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Assessing hospital impact on pharmaceutical levels in a rural 'source-to-sink' water system

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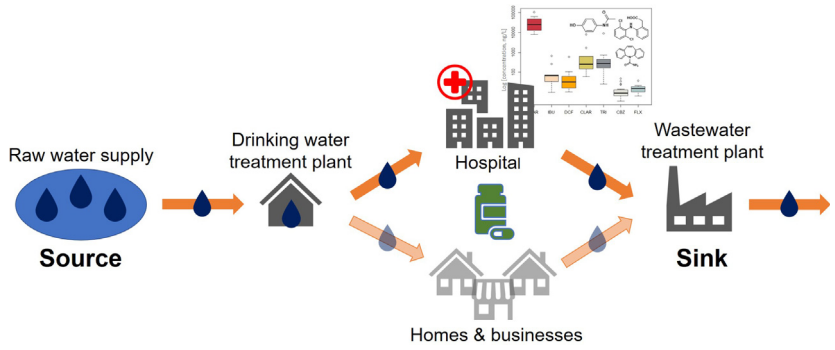
HIGHLIGHTS

- Less advanced wastewater treatment plants may treat rural hospital wastewater.
- Study of pharmaceuticals and water quality in hospital and municipal wastewater.
- Focus on 'source-to-sink' system from raw water supply to final treated effluent.
- Significant pharmaceutical concentrations in hospital discharge and treated effluent.
- Environmental impact of pharmaceuticals remains uncharacterised in rural regions.

GRAPHICAL ABSTRACT



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ABSTRACT

It is widely recognised that inadequate removal of pharmaceuticals in wastewater may lead to their presence in surface waters. Hospitals are key point-sources for pharmaceuticals entering municipal waterways, and rural hospitals are of concern as receiving wastewater treatment plants (WWTPs) may be smaller, less advanced and thus less efficient. While most research has focused on urban settings, here we present results from a rural "source-to-sink" study around a hospital. The aim was to determine the contribution of pharmaceuticals discharged to a municipal wastewater system, and, to assess pharmaceutical removal efficiency in the WWTP. Samples were collected daily for one month to assess water quality and pharmaceuticals in the broader water cycle: (i) raw water supply; (ii) treated hospital tap water; (iii) hospital wastewater discharge; (iv) combined WWTP influent; and (v) final WWTP effluent. Target compounds included analgesics/antiinflammatories, antibiotics, psychiatric drugs, and a synthetic estrogen hormone. Concentrations ranged from: 3 ng/L (carbamazepine) to 105,910 ng/L (paracetamol) in hospital discharge; 5 ng/L (ibuprofen) to 105,780 ng/L (paracetamol) in WWTP influent; and 60 ng/L (clarithromycin) to 36,201 ng/L (paracetamol) in WWTP effluent. WWTP removal ranged from 87% (paracetamol) to <0% (carbamazepine and clarithromycin), and significant correlations with water quality characteristics and WWTP flow data were observed for some compounds. Results suggested that the hospital is an important source of certain pharmaceuticals entering municipal wastewater, and associated water quality parameters are impacted. Pharmaceutical persistence in the WWTP effluent highlighted the direct pathway these compounds have into receiving surface water, where their impact remains uncharacterised. Rural

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regions may face future challenges mitigating environmental risk as WWTP infrastructure ages, populations grow and pharmaceutical use and diversity continue to increase.

1. Introduction

Numerous studies have shown that pharmaceuticals, and their metabolites/degradation products, are present in surface, ground, tap and drinking waters around the world (aus der Beek et al., 2016; Liu and Wong, 2013; Loos et al., 2010; Stuart et al., 2012). The introduction of these compounds into natural waters is a multi-faceted process, and a range of sources and pathways into the environment have been proposed. Generally, introduction results from veterinary and human use, and through inadequate treatment processes in wastewater treatment plants (WWTPs) (Gardner et al., 2013; Verlicchi et al., 2012a; Wilkinson et al., 2017). Most current treatment processes do not fully remove or degrade these compounds, hence pharmaceuticals enter the environment as constituents of treated effluent from WWTPs (Comber et al., 2018; Michael et al., 2013; Wilkinson et al., 2017). Potential effects from pharmaceutical pollution may include chronic toxicity to aquatic organisms (i.e., driving adverse behavioural or physiological changes (Foster et al., 2010; Niemuth and Klaper, 2015)); promotion of antimicrobial resistant bacteria (Johnson et al., 2015); and, contamination of potable water sources (Ebele et al., 2017).

Hospitals, wherein a diverse range of compounds are used, are critical and key point sources for pharmaceuticals entering municipal sewers. The main therapeutic classes of drugs consumed in hospitals are contrast media, laxatives, analgesics, anti-inflammatories and antibiotics (Daouk et al., 2016; Herrmann et al., 2015). However, complex mixtures of pharmaceutical compounds (and their metabolites) have been detected in the mid to high nanogram per litre range in hospital wastewaters (Oliveira et al., 2018; Santos et al., 2013; Verlicchi et al., 2010; Verlicchi and Zambello, 2016). The subsequent impact that hospital wastewater has on the combined load entering WWTPs may be challenging to quantify, and values fluctuate between studies. Studies have reported total hospital contributions of 1–76% (Switzerland; Daouk et al., 2016), 10–25% (Germany; Kümmerer and Henninger, 2003), 2–12% (Norway; Langford and Thomas, 2009) and 5–56% (Australia; Ort et al., 2010). Variability is strongly dependent on study site (e.g., hospital size, location, water usage, sewer systems), complexity of the wastewater matrix (e.g., heterogeneity, temporal changes), and experimental methods (e.g., sampling technique, target compounds, instrumental analysis). Also, it is expected that specific drug classes (and individual compounds) will result in higher hospital contributions, based on prescribing practices (e.g., hospital-specific substances) and national formularies. For example, the hospital related contribution to clarithromycin (an antibiotic) load has been reported as 36% (UK; Helwig et al., 2013), 53% (Italy; Verlicchi et al., 2012b) and 94% (Germany; Beier et al., 2011).

To better control pharmaceutical pollution, methods to effectively treat wastewater, or, separate (at source) pharmaceutical-rich hospital effluent from domestic wastewater are now needed. Indeed, the possibility of separating hospital wastewater has been explored (Chonova et al., 2016; Rodriguez-Mozaz et al., 2018; Wiest et al., 2018), and is now a topic of discussion for water regulators and government legislators within the UK and Europe (Helwig et al., 2016; Verlicchi, 2018). A framework developed by Al Aukidy et al. (2014), has evaluated the environmental risk from hospital effluents to aid guidance of hospital management and environmental regulations, however variations between hospitals, receiving WWTPs and compound concentrations indicated that interventions may need to be formulated on a case-by-case basis. Therefore, for such interventions to become a reality, further site-specific research into micropollutant loads in hospital wastewaters and their impact on receiving municipal WWTPs is needed. Knowledge around the impacts of hospitals in rural settings on the rural water cycle is particularly lacking. Such hospitals may produce wastewater that is treated at smaller, less advanced WWTPs, and the potential of applying advanced treatment techniques to such WWTPs and/or 'at source' solutions may be financially and logistically challenging. Research into rural hospitals, their pharmaceutical discharges and subsequent treatment efficiency at receiving WWTPs will provide evidence for policymakers, health care representatives and water regulators looking to minimise pharmaceutical pollution (and its subsequent environmental impact) from hospitals.

Here, we present data from an intensive 'source-to sink' study focussed on Caithness General Hospital (CGH) in Wick, a town with a population of ~7000, in the Northern Highlands of Scotland. The main objective was to determine the impact of CGH on pharmaceuticals entering the local wastewater system, and, to consider the efficiency of the WWTP in removing the combined hospital and municipal pharmaceutical load. The study was carried out within the context of the broader water cycle and involved quantification of water quality parameters and pharmaceutical concentrations in: (i) the untreated potable water supply; (ii) the treated tap water entering the hospital; (iii) the combined hospital wastewater discharge; (iv) the combined municipal WWTP influent; and (v) the final WWTP treated effluent. This is the first 'source-to-sink' study to date to provide data regarding water quality and pharmaceutical loads in relation to a rural hospital in the UK.

