at downstream locations and inform future laboratory studies. As discussed earlier, prior laboratory studies evaluating environmental fate of neuro-active compounds have focused primarily upon fluoxetine, carbamazepine, and venlafaxine and their metabolites, whereas considerably less information is available on the other neuro-active compounds evaluated in this study. For those compounds in which information is available, the relative rates of attenuation determined in this study are consistent with environmental detections and/or attenuation mechanisms in controlled laboratory studies. For example, fluoxetine ($t_{1/2}$ 3.6 ± 0.3 h) was the most rapidly attenuated neuro-active compound in this study, and laboratory studies have shown that it is rapidly removed by sorption, although relatively resistant to photolysis and biodegradation.[22,23] Sorption onto biosolids in a wastewater treatment plant was a primary mechanism of removal for fluoxetine, whereas carbamazepine, venlafaxine, and DMV were found to remain primarily in the aqueous phase.[47] In-stream attenuation of venlafaxine and DMV was not observed in this study, whereas in laboratory studies other researchers demonstrated biodegradation and photolysis of venlafaxine and DMV, although half-lives varied considerably between different studies; biodegradation half-lives ranged from 3.4[28] to >100 d[27] and indirect photolysis half-lives ranged from 2.4[27] to 137 d.[28] These divergent results highlight the importance of in situ studies to provide environmentally relevant information for comparisons with laboratory results. Carbamazepine is frequently detected in surface waters[2,4,30] and has been shown to resist photolysis and biodegradation in controlled laboratory studies,[20,21,25,26] and thus it is not surprising that its in-stream half-life ($t_{1/2}$ 21 ± 4.5 h) was the highest relative to the other neuro-active pharmaceuticals evaluated. The carbamazepine half-life from this study was consistent with a previous study on Boulder Creek[31] conducted in 2005 that showed statistically insignificant removal. Environmental persistence of carbamazepine from the aqueous phase was evaluated in water:sediment mesocosms, and the time required for 50% reduction in aqueous phase ranged from 47 to 82 d.[20,21] In this study, limited sampling showed that bupropion, carbamazepine, DiOH-CBZ, 10-OH-CBZ, fluoxetine, lamotrigine, venlafaxine, and DMV sequestered into the stream biofilm. Stream biofilms have been shown to effectively remove

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17β-estradiol (K_{ow} = $10^{3.94}$; pK_a = 10.7)[48,49] and 4-nonylphenol (K_{ow} = $10^{4.48}$; pK_a = 10.7)[50,51] from a stream, primarily due to hydrophobic partition.[52] Additionally, stream biofilms were believed to control sorption of antibiotics.[53] In summary, available data on attenuation mechanisms indicate limited photolysis and biodegradation of neuro-active pharmaceuticals, and thus it is postulated that interactions with bed sediments and stream biofilm play an important role their fate and transport in surface waters.

Column Experiment. To investigate the relative potential for attenuation of neuro-active pharmaceuticals due to interactions with the bed sediment and associated biofilm, a column experiment was performed in which Boulder WWTP effluent was passed through Boulder Creek unsterilized bed sediment material (Figure SI3, Supporting Information). Relative attenuation of the targeted compounds was evaluated by comparing maximum C/C_0 values and retardation factors (R_f) relative to sodium bromide (Table 1). The point of this limited experiment was to evaluate if the order of removal for the targeted compounds determined from the column study (indicative of stream biofilm and bed sediment interactions) was consistent with measured in-stream attenuation determined from the tracer study. Fluoxetine, DMCit, citalaprom, venlafaxine, and DMV were substantially removed in the column (C/C_0 < 0.2, R_f > 20); lamotrigine, Gluc-LMG, bupropion, and threo-hydrobuprion were attenuated in the column ($C/C_0 \leq 0.6$, $R_f \geq 10$); carbamezepine, DiOH-CBZ, 10-OH-CBZ, oxcarbazepine, and erythro-hydro-bupropion were partially attenuated by the column (C/C_0 > 0.6, R_f < 6). For most of the evaluated compounds, the results of the column experiment were consistent with observed in-stream attenuation. For example, carbamazepine was minimally attenuated by interactions with bed sediments in the column experiment and was the most persistent compound in the tracer study. No breakthrough was observed for fluoxetine and DMCit in the column experiment, and these compounds had the highest rates of in-stream attenuation. However, citalopram, venlafaxine, and DMV were almost completely removed in the column experiment, yet their concentrations were not attenuated in the tracer study.