2. Materials and methods

2.1. Study sites

The study locations for this work are shown on Fig. 1, alongside a schematic diagram showing the sample points tested. The first sampling site, Loch Calder, provides potable water for much of the county of Caithness, Scotland, including the town of Wick (Fig. 1). Raw water is drawn from the middle of the loch and taken through mechanically raked fine screens. Lime and aluminium sulphate are added for pH correction and coagulation prior to passing through flocculation tanks and sand/anthracite filters (Bateman, 2003). After disinfection with sodium hypochlorite, final pH correction (with lime) and dechlorination (with ammonium sulphate), resultant drinking water is held in tanks before pumping to local service reservoirs that supply water to households and businesses in Caithness towns, including CGH (Bateman, 2003).

CGH is a small, rural hospital in Wick operated by National Health Service (NHS) Highlands, which offers general medicine/surgery services, diagnostics (X-ray, ultrasound and CT), accident and emergency, and limited high dependency, renal and palliative care services. This hospital serves a population of approx. 26,000, and is the referral centre for acute medical services across the Caithness Highland region covering approx. 1600 km^2 (Healthcare Improvement Scotland, 2019). The hospital has 20 medical and 42 surgical beds, a limited obstetric/midwifery unit (six beds) and an on-site laboratory and pharmacy (Caithness General Hospital, Services, NHS Highland, 2020). Wastewater from all points (patient wards and surgeries, the laboratory and pharmacy, and the kitchen and laundry services) is routed to one main wastewater outflow which then joins directly to the Wick sewerage system (containing all other Wick municipal wastewater); all of which is then pumped to the Wick WWTP.

Wick WWTP (operated by Scottish Water, 2003) was designed for a population equivalent (PE) of ~13,500 PE, and includes primary and

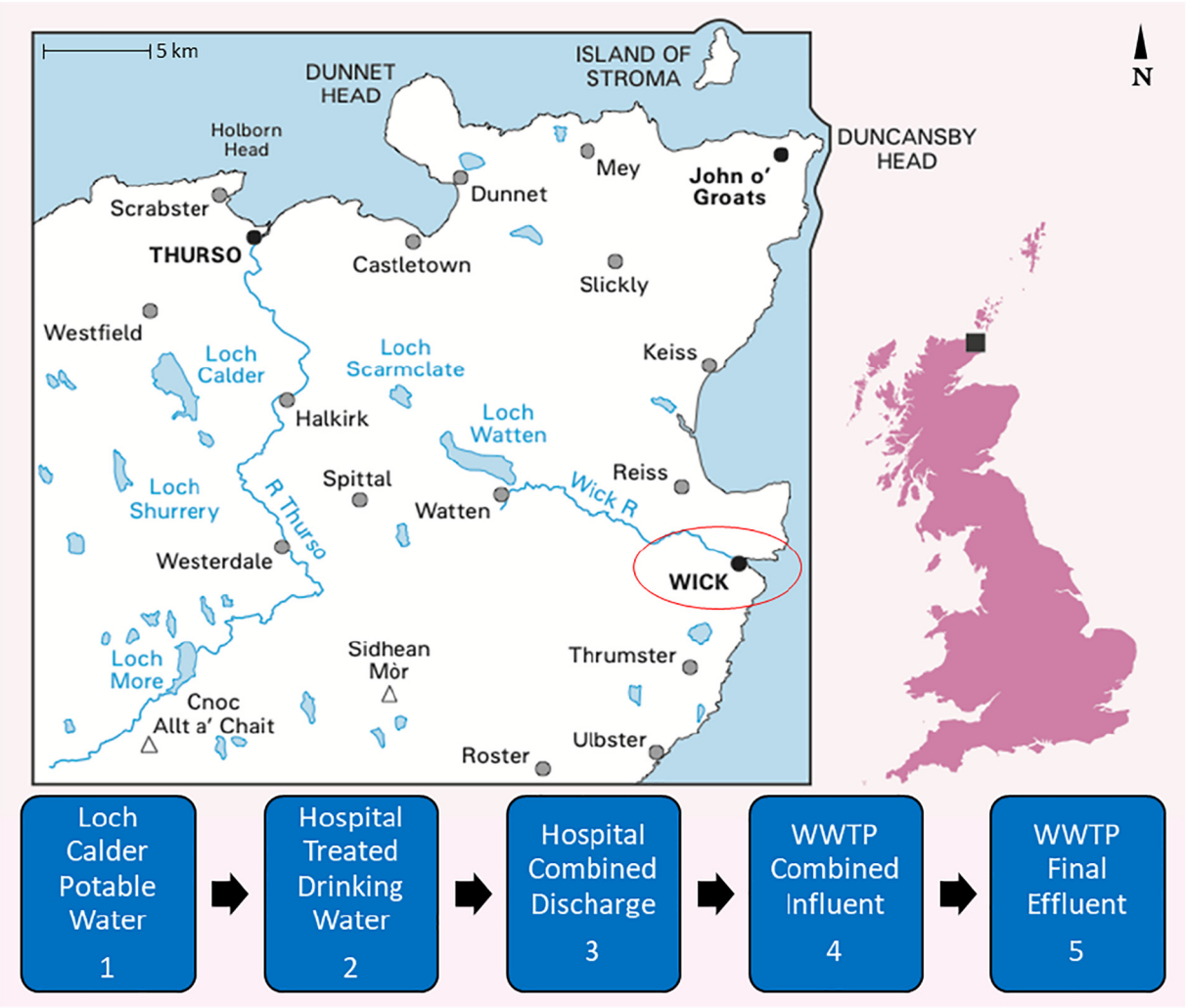

Fig. 1. Caithness, Scotland map with Wick town indicated, and sampling sites shown within the water cycle surrounding Caithness General Hospital (CGH) in Wick.

secondary conventional activated sludge (CAS) treatment. Upon entry, raw wastewater is screened (6 mm mesh) and grit is separated (Samson, 2003). Wastewater is then pumped into a primary holding tank, operated on an ad-hoc basis to control flow-to-full treatment (FFT), before entering primary settlement (Samson, 2003). The maximum FFT capacity is 14,774 cubic metres per day (CMD), and the daily average FFT is recorded (Spreight, 2019). The CAS process is used for aeration and settlement in two open-air basins; with cycles following six four-hour or eight three-hour cycles in a day (Samson, 2003). Sludge is stored for five days, before dewatering (to ~22% dry solids), caking and transport off-site. Treated effluent is decanted every 3 or 4 h (following CAS cycle completion) from CAS basins and released into the North Sea through a 500 m long offshore pipe discharging north of Wick harbour.

2.2. Sample collection

Sampling (grab) was performed over four consecutive weeks in February 2018. The CGH discharge, WWTP influent and WWTP effluent were collected every day (alternating between morning and afternoon each consecutive day), except on weekends (when samples were not collected). One sample per week was also taken from Loch Calder and from the CGH kitchen tap water, as chemical variations in these were expected to be minimal (source and treated waters). Amber glass bottles (2.5 L) and plastic HDPE bottles (1 L) were used to collect samples for pharmaceutical and water quality (WQ) analysis respectively. Before use, all sample bottles for WQ were cleaned with tap water, soaked in 3% Decon® for 24 h and then rinsed with Milli-Q® Type I water three times. Amber glass bottles were cleaned consecutively with tap water, methanol and Milli-Q water (three rinses with each). A stainless-steel bucket on a chain was used to collect wastewater samples; while surface water and tap water was collected directly into bottles. All sampling materials were rinsed in triplicate with the water being sampled, prior to sample collection. Bottles containing wastewater were cleaned externally with 10% high level laboratory disinfectant (HLD_4L, ChemGene®) antibacterial spray. Samples were transported back to the laboratory in cool boxes. Samples were refrigerated at 4 °C on return to the laboratory and processed immediately or within 24 h of collection.

2.3. Chemicals and reagents

All pharmaceutical standards were of high purity (>98%) and supplied from Sigma-Aldrich (UK). Isotopically labelled internal standard (ILIS) solutions (100 mg/L, in pure solvent) were purchased from QMX (UK). Stock standards of target compounds (1000 mg/L) and ILIS (1 mg/L) were prepared by weight in 100% methanol (MeOH), and then further diluted to create calibration and reference standards in 1:1 (v:v) MeOH:Milli-Q water. All such solutions were para-filmed and then stored in amber glass vials at −20 °C until use. HPLC-grade pure organic solvents (ethyl acetate, EtOAc; acetone, ACE; acetonitrile,

ACN; methanol, MeOH) were supplied from VWR Chemicals (UK). Formic acid and ammonium hydroxide buffers were prepared from analytical grade standards purchased from Fluka (Germany).

2.4. Pharmaceutical analysis

2.4.1. Target compounds

Eight pharmaceutical compounds were monitored: paracetamol, diclofenac and ibuprofen (analgesics/anti-inflammatories), clarithromycin and trimethoprim (antibiotics), carbamazepine and fluoxetine (psychiatric drugs) and 17α-ethynylestradiol (synthetic hormone) (Supplementary Material, Table S1). These were chosen as they represented four different pharmaceutical classes, have a range of physicochemical properties, have high usage in Scotland, and have been regularly detected in final effluent and surface waters (aus der Beek et al., 2016; Information Services Division, 2016; Verlicchi et al., 2012a). Additionally, several are of regulatory concern, i.e., are present on European and/or UK WQ Watch or Control Lists (Carvalho et al., 2015; Gardner et al., 2013; Loos et al., 2018).

2.4.2. Sample preparation and solid phase extraction

All water and wastewater samples (1 L) were vacuum filtered through 0.7 μm glass microfiber filters (47 mm diameter, MF300, Fisherbrand). Solid phase extraction (SPE) was performed following the method detailed in Supplementary Material. Following SPE, all samples were reconstituted in 1:1 (v:v) MeOH:Milli-Q water and transferred to 2 mL amber glass vials and stored at −20 °C prior to analysis.

2.4.3. Instrumentation and analysis

All pharmaceutical analysis was performed using reverse-phase liquid chromatography (LC) coupled to an electrospray ionisation (ESI) source tandem mass spectrometer (MS/MS) using an Agilent 1100 LC stack (with CTC Analytics PAL autosampler) and a Micromass Quattro Ultima Platinum triple quadrupole MS/MS system. LC-MS/MS analysis was carried out using multiple reaction monitoring (MRM) mode, in positive and negative ESI modes (ESI^+ and ESI^-). Paracetamol, trimethoprim, carbamazepine, clarithromycin and fluoxetine were analysed with ESI^+; ibuprofen, diclofenac and 17α-ethynylestradiol with ESI^-. The solvent gradients, optimised MS/MS parameters for each compound (e.g., MS/MS settings, cone voltage, collision energy and MRM ion transitions) and example chromatograms are detailed in Supplementary Material. Data acquisition and processing was carried out using MassLynx 4.1 software.

2.4.4. Quality control

All samples were analysed alongside Milli-Q water blanks and mixed pharmaceutical calibration standards at concentrations of 2, 10, 25, 50, 75, 100, 200, 300, 400 and 500 μg/L. A mixed reference standard containing all eight pharmaceuticals (at 500 μg/L) and ILIS (at 50 μg/L) was also analysed after every 10 injections to monitor, and correct for, instrument drift in sensitivity during the analysis. The frequent injection of blanks enabled observation of compound carry over (which was not observed). Pharmaceuticals were identified using retention time (RT) and two MRM transitions per analyte. The most abundant product ion was used for quantification, and the second for confirmation. Final reported concentrations were corrected against recovery of the ILIS (50 μg/L final concentration after SPE enrichment), using the relative response factor (RF) equation (Eq. (1)).

$$RF = \left(\frac{Analyte\ area}{Analyte\ concentration}\right) \times \left(\frac{ILIS\ concentration}{ILIS\ area}\right) \quad (1)$$

Standard calibration plots were tested for linearity (correlation coefficient, r^2), and these were consistently good (i.e. $r^2 > 0.99$ for each compound). The limit of quantitation (LOQ) was determined as the lowest concentration which gave a signal to noise ratio (s:n) of ≥10 (Huber et al., 2016; Nebot et al., 2015).

2.5. Water quality determination

Twenty-five WQ parameters were monitored in the five water types. These included: pH, conductivity, turbidity, total suspended solids (TSS), chemical oxygen demand (COD), dissolved organic carbon (DOC), dissolved inorganic carbon (DIC), total oxidised nitrogen (TON), soluble reactive phosphate (SRP), dissolved ammonium, sulphate, dissolved metals and chloride. The dissolved metals were: copper (Cu), iron (Fe), zinc (Zn), lead (Pb), cadmium (Cd), nickel (Ni), aluminium (Al), sodium (Na), magnesium (Mg), potassium (K), calcium (Ca), manganese (Mn) and arsenic (As). These parameters were chosen as a typical WQ monitoring suite. Methods and instrumentation are described in detail in the Supplementary Material.

2.6. Statistical analysis

Microsoft Excel (version 2016), and R Studio (version 0.95.501; R Core Team, 2017) were used for statistical analysis. One-way and two-way ANOVA's were used to test significant difference in variance ($p < 0.05$) between parameters, depending on agreement with the Shapiro-Wilk's test for normality and Levene's test for homogeneity of variance. Otherwise, non-parametric Kruskal-Wallis tests were performed. Where appropriate, Tukey's honestly significant difference test, or the Wilcoxon rank sum test for multiple comparisons, was performed for post hoc analysis between variables (i.e., pharmaceutical concentrations) and treatments (i.e., water type, sampling week, sampling time). To elucidate potential relationships within the full pharmaceutical-WQ dataset, Spearman's correlation coefficients were calculated and a correlation matrix produced (package *corrplot*; R Core Team, 2017) with the dataset bounded at zero and significance identified at the 95% confidence level (Wei and Viliam, 2017). Principal component analysis (PCA, package *stats*; R Core Team, 2017) was carried out as a way of holistically visualising measured pharmaceutical and WQ data points by splitting the dataset into PC axes which explained the most variation within the dataset.

3. Results

3.1. Pharmaceutical trends

Table 1 summarises the CGH and WWTP data obtained for each pharmaceutical, with average values expressing the mean of concentrations above LOQ. No pharmaceuticals were detected in Loch Calder source water or CGH kitchen tap water. The pharmaceutical concentrations in CGH discharge, WWTP influent and WWTP effluent are grouped by site in Fig. 2. Overall, concentrations ranged from below LOQ – 29 ng/L (for fluoxetine, WWTP effluent), up to 7959–105,910 ng/L (for paracetamol, CGH discharge). Of the individual compounds, the highest average concentrations for paracetamol, ibuprofen, diclofenac and fluoxetine were measured in the WWTP combined influent. Highest average levels for clarithromycin and trimethoprim were detected in the CGH discharge; while carbamazepine was highest in the WWTP effluent. Concentration differences between sampling points were only statistically significant for paracetamol, diclofenac and carbamazepine, with the Wilcoxon rank sum test indicating significant differences between carbamazepine and paracetamol for all wastewater types, and for diclofenac only between CGH discharge and WWTP influent. Paracetamol and carbamazepine were the only compounds with a 100% detection rate in all wastewater samples; while EE2 was never detected (although this had the highest LOQ, at 4.01 ng/L). Ibuprofen and trimethoprim were detected in 100% of WWTP influent samples, and clarithromycin in 100% of WWTP effluents samples.