Chemical transformation between venlafaxine and its metabolite DMV does not explain their observed concentration increases in the aqueous phase (nearly 300% for DMV from the theoretical mixing point to the sampling location at BC4; Figure SI3, Supporting Information). Glucuronide metabolites of both venlafaxine and DMV were looked for using LC-TOF-MS and were not identified at concentrations above detection limits. Substantial variations in effluent concentrations were observed for DMV the day of the tracer study (5:00, 332 ng L^{-1}; 9:00, 67 ng L^{-1}; 13:00, 258 ng L^{-1}). To see if advection and dispersion could account for the observed increases in the concentrations of DMV, the impact of variable effluent concentrations at each downstream sampling site was modeled (stream characteristics determined by OTIS as described earlier, assuming no in-stream decay). Results from this modeling exercise indicated that advection and dispersion moderately increase concentrations of DMV in the Lagrangian parcel moving downstream (up to 125%), but clearly cannot explain the observed 300% increase. Therefore, some other mechanism is controlling concentrations of DMV as the Lagrangian parcel is transported downstream. Possible in-stream processes that could be responsible for observed production include desorption from bed sediment and associated biofilms and desorption from suspended particulate matter. Suspended sediment concentrations were less than 5 mg L^{-1} based on analyses of dissolved and particulate inorganic elements. During the tracer study, diel cycles were observed (pH increased from 7.5 to 8.5, temperature increased from 7 to 13 °C, measured by in-stream data loggers) and increases in UV light and dissolved oxygen could also have implications on sorption and desorption of antidepressants from particulates, stream biofilms, and bed surfaces. Concentrations of the targeted compounds in an effluent sample 5 d after collection (Table SI1, Supporting Information, maintained at ambient temperature ~21 °C) were ±14% of their initial concentration, and thus biological activity in the water column is not believed to be a major attenuation and/or transformation factor.

Sorption of organic compounds onto solid matrices is controlled by multiple interactions that include hydrophobic partitions into organic matter, ionic exchange, and interactions with specific chemical moieties. Because many environmental contaminants sorb to organic matter, the hydrophobic partition and octanol−water partition coefficient (K_{ow}) of compounds have been successfully applied to predict sorptive removal in environmental systems. For ionizable compounds, the use of the octanol−water distribution coefficient (D_{ow}) is used to predict hydrophobic partition of the neutral species at a specified pH. However, this parameter cannot be used to predict sorption by ionic exchange, which may be important for organic cations such as the neuro-active pharmaceuticals investigated in this study. Laboratory studies investigating fluoxetine sorption to soils and sediments indicated that K_{ow} and D_{ow}[9] had only limited utility in predicting sorption behavior,[9] whereas pH played an important role in controlling sorption.[23] Fluoxetine (pK_a = 9.5[54]), citalopram (pK_a = 9.5[55]), venlafaxine (pK_a = 9.4[56]), DMV (pK_a = 8.34[57]), and bupropion (pK_a = 7.9[58]) are weak bases and predominantly positively charged at circumneutral pH values, and pH changes will influence electrostatic interactions with bed sediments, biofilms, and suspended sediments. For example, as pH changed during the course of the tracer study (7.5−8.5), the percentage of venlafaxine and DMV existing as the organic cation would decrease from 99% to 89% and 96% to 41%, respectively. In contrast, lamotrigine (pK_a = 5.7[59]) exists primarily as an uncharged molecule at circumneutral pH levels. Carbamazepine is not charged at environmentally relevant pH values. Results from the column experiment (pH of the column effluent was 7.2 ± 0.3) indicate a relation between the column breakthrough of the antidepressant compounds and their pK_a values (r^2 = 0.81, p = 0.01); compounds with higher pK_a values (existing primarily as the cationic species) were more effectively removed by the sediment in the columns (Figure 4). In contrast, the correlation between log K_{ow} (estimated using Virtual Computation Chemistry Laboratory[60]) and column breakthrough was limited (Figure 4). The importance of electrostatic interactions with organic matter for organic cations has been demonstrated in sediments and soil organic matter.[24,61,62] In another study, metroprolol, a pharmaceutical beta-blocker (pK_a = 9.7),[63] was postulated to be removed primarily by sorption to stream biofilms and bed sediments.[46]