Table 1
Average concentration (± standard deviation) and range of pharmaceuticals quantified in CGH discharge and Wick WWTP influent and effluent[+]. The limit of quantification (LOQ, ng/L), number of detects >LOQ (n), detection frequency (DF, %) and relative standard deviation (RSD, %) are included. Results of Kruskal-Wallis tests (*p* value, *significant difference) are indicated, and lowercase superscript letters indicate results of post hoc significant difference test. Comparison to literature concentrations in hospital wastewater (number of beds indicated), WWTP influent and effluent.

Pharmaceutical	Sample	LOQ (ng/L)	n	DF (%)	Range (ng/L)	Avg Conc (± SD) (ng/L)	RSD (%)	p value	Literature Concentrations (ng/L)[REF.] (number of hospital beds)
Paracetamol (PAR)	CGH Discharge[a]	0.78	20	100	7959–105,910	33,267 (± 24,961)	75	<0.001*	2270–57,000 (110)[A]/5000–1,370,000 (741)[B]/15,100–44,300 (1000)[C]
	WWTP Influent[b]		19	100	5849–105,780	67,483 (± 27,952)	41		80–9290[A]/108,000–246,000[D]/79,100–105,817[P]
	WWTP Effluent[c]		19	100	516–36,201	8567 (± 8455)	98		83–106[A]/80–1575[D]/762–22,782[E]/727–1374[P]
Ibuprofen (IBU)	CGH Discharge	0.78	9	45	ND – 675	139 (± 214)	153	0.521	1260–38,100 (110)[A]/70–43,000 (741)[B]/380–3200 (900)[F]
	WWTP Influent		19	100	5–6018	471 (± 1361)	288		<LOQ–4926[A]/984–6328[D]/14,000[G]/<LOQ–604[M]
	WWTP Effluent		14	73	ND – 178	73 (± 63)	85		<LOQ–369[A]/65–491[D]/278–2206[E]/604–4617[G]/<LOQ–55[M]
Diclofenac (DCF)	CGH Discharge[a]	0.77	15	75	ND – 593	77 (± 146)	188	0.009*	ND–169 (110)[A]/170–460 (300)[F]/240–15,000 (741)[B]/ND–189 (1456)[A]
	WWTP Influent[b]		12	63	ND – 392	196 (± 120)	61		<LOQ–269[A]/57–1161[D]/107–981[I]/318–390[P]
	WWTP Effluent[ab]		7	36	ND – 250	102 (± 91)	89		6–496[D]/172–927[E]/228–2830[G]/599[H]/90–850[J]
Clarithromycin (CLAR)	CGH Discharge	0.81	9	45	ND – 7940	1271 (± 2250)	200	0.203	ND–960 (110)[A]/50–14,000 (900)[F]/78–498 (1000)[C]/2–199 (1456)[A]
	WWTP Influent		11	57	ND – 830	246 (± 230)	93		ND–52.3[A]/524[K]/330–600[L]
	WWTP Effluent		19	100	60–836	371 (± 220)	59		12–40[A]/92[K]/150–460[L]
Trimethoprim (TRI)	CGH Discharge	0.78	17	85	ND – 9111	818 (± 2146)	262	0.083	12–1080 (110)[A]/800–1800 (300)[F]/10–15,000 (741)[B]/1600–4800 (1000)[C]
	WWTP Influent		19	100	155–2170	621 (± 547)	88		ND–360[A]/1514–4673[D]/79–810[Q]/210–440[L]
	WWTP Effluent		16	84	ND – 634	440 (± 127)	28		66–299[A]/385–1218[D]/266–969[E]/18–580[Q]
Carbamazepine (CBZ)	CGH Discharge[a]	0.81	20	100	3–47	13 (± 11)	86	<0.001*	19–2040 (110)[A]/640–870 (300)[F]/540–2000 (741)[B]/428–1050 (1456)[A]
	WWTP Influent[b]		19	100	40–684	306 (± 184)	60		437–673[A]/104–3110[D]/323–339[P]/815–2436[R]
	WWTP Effluent[c]		19	100	212–709	459 (± 133)	29		364–496[A]/152–2324[D]/230–1110[N]/1020–2309[R]
Fluoxetine (FLX)	CGH Discharge	3.60	7	32	ND – 37	16 (± 10)	61	0.948	ND–128 (96)[A]/ND–18 (300)[F]/18–43 (350)[A]
	WWTP Influent		5	26	ND – 46	19 (± 15)	82		70[I]/4–175[O]/41[S]
	WWTP Effluent		3	15	ND – 29	16 (± 12)	74		23[I]/5–90[J]/5–44[O]/41[S]

[+] 17α-ethynylestradiol (EE2) was not detected. ND = not detected. References: A) Santos et al., 2013; B) Oliveira et al., 2018; C) Mendoza et al., 2015; D) Kasprzyk-Hordern et al., 2009; E) Nebot et al., 2015; F) Verlicchi et al., 2012b; G) Kay et al., 2017; H) Ashton et al., 2004; I) Gardner et al., 2013; J) Gardner et al., 2012; K) Singer et al., 2014; L) Göbel et al., 2005; M) Santos et al., 2009; N) Liu and Wong, 2013; O) Baker and Kasprzyk-Hordern, 2013; P) Tran and Gin, 2017; Q) Guerra et al., 2014; R) Gurke et al., 2015; S) Petrie et al., 2014

Temporal trends in pharmaceutical data were assessed according to intra-day (AM vs PM) and inter-week (weeks one – four) variations in wastewater samples. Pharmaceutical levels were comparable in AM and PM samples for all wastewater types and compounds, with two-sample *t*-tests showing no statistical difference between values ($p > 0.05$; Table S3 Supplementary Material summarises the AM vs PM data). Assessment of inter-week trends was performed using two-way ANOVAs (Type III, sum of squares) as test assumptions were satisfied for all pharmaceuticals (except for fluoxetine, due to a small sample size across the four weeks). For the remaining compounds, the four weeks were compared for the three different wastewater types, and the relationship assessed (indicated by significant week * wastewater type interaction; Table S3). No significant week * wastewater type relationships were found for the majority of pharmaceuticals tested ($p > 0.05$). However, for carbamazepine, the relationship was statistically significant ($p = 0.015$). Tukey post hoc tests indicated significant differences in carbamazepine concentrations between week one as compared to weeks two, three and four (for all three wastewater types). The relationship between carbamazepine concentration and sampling site was therefore related to week of sampling.

3.2. WWTP flow and pharmaceutical concentrations

The WWTP flow data was gathered by the WWTP operators, and was recorded as the daily average over the 24-h period. The average FFT into the WWTP during the sampling campaign was 5212 CMD (m^3 per day) ± 2058 (39% RSD). There were peak FFTs in the first and fourth sampling weeks (01/02/18 and 19/02/18) which corresponded to two rain events (Spreight, 2019). The recorded FFT for these dates were 11,385 CMD and 6789 CMD, respectively. No statistically significant correlation was observed for the total influent ($p = 0.105$) and effluent ($p = 0.678$) loads vs FFT (through linear regression modelling; Fig. S3 Supplementary Material). However, plotting the combined concentration of all pharmaceuticals detected in the WWTP influent and effluent (as a proxy for 'total' pharmaceutical load) against FFT visually indicated a weak negative correlation between FFT and pharmaceutical load (Fig. 3A). Periods of very high flow (i.e., around the 01/02/18 rain event) seemingly corresponded to comparably low influent and effluent totals. Likewise, increased pharmaceutical concentrations (i.e., in week 3) was observed during periods of consistently low flow. However, for the individual pharmaceuticals, a statistically significant correlation (*p*

= 0.029) was observed only between FFT and carbamazepine effluent concentration (Fig. 3B, linear regression model shown in Fig. S3 Supplementary Material).