It is important to recognize that solutes transported downstream interact with surficial bed sediments and stream biofilms even if transient storage/hyporheic exchange is not substantial (<10% in this study). Vertical mixing happens over a very short distance due to turbulence generated by friction with the bed surface,[64] and solutes with a high degree of affinity for

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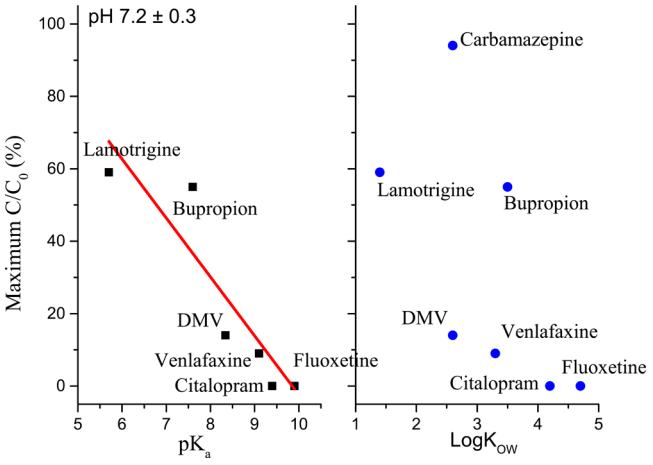

Figure 4. Relation between (a) pK_a and (b) log K_{ow} of parent compounds and relative rate of removal (C/C_0) in column experiment; DMV = *O*-desmethyl-venlafaxine; K_{ow} values were estimated using Virtual Computation Chemistry Laboratory.[60]

the bed sediments have been shown to only interact with a very thin layer of bed surface.[65] Results from the column study indicate that several of the evaluated neuro-active compounds (citalopram, DMCit, fluoxetine, venlafaxine, DMV) are removed from the aqueous phase due to sorption to the bed sediments. It is likely that interactions with bed sediments and associated biofilms play an important role in attenuating these compounds, particularly in shallow streams similar to Boulder Creek.

Neuro-active compounds introduced into surface waters are conveyed downstream, hence their detection in drinking water sources.[6−8] In-stream attenuation rates determined in this study indicate that shallow streams have the ability to substantially reduce aqueous concentrations downstream from effluent outfalls and thus provide a valuable ecosystem service. Interactions with bed sediment and suspended particulate surfaces are likely important processes controlling removal of many neuro-active pharmaceuticals from the aqueous phase, and limited sampling on Boulder Creek indicates that these compounds accumulate in sediments[4] and stream biofilms (this study). However, although these compounds are removed from the aqueous phase, the overall mass of these bioactive compounds in the water−bed sediment system is not necessarily reduced. Additionally, senescence of the biofilm and/or sediment resuspension can transport sorbed compounds downstream during higher stream velocities. Thus, from an ecological standpoint the neuro-active compounds are still present, and further research is warranted to determine if these compounds are biodegraded in this matrix. Steroidal hormones and 4-nonylphenol were shown to undergo only limited biodegradation in stream biofilms relative to bed sediments.[66]