3.3. Pharmaceutical removal

A range of differences between WWTP influent and effluent were observed for the studied pharmaceuticals reflecting variable removal rates and efficiency of the WWTP process (Fig. 4). Concentrations of both carbamazepine and paracetamol were found to differ significantly (through one-way ANOVA) between influent and effluent ($p < 0.05$). Average removal calculation demonstrated appreciable removal of paracetamol (87%), ibuprofen (54%) and diclofenac (47%), little removal of trimethoprim (29%) and fluoxetine (15%), and that clarithromycin (−51%) and carbamazepine (−50%) concentration appeared to increase during treatment.

3.4. Water quality characterisation

The WQ data for all samples, and associated one-way ANOVA statistical results, are shown in detail in the Supplementary Material. Highest average values of TSS (182 ± 140 mg/L), COD (439 ± 295 mg/L), DOC (107 ± 78 mg/L), SRP (3.9 ± 3.0 mg/L), K (14,349 ± 3358 μg/L), Cu (18 ± 8 μg/L), Pb (16 μg/L, one detect >LOQ) and Zn (166 ± 116 μg/L) were observed in the CGH discharge. Highest average values of pH (7.75 ± 0.16), turbidity (85 ± 52 NTU), DIC (52 ± 10 mg/L), ammonium (10 ± 4 mg/L), TON (0.78 ± 0.44 mg/L), sulphate (66 ± 19 mg/L), Al (30 ± 14 μg/L), Ca (65,308 ± μg/L), Fe (285 ± μg/L), Mg (21,225 ± 9589 μg/L), Ni (3.9 ± 1.4 μg/L) and S (22,426 ± 6587 μg/L) were observed in WWTP influent; while minimum pH (7.34 ± 0.12), and highest average values of conductivity (1242 ± 348 μS/cm), chloride (298 ± 119 mg/L), As (49 ± 30 μg/L), Mn (105 ± 50 μg/L) and Na (177,696 ± 63,406 μg/L) were observed in WWTP effluent. Boxplots of the full WQ dataset are in Supplementary Material, Fig. S4. No boxplots appear for As and Pb due to the low number of samples >LOD ($n = 4$, $n = 2$, respectively), and Cd was not detected in any samples. No significant differences were observed for Cl and Ni concentrations between the five water types.

3.5. Pharmaceutical and water quality correlations

Relationships to help consider which WQ characteristics (if any) may influence or vary in association with pharmaceutical concentrations relationships in data sets were explored using a correlation matrix. The correlation matrix (Fig. 5) plotted significant correlations at the 95% confidence level between all detected variables (excluding EE2, Cd, As and Pb). Loch Calder source water and CGH tap water data were also excluded as no pharmaceuticals were detected. While many relationships between individual WQ parameters were observed, e.g., Na and chloride; TSS, turbidity, DOC and COD; Mg, Ca and S, relationships where $r \geq 0.9$ between pharmaceutical and WQ data were not observed. Spearman's correlations did indicate significant correlations between: paracetamol and turbidity and pH ($r > 0.5$); carbamazepine and ammonium and Mn ($r > 0.7$); and carbamazepine and S, Ca, Mg, sulphate and DIC ($r > 0.5$). Weak relationships ($r < 0.4$) were observed between diclofenac and paracetamol and ammonium. The strongest negative correlations within the dataset ($r < -0.8$) were observed for carbamazepine and DOC and Cu.

3.6. Principal component analysis

PCA of the full dataset (with all sites included) revealed that >45% of the variance in the data could be explained with the first two PC axes (PC1 27.6%, PC2 18.2%). A biplot (Fig. 6A) showed that PC1 was strongly associated with Ca, Mn, Mg, S, sulphate, ammonium, DIC and carbamazepine; while PC2 was most strongly associated with TSS, turbidity, COD, DOC, K, Fe and paracetamol. In examining the correlation matrix, relationships were found between many of these parameters. The lack of chemical similarity between the "clean" water sites (Loch Calder and CGH tap water) and the various wastewater types sampled is also evident on Fig. 6A. Confidence ellipses (at the 95% level) are also included on the PC biplot – and the complete overlap for Loch Calder and the CGH tap water indicates their close similarity, and, shows how little the

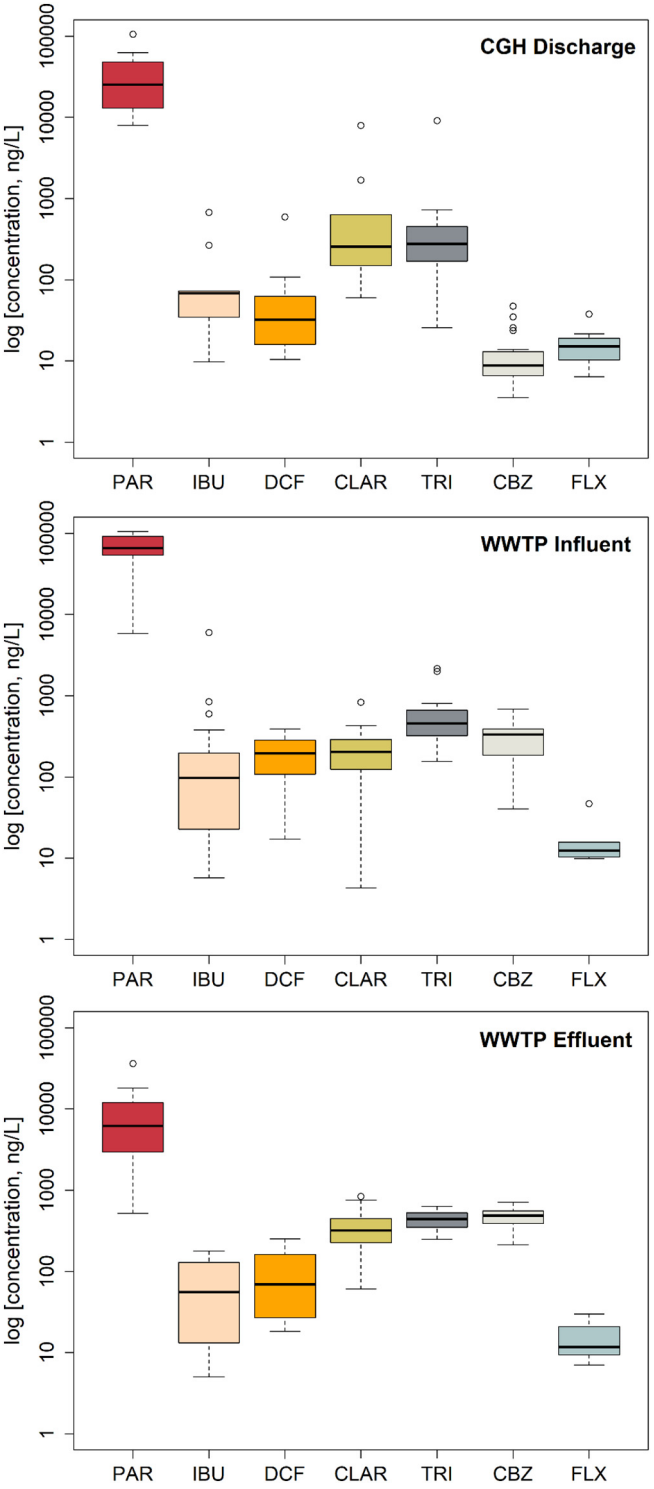

Fig. 2. Boxplots of pharmaceutical concentrations in CGH discharge, WWTP influent and WWTP effluent, on a logarithmic scale. Boxes represent the interquartile range and notches indicate the median. The whiskers show the range of concentrations (those <3× the interquartile range), otherwise points appear as outliers (circles).