The observed increase in concentration for citalopram and DMV downstream from the effluent outfall indicates that there are other important dynamic in-stream processes that influence the fate and transport of these compounds. Possible in-stream processes that warrant further consideration include the influence of diel cycling on bed sediment sorption and resuspension of particulate matter. Additionally, continued research in different environmental systems (using both controlled laboratory studies and studies conducted under natural conditions) is needed to investigate how in-stream attenuation in deeper rivers compares to results from this study. Increased urbanization coupled with the increased likelihood of drought conditions[67] will increase the influence of wastewater effluent on water resources; consequently, developing a better understanding of the dynamic processes that control transport of these compounds in surface waters will improve evaluation of potential effects on downstream ecosystems and water users.

■ ASSOCIATED CONTENT

Supporting Information

Detailed description of analytical methods. Measured concentrations of neuro-active compounds in Boulder Creek (Table SI1). Locations of sampling points on Boulder Creek, CO, upstream and downstream from the City of Boulder wastewater treatment plant (Figure SI1). Targeted neuro-active compounds and major metabolites (Figure SI2). Concentration profiles of neuro-active pharmaceuticals and associated metabolites in Boulder Creek (Figure SI3). Column breakthrough curves (Figure SI4). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Stagnitti, M. N. *Antidepressant Use in the U.S. Civilian Non-Institutionalized Population, 2002*; Statistical Brief #77; Agency for Healthcare Research and Quality: Rockville, Md, May 2005.http://meps.ahrq.gov/mepsweb/data_files/publications/st77/stat77.pdf (accessed January 2012).

(2) Miao, X. S.; Yang, J. J.; Metcalfe, C. D. Carbamazepine and its metabolites in wastewater and in biosolids in a municipal wastewater treatment plant. *Environ. Sci. Technol.* **2005**, *39*, 7469−7475.

(3) Leclercq, M.; Mathieu, O.; Gomez, E.; Casellas, C.; Fenet, H.; Hillaire-Buys, D. Presence and fate of carbamazepine, oxcarbazepine, and seven of their metabolites at wastewater treatment plants. *Arch. Environ. Contam. Toxicol.* **2009**, *56*, 408−415.

(4) Schultz, M. M.; Furlong, E. T.; Kolpin, D. W.; Werner, S. L.; Schoenfuss, H. L.; Barber, L. B.; Blazer, V.; Norris, D. O.; Vajda, A. M. Antidepressant pharmaceuticals in two U.S. effluent-impacted streams: Occurrence and fate in water and sediment, and selective uptake in fish neural tissue. *Environ. Sci. Technol.* **2010**, *44*, 1918−1925.

(5) Lee, K. E.; Langer, S. K.; Barber, L. B.; Writer, J. H.; Ferrey, M. L.; Schoenfuss, H. L.; Furlong, E. T.; Foreman, W. T.; Gray, J. L.; ReVello, R. C.; Martinovic, D.; Woodruff, O. P.; Keefe, S. H.; Brown, G. K.; Taylor, H. E.; Ferrer, I.; Thurman, E. M. 2011, Endocrine active chemicals, pharmaceuticals, and other chemicals of concern in surface water, wastewater-treatment plant effluent, and bed sediment, and biological characteristics in selected streams, Minnesota—Design, methods, and data, 2009. *U.S. Geological Survey Data Series 575*, **2011**, 54 p., with appendixes.

(6) Benotti, M. J.; Trenholm, R. A.; Vanderford, B. J.; Holady, J. C.; Stanford, B. D.; Snyder, S. A. Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water Environ. *Sci. Technol.* **2008**, *43*, 597−603.
(7) Focazio, M. J.; Kolpin, D. W.; Barnes, K. K.; Furlong, E. T.; Meyer, M. T.; Zaugg, S. D.; Barber, L. B.; Thurman, M. E. A national reconnaissance for pharmaceuticals and other organic wastewater contaminants in the United States — II) Untreated drinking water sources. *Sci. Total Environ.* **2008**, *402*, 201−216.
(8) Vulliet, E.; Cren-Olivé, C. Screening of pharmaceuticals and hormones at the regional scale, in surface and groundwaters intended to human consumption. *Eviron Pollut.* **2011**, *159*, 2929−34.
(9) Oakes, K.; Coors, A.; Escher, B.; Fenner, K.; Garric, J.; Gust, M.; Knacker, T.; Kuster, A.; Kussatz, C.; Metcalfe, C.; Monteiro, S.; Moon, T.; Parrott, J.; Pery, A.; Ramil, M.; Tarazona, J. V.; Sanchez-Arguello, P.; Ternes, T.; Trudeau, V.; VanDer Kraak, G.; Servos, M. An environmental risk assessment for the serotonin re-uptake inhibitor fluoxetine: A case study utilizing the European risk assessment framework. *Integr. Environ. Assess. Manage.* **2010**, *6*, 524−539.
(10) Brooks, B. W.; Turner, P. K.; Stanley, J. K.; Weston, J. J.; Glidewell, E. A.; Foran, C. M.; Slattery, M.; La Point, T. W.; Huggett, D. B. Waterborne and sediment toxicity of fluoxetine to select organisms. *Chemosphere* **2003**, *52*, 135−142.
(11) Lister, A.; Regan, C.; Van Zwol, J.; Van Der Kraak, G. Inhibition of egg production in zebrafish by fluoxetine and municipal effluents: A mechanistic evaluation. *Aquat. Toxicol.* **2009**, *95*, 320−329.
(12) Mennigen, J. A.; Lado, W. E.; Zamora, J. M.; Duarte-Guterman, P.; Langlois, V. S.; Metcalfe, C. D.; Chang, J. P.; Moon, T. W.; Trudeau., V. L. Waterborne fluoxetine disrupts the reproductive axis in sexually mature male goldfish, *Carassius auratus*. *Aquat. Toxicol.* **2010**, *100*, 354−364.
(13) Lajeunesse, A.; Gagnon, C.; Gagné, F.; Louis, S.; Cejka, P.; Sauvé, S. Distribution of antidepressants and their metabolites in brook trout exposed to municipal wastewaters before and after ozone treatment—Evidence of biological effects. *Chemosphere* **2011**, *83*, 564−71.
(14) Painter, M. M.; Buerkley, M. A.; Julius, M. L.; Vajda, A. M.; Norris, D. O.; Barber, L. B.; Furlong, E. T.; Schultz, M. M.; Schoenfuss, H. L. Antidepressants at environmentally relevant concentrations affect predator avoidance behavior of larval fathead minnows (Pimephales promelas). *Environ. Toxicol. Chem.* **2009**, *28*, 2677−84.
(15) Guler, Y.; Ford, A. T. Anti-depressants make amphipods see the light. *Aquat. Toxicol.* **2010**, *99*, 397−404.