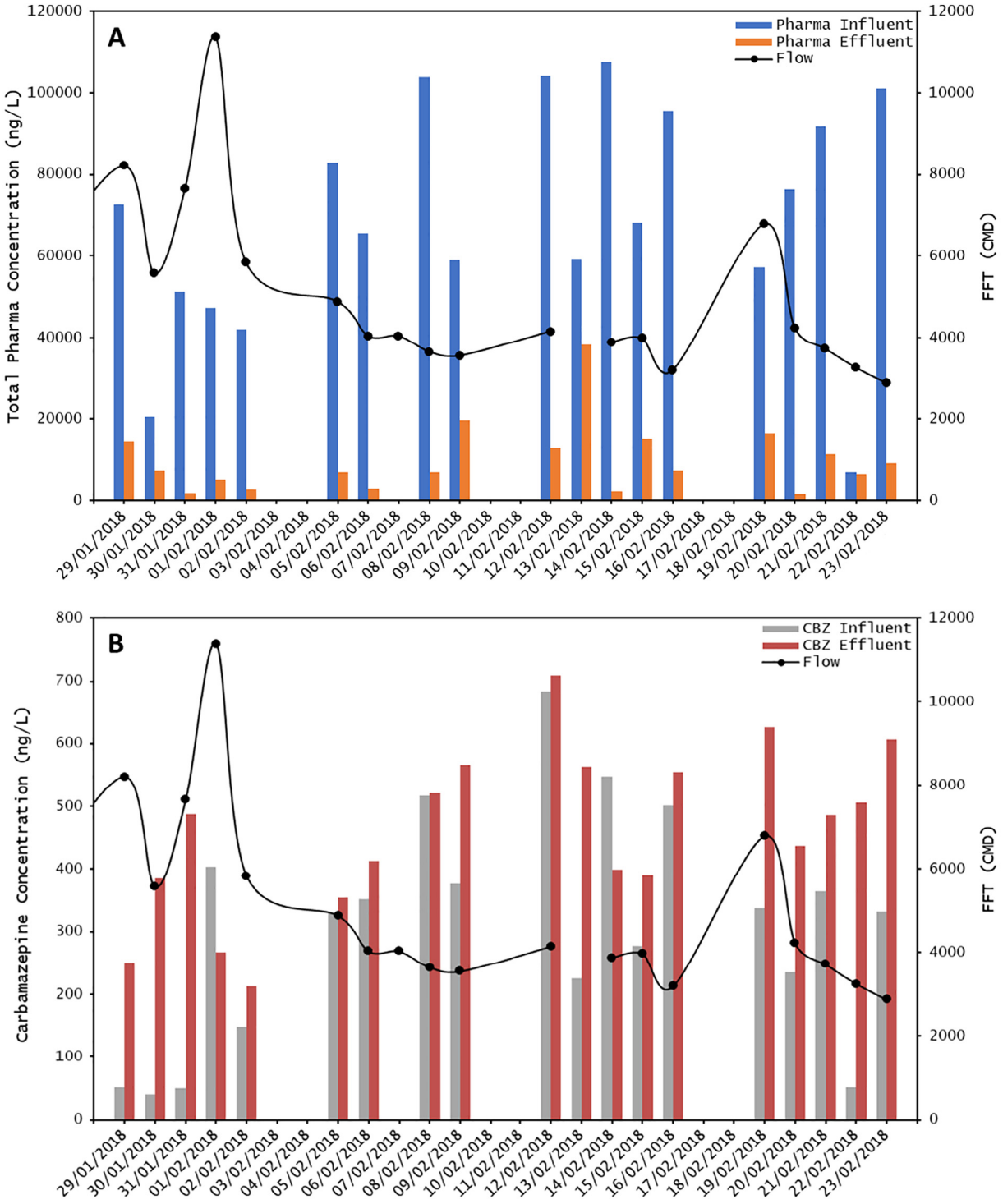

Fig. 3. A: Combined pharmaceutical concentrations in WWTP influent and effluent plotted against Wick WWTP flow to full treatment (FFT, m^3 per day (CMD)). B: Carbamazepine concentrations in WWTP influent and effluent plotted against Wick WWTP FFT (CMD). Dates cover 29/01/2018–23/02/2018. Flow data is missing for weekends and 13/02/2018, as is pharmaceutical data for 07/02/2018.

samples varied over time (points tightly spaced). Much larger variance was observed within the wastewater data as indicated by the scattering of the individual points and increased size of the ellipses (with the WWTP effluent being slightly more chemically consistent in nature). The lack of overlap between the CGH discharge and the WWTP influent in the biplot also highlights the dissimilarity between these sample types. Additionally, it is evident that most pharmaceuticals are associated with PC2 (paracetamol, diclofenac, trimethoprim, ibuprofen, clarithromycin and fluoxetine), although the PCA loadings (indicated by length of red arrows) indicate that these are weak overall patterns for all but paracetamol.

A second PCA biplot (Fig. 6B) explored correlations between the three wastewaters only. This biplot showed that PC1 (29.3% of dataset variation) was strongly associated with Ca, Mn, DIC, Zn and carbamazepine; PC2 (11.9% of dataset variation) was most strongly associated with paracetamol, ibuprofen, Al and Fe. As previously observed, the size of the confidence ellipses (and scattering of points) indicated the large variance between samples (over time), which was most evident

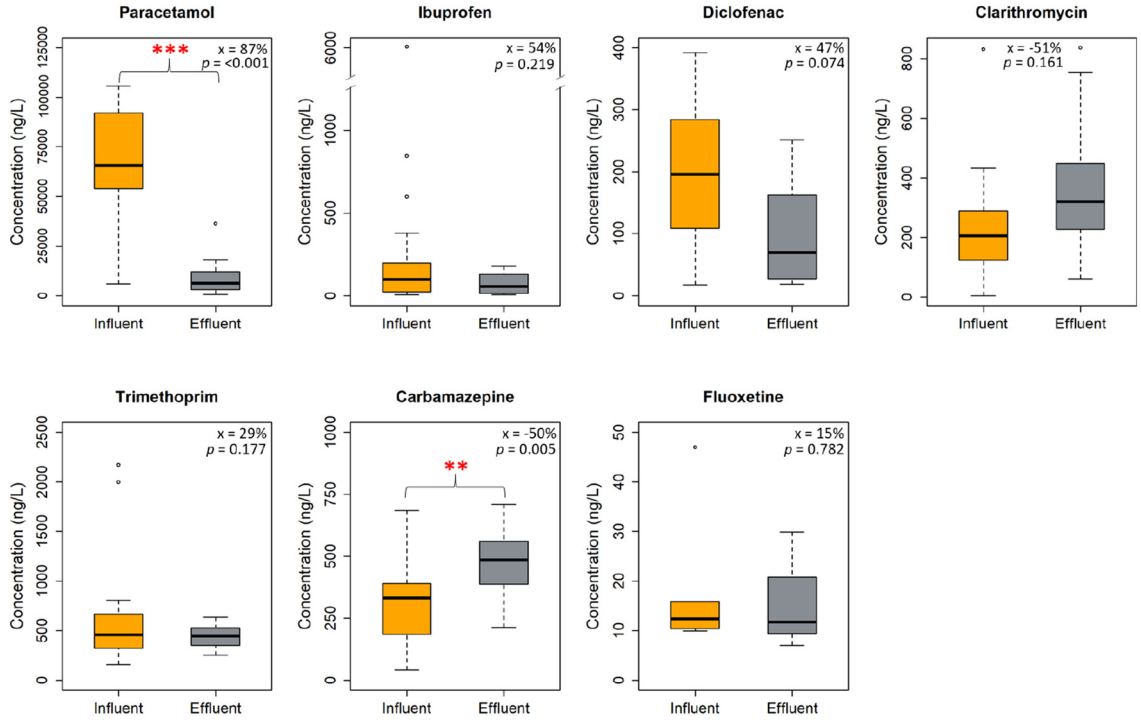

Fig. 4. Paired boxplots for individual pharmaceuticals in WWTP influent and WWTP effluent, with average removal (x, in %) and results of the two sample *t*-test (*p* value given, and significance indicated by *, **, or *** - whereby $p < 0.05$, <0.01 or <0.001, respectively).

within the CGH discharge (and least evident in the WWTP effluent). The lack of overlap between ellipses again showed the dissimilarity between these sample types. Of the pharmaceuticals, only carbamazepine had a distinct association within this biplot, towards the WWTP effluent (as indicated by the orientation and length of the red arrow). Paracetamol appeared to be more closely associated with the WWTP influent cluster, but the presence of CGH discharge points within the lower right quadrant of the biplot indicates similarity to these samples too.