(16) Fong, P. P.; Hoy, C. H. Antidepressants (venlafaxine and citalopram) cause foot detachment from the substrate in freshwater snails at environmentally relevant concentrations. *Mar. Behav. Physiol.* **2012**, *45*, 145−153.
(17) Schultz, M. M.; Painter, M. M.; Bartell, S. E.; Logue, A.; Furlong, E. T.; Werner, S. L.; Schoenfuss, H. L. Selective uptake and biological consequences of environmentally relevant antidepressant pharmaceutical exposures on male fathead minnows. *Aquat. Toxicol.* **2011**, *104*, 38−47.
(18) Brooks, B. W.; Chambliss, C. K.; Stanley, J. K.; Ramirez, A. J.; Banks, K. E.; Johnson, 480 R.D.; Lewis, R. J. Determination of select antidepressants in fish from an effluent-dominated stream. *Environ. Toxicol. Chem.* **2005**, *24*, 464−469.
(19) Schwarzenbach, R. P.; Escher, B. I.; Fenner, K.; Hofstetter, T. D.; Johnson, C. A.; von Gunten, U.; Wehrli, B. The challenge of micropollutants in aquatic systems. *Science* **2006**, *313*, 1072−1077.
(20) Lam, M. W.; Young, C. J.; Brain, R. A.; Johnson, D. J.; Hanson, M. A.; Wilson, C. J.; Richards, S. M.; Solomon, K. R.; Mabury, S. A. Aquatic persistence of eight pharmaceuticals in a microcosm study. *Environ. Toxicol. Chem.* **2004**, *23*, 1431−1440.
(21) Löffler, D.; Römbke, J.; Meller, M.; Ternes, T. A. Environmental fate of pharmaceuticals in water/sediment systems. *Environ. Sci. Technol.* **2005**, *39*, 5209−5218.
(22) Kwon, J.; Armbrust, K. L. Persistence and fate of fluoxetine in aquatic environments. *Environ. Toxicol. Chem.* **2006**, *25*, 2561−2568.
(23) Kwon, J.; Armbrust, K. L. Aqueous solubility, octanol−water partition coefficient, and sorption of five selective serotonin reuptake inhibitors to sediments and soils. *Bull. Environ. Contam. Toxicol.* **2008**, *81*, 128−135.
(24) Stein, K.; Ramil, M.; Fink, G.; Sander, M.; Ternes, T. A. Analysis and sorption of psychoactive drugs onto sediment. *Environ. Sci. Technol.* **2008**, *42*, 6415−6423.
(25) Yamamoto, H.; Nakamura, Y.; Moriguchi, S.; Nakamura, Y.; Honda, Y.; Tamura, I.; et al. Persistence and partitioning of eight selected pharmaceuticals in the aquatic environment: Laboratory photolysis, biodegradation, and sorption experiments. *Water Res.* **2009**, *43*, 351−362.
(26) Calisto, V.; Domingues, M. R. M.; Erny, G. L.; Esteves, V. I. Direct photodegradation of carbamazepine followed by micellar electrokinetic chromatography and mass spectrometry. *Water Res.* **2011**, *45*, 1095−1104.
(27) Rúa-Gómez, P. C.; Püttmann, W. Degradation of lidocaine, tramadol, venlafaxine and the metabolites O-desmethyltramadol and O-desmethylvenlafaxine in surface waters. *Chemosphere* **2013**, *90*, 1952−1959.
(28) Li, Z.; Gomez, E.; Fenet, H.; Chiron, S. Chiral signature of venlafaxine as a marker of biological attenuation processes. *Chemosphere* **2013**, *90*, 1933−1938.
(29) Kunkel, U.; Radke, M. Reactive tracer test to evaluate the fate of pharmaceuticals in rivers. *Environ. Sci. Technol.* **2011**, *45*, 6296−6302.
(30) Metcalfe, C. D.; Chu, S.; Judt, C.; Li, H.; Oakes, K. D.; Servos, M. R.; Andrews, D. M. Antidepressants and their metabolites in municipal wastewater, and downstream exposure in an urban watershed. *Environ. Toxicol. Chem.* **2010**, *29*, 79−89.
(31) Barber, L. B.; Keefe, S. H.; Brown, G. K.; Furlong, E. T.; Gray, J. L.; Kolpin, D. W.; Meyer, M. T.; Sandstrom, M. W.; Zaugg, S. D. Persistence and potential effects of complex organic contaminant mixtures in wastewater-impacted streams. *Environ. Sci. Technol.* **2013**, *47*, 2177−2188.
(32) Nelson, E. D.; Do, H.; Lewis, R. S.; Carr, S. A. Diurnal variability of pharmaceutical, personal care product, estrogen and alkylphenol concentrations in effluent from a tertiary wastewater treatment facility. *Environ. Sci. Technol.* **2011**, *45*, 1228−1234.
(33) Murphy, S. F.; Verplanck, P. L.; Barber, L. B. *Comprehenisive Water Quality of the Boulder Creek Watershed, Colorado, During High-Flow and Low-Flow Conditions*; Water-Resources Investigations Report 03-4045; *U.S. Geological Survey Water-Resources Investigations Report 03-4045*, **2003**, 198 p.
(34) Barber, L. B.; Murphy, S. F.; Verplanck, P. L.; Sandstrom, M. W.; Taylor, H. E.; Furlong, E. T. Chemical loading into surface water along a hydrological, biogeochemical, and land use gradient: a holistic watershed approach. *Environ. Sci. Technol.* **2006**, *40*, 475−486.
(35) Barbour, M. T.; Gerritsen, J.; Snyder, B. D.; Stribling, J. B. *Rapid Bioassessment Protocols for Use in Streams and Wadeable Rivers: Periphyton, Benthic Macroinvertebrates and Fish*, 2nd ed.; EPA 841-B-99-002; Office of Water, U.S. Environmental Protection Agency; Washington, DC, 1999.
(36) Runkel, R. L. A new metric for determining the importance of transient storage. *J. N. Am. Benthol. Soc.* **2002**, *21*, 529−543.
(37) Garbarino, J. R.; Taylor, H. E. Inductively Coupled Plasma-Mass Spectrometric Method for the Determination of Dissolved Trace Elements in Natural Water; Open-File Report 94-358; U.S. Geological Survey : Denver, CO, 1995.
(38) Taylor, H. E. *Inductively Coupled Plasma-Mass Spectrometry: Practices and Techniques*; Academic Press: San Diego, 2001.
(39) Ferrer, I.; Thurman, E. M. Analysis of 100 pharmaceuticals and their degradates in water samples by liquid chromatography/quadropole time of flight mass spectrometry. *J. Chromatogr., A* **2012**, *1259*, 148−157.
(40) Writer, J. H.; Ferrer, I.; Barber, L. B.; Thurman, E. M. Widespread occurrence of neuro-active pharmaceuticals and metabolites in 24 Minnesota rivers and wastewaters. *Sci. Total Environ.* **2013**, *461−462*, 519−527.