4. Discussion

4.1. General remarks

This study offers a one month "snapshot" of the WQ and pharmaceutical concentrations in a rural water cycle around a hospital in the rural Scottish Highlands. It is recognised that water chemistry within sewer systems can change rapidly and that the grab sampling used in this work has limitations (Huber et al., 2016). This study therefore does not seek specifically to quantify variability through comparisons with flow patterns, or, accurately assess drug mass balance within the hospital discharge to WWTP influent to WWTP effluent 'process'. Rather, it provides initial insights into the presence and temporal variability of selected pharmaceuticals alongside WQ parameters, and the relative significance of a hospital on pharmaceutical loads.

4.2. Pharmaceutical characterisation

4.2.1. Loch Calder and CGH tap water

The lack of quantifiable pharmaceuticals in the Loch Calder source water and CGH tap water was largely expected, as Loch Calder does not receive WWTP effluent, nor, any drainage from domestic septic tanks, etc. While there is some low intensity sheep grazing in fields in the vicinity of the loch, it was not expected that the pharmaceuticals targeted in this study would enter surface water through veterinary/animal use. Pharmaceutical monitoring is not performed by Scottish Water at these two sites, but testing is carried out for other organic pollutants including trihalomethanes, pesticides, herbicides and hydrocarbons (e.g., phenols; Water Quality Standards, Scottish Water, 2015).

4.2.2. CGH discharge

The drugs used in greatest quantities in Scottish hospitals are analgesics, anti-inflammatories, antibiotics, contrast media, laxatives and cytostatic drugs, with paracetamol listed as one of the most commonly used compounds (Helwig et al., 2013). This was clearly reflected in the CGH discharge data, where paracetamol concentrations were two to three orders of magnitude greater than the other target pharmaceuticals. Overall, average concentrations followed the trend: paracetamol ≫ trimethoprim > clarithromycin > ibuprofen > diclofenac > carbamazepine > fluoxetine. Paracetamol, diclofenac, clarithromycin and trimethoprim were observed at their highest concentration in the CGH discharge compared to the other wastewater types sampled. This indicates the elevated use of these compounds within CGH, which reflects the general medicine/A&E services provided here. Hospitals with multiple specialised wards (e.g., oncology, geriatric, psychiatric, maternity, paediatric, etc.) can be expected to produce wastewater with a much wider range of pharmaceuticals, as a greater number of different drugs will be routinely used (Oliveira et al., 2018; Santos et al., 2013).

It is reported that pharmaceutical load/output in hospital wastewater will be impacted by other factors apart from prescribing practices, including number of medical beds, size and facilities (Oliveira et al., 2018). CGH discharge concentrations were compared to literature values from hospitals with 96 to 1456 medical beds (Table 1), and paracetamol, fluoxetine and the antibiotics were detected in similar concentrations to those observed in literature. For example, fluoxetine concentrations ranged from <LOD – 37 ng/L (our study), <LOD – 128 ng/L (Santos et al., 2013) and <LOD – 18 ng/L (Verlicchi et al., 2012b) for hospitals with 68, 96 and 300 beds respectively. This suggests little correlation between hospital size (defined by number of beds) and pharmaceutical concentrations. Ancillary services performed at the hospital will also impact observed pharmaceutical loads. Hospitals undertake a large number of non-medical activities; and dilution from laundry, kitchen and cleaning services was observed at CGH discharge sampling point. This will have a direct impact on the detection of

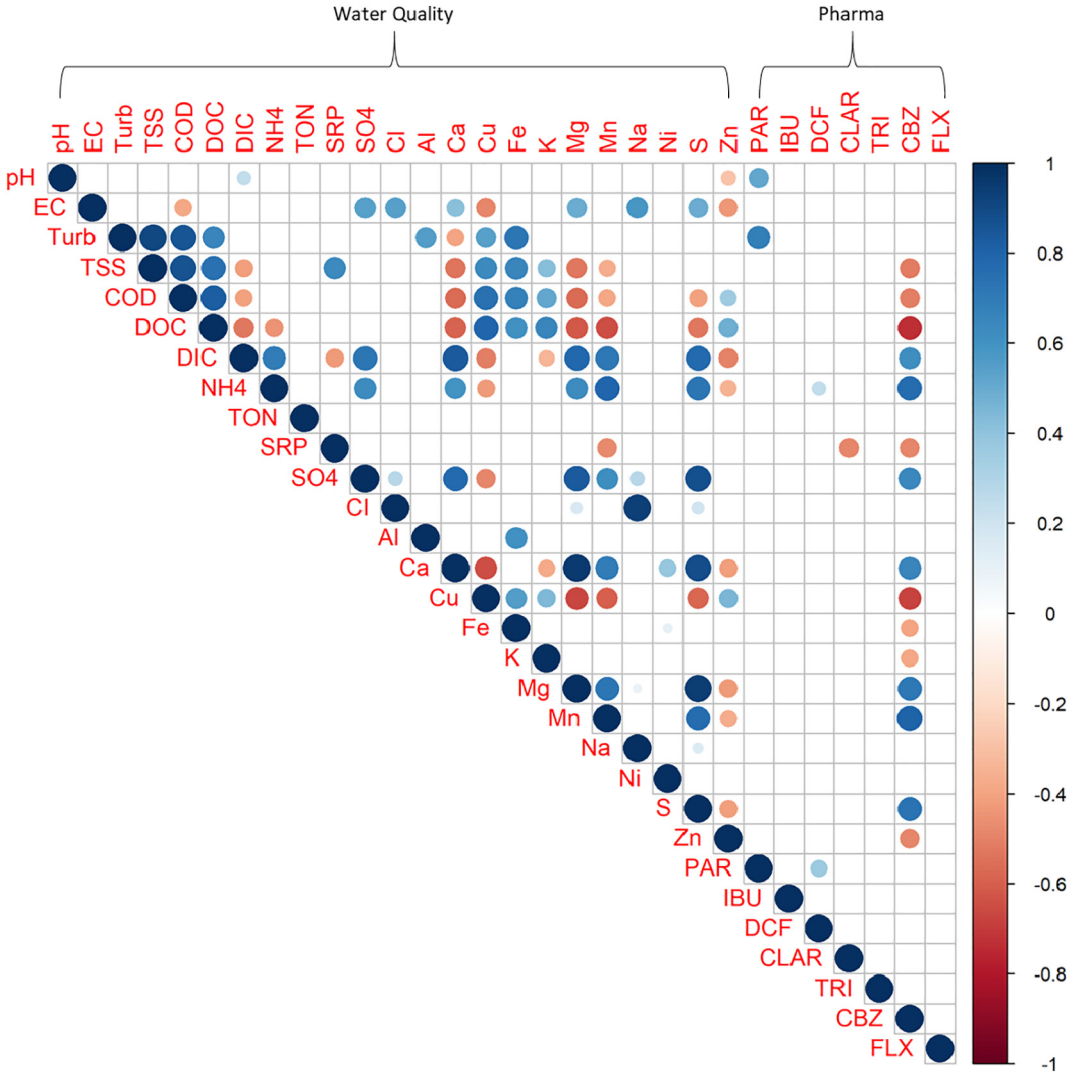

Fig. 5. A correlation matrix plotting Spearman's correlation coefficients between pharmaceuticals and WQ parameters. Circles indicate significant correlations at the 95% confidence level, with size and colour of circles indicating strength and direction (SO_4 = sulphate, NH_4 = ammonium, Cl = chloride, EC = conductivity).

pharmaceuticals, with high flow generally corresponding to reduced pharmaceutical detection from dilution effects.

The impact of hospital discharges on pharmaceutical loads in municipal wastewater is highly variable, as hospitals are only one of several important pharmaceutical sources (e.g., households, elderly care facilities, businesses, etc.) and their contribution is dependent on multiple factors (e.g., hospital services, prescribing practices, wastewater management, season, etc.) (Chonova et al., 2018; Helwig et al., 2013; Kosma et al., 2019). Hospital contributions can be particularly pronounced for certain groups of pharmaceuticals, such as contrast media and antibiotics e.g. hospital contributions of such drugs to municipal wastewater are reported to be as high as 80% for iopromide (contrast agent, Santos et al., 2013), 79% for iopamidol (contrast agent, Helwig et al., 2013), 53% for sulfamethoxazole (antibiotic, Helwig et al., 2013), 56% for roxithromycin (antibiotic, Ort et al., 2010) and 67% for ofloxacin (antibiotic, Verlicchi et al., 2012b). However, less significant contributions tend to occur for commonly used over-the-counter drugs (such as anti-inflammatories and analgesics), with reported hospital contributions of 8% for ibuprofen (Ort et al., 2010), 12% for paracetamol (Langford and Thomas, 2009) and < 9% for diclofenac (Helwig et al., 2013).

Our study observed paracetamol and diclofenac at their maximum concentrations in the CGH discharge, and that there was a significant difference between paracetamol concentrations in CGH discharge compared to WWTP influent and effluent. This suggests that CGH is a significant source of paracetamol to the Wick municipal wastewater system. However, it is important to note that dilution effects would likely be far lower for the CGH discharge vs the WWTP influent, due to the high volume of additional waste entering the WWTP from other sources (e.g., road run-off, industry, businesses, schools, households, etc.).

4.2.3. Wick WWTP influent and effluent

Pharmaceutical concentrations are known to be highly variable in wastewater influents and effluents, and reported values in the literature (and the current study) span several orders of magnitude for most compounds. In this study, WWTP influent average concentrations followed the order: paracetamol ≫ ibuprofen > trimethoprim > clarithromycin > carbamazepine > diclofenac > fluoxetine. Analgesics/anti-inflammatories and antibiotics were observed at the highest overall concentrations. In the effluent, the order was: paracetamol ≫ clarithromycin > carbamazepine > trimethoprim > diclofenac > ibuprofen > fluoxetine.

Paracetamol was consistently found at the highest concentration (in both WWTP influent and effluent), as expected due to its extensive use in Scotland, i.e., 2.39 million prescriptions dispensed in the community in 2018–2019 (Information Services Division, 2019) which does not

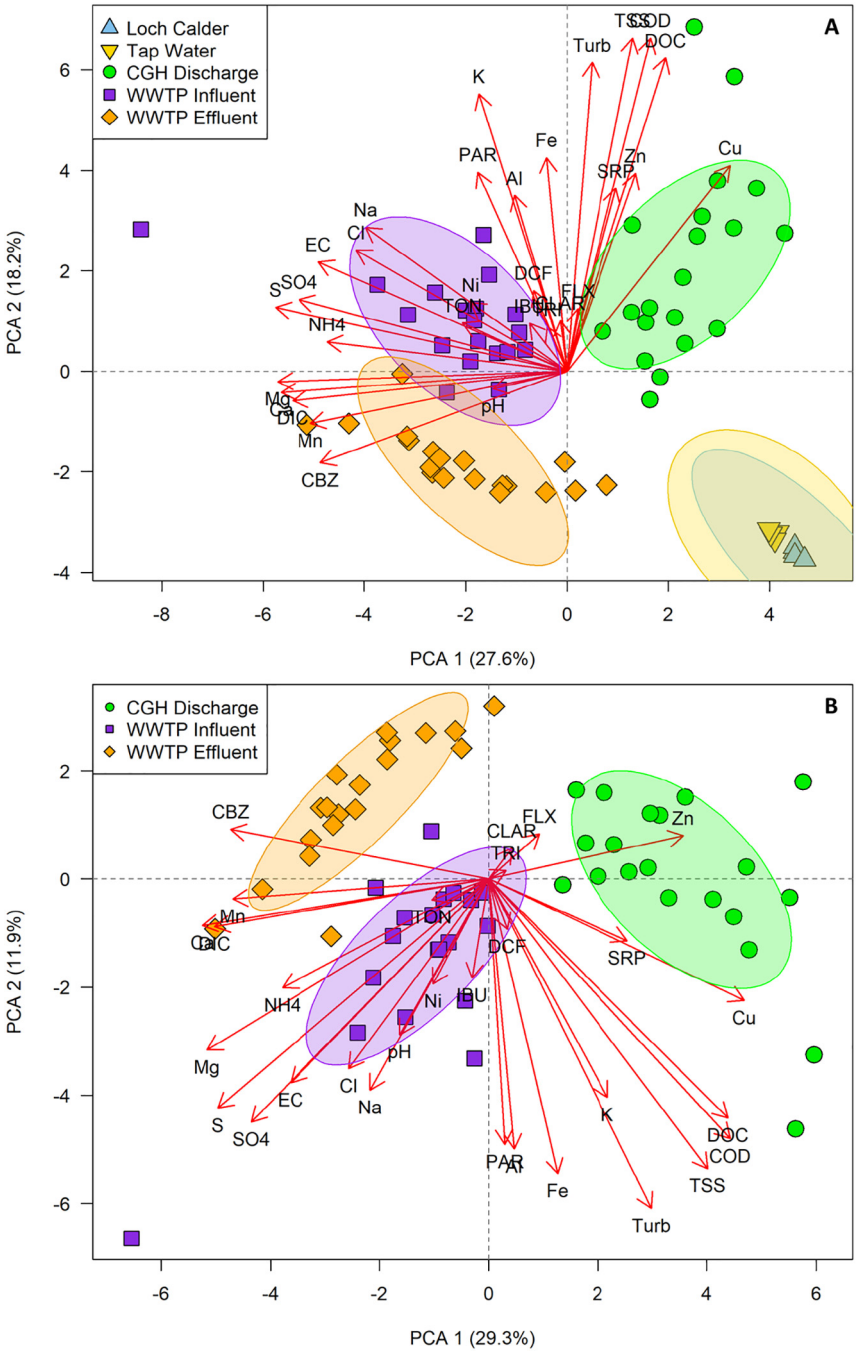

Fig. 6. A: PCA biplot includes full dataset, all 66 samples and all sites. B: PCA biplot includes wastewater samples only, 58 samples from 3 sites. The individual samples are indicated, with groupings shown in the legend. 95% confidence ellipses also highlight groupings by sample site.

account for additional over the counter purchases. Comparisons between our Wick WWTP data and that of other studies are given in Table 1, which broadly shows good agreement between studies. Nebot et al. (2015) also investigated effluents from two rural WWTPs in Scotland, and reported average concentrations of paracetamol (22,782 ng/L), ibuprofen (2206 ng/L), diclofenac (927 ng/L) and trimethoprim (969 ng/L) which are comparable with this study. However, our clarithromycin concentrations in WWTP effluent were not in good agreement with literature, which may be linked to the persistence of macrolide antibiotics during CAS secondary treatment, such as employed in Wick (Verlicchi et al., 2012a).

No significant intra-day or inter-week differences were observed for most WWTP influent and effluent pharmaceutical concentrations. However, there was a significant difference in carbamazepine levels in both matrices between week 1 and the subsequent three weeks. This may relate to rainfall levels as data from the closest gauging station, 16.5 miles from Wick, showed two large rain events in the first and final sampling weeks (9 and 10 mm of rainfall in a day, respectively; (SEPA, 2018). Additionally, the WWTP FFT data showed two spikes (11,385 CMD and 6789 CMD), in the first and fourth weeks of sampling. As a significant linear relationship was observed between flow and carbamazepine effluent concentrations, the peak FFT in week one correlated with statistically lower carbamazepine concentration in final effluent in week one (compared to the other weeks). The lack of consistent daily or weekly trends was to be expected, given