(41) Hiemke, C.; Härtter, S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol. Ther.* **2000**, *85*, 11−28.
(42) Ort, C.; Lawrence, M. G.; Rieckermann, J.; Joss, A. Sampling for pharmaceuticals and personal care products (PPCPs) and illicit drugs in wastewater systems: Are your conclusions valid? A critical review. *Environ. Sci. Technol.* **2010**, *44*, 6024−6035.
(43) Barber, L. B.; Vajda, A. M.; Douville, C.; Norris, D. O.; Writer, J. H. Fish endocrine disruption responses to wastewater treatment plant infrastructure modifications and long-term variability in contaminant sources. *Environ. Sci. Technol.* **2012**, *46*, 2121−2131.
(44) USGS 06730200 Boulder Creek at North 75th St. Near Boulder, CO. http://waterdata.usgs.gov/usa/nwis/uv?06730200 (accessed September 2011).
(45) Runkel, R. L. *One-Dimensional Transport with Inflow and Storage (OTIS): A Solute Transport Model for Streams and Rivers*; Water-Resources Investigation Report 98-4018; U.S. Geological Survey: Denver, CO, 1998.
(46) Riml, J.; Wörman, A.; Kunkel, U.; Radke, M. Evaluating the fate of six common pharmaceuticals using a reactive transport model: Insights from a stream tracer test. *Sci. Total Environ.* **2013**, *458*, 344−354.
(47) Lajeunesse, A.; Smyth, S. A.; Barclay, K.; Sauvé, S.; Gagnon, C. Distribution of antidepressant residues in wastewater and biosolids following different treatment processes by municipal wastewater treatment plants in Canada. *Water Res.* **2012**, *46*, 5600−5612.
(48) Lai, K. M.; Johnson, K. L.; Scrimshaw, M. D.; Lester, J. N. Binding of waterborne steroid estrogens to solid phases in river and estuarine systems. *Environ. Sci. Technol.* **2000**, *34*, 3890−3894.
(49) Lewis, K. M.; Archer, R. D. pKa Values of estrone, 17β-estradiol and 2-methoxyestrone. *Steroids* **1979**, *34*, 485−499.
(50) Ahel, M.; Giger, W. Aqueous solubility of alkylphenols and alkylphenol polyethoxylates. *Chemosphere* **1993**, *26*, 1461−1470.
(51) Düring, R.; Krahe, S.; Garth, S. Sorption behavior of nonylphenol in terrestrial soils. *Environ. Sci. Technol.* **2002**, *36*, 4052−4057.
(52) Writer, J. H.; Ryan, J. N.; Barber, L. B. Fate of 4-nonylphenol and 17β-estradiol in the Redwood River of Minnesota. *Environ. Sci. Technol.* **2012**, *46*, 860−868.
(53) Wunder, D. B.; Bosscher, V. A.; Cok, R. C.; Hozalski, R. M. Sorption of antibiotics to biofilm. *Water Res.* **2011**, *45*, 2270−80.
(54) Product Monograph "Prozac" fluoxetine hydrochloride, Eli Lily Canada, date revised July 25, 2012.
(55) Product Monograph Celexa® citalopram hydrobromide, Lunbeck Canada, date revised November 17, 2006.
(56) Product Monograph Effexor® venlafaxine hydrochloride, Pfizer Canada, date revised July 18, 2012.
(57) Product Monograph Pristiq® desvenlafaxine succinate, Wyeth Canada, date revised January 28, 2009.
(58) Bryant, S. G.; Guernsey, B. G.; Ingrim, N. B. Review of Bupropion. *Clin. Pharm.* **1983**, *2*, 525−537.
(59) Product Monograph Lamictal® lamotrigine, GlaxoSmithKline, date revised July 3, 2009.
(60) VCCLAB, Virtual Computational Chemistry Laboratory,2005. http://www.vcclab.org (accessed July 2, 2012).
(61) Ramil, M.; El Aref, T.; Fink, G.; Scheurer, M.; Ternes, T. A. Fate of beta blockers in aquatic-sediment systems: Sorption and biotransformation. *Environ. Sci. Technol.* **2010**, *44*, 962−970.
(62) Droge, S. T. J.; Goss, K.-U. Effect of sodium and calcium cations on the ion-exchange affinity of organic cations for soil organic matter. *Environ. Sci. Technol.* **2012**, *46* (11), 5894−5901.
(63) Jouyban, A.; Khoubnasabjafari, M.; Chan, H. K.; Altria, K. D.; Clark, B. J. Predicting electrophoretic mobility of beta-blockers in a water-methanol based electrolyte system. *Chromatographia* **2003**, *57*, 191−195.
(64) Rutherford, J. C. *1994 River Mixing* ; John Wiley and Sons, Ltd.: West Sussex, England.
(65) Zaramella, M.; Marion, A.; Packman, A. I. Applicability of the transient storage model to the hyporheic exchange of metals. *J. Contam. Hydrol.* **2006**, *84*, 21−35.
(66) Writer, J. H.; Ryan, J. N.; Barber, L. B.; Bradley, P. M. Biodegradation and attenuation of steroidal hormones and alkylphenols by stream biofilms and sediments. *Environ. Sci. Technol.* **2011**, *45*, 4370−4376.
(67) Strzepek, K.; Yohe, G.; Neumann, J.; Boehlert, B. Characterizing changes in drought risk for the United States from climate change. *Environ. Res. Lett.* **2010**, *5*, 1−9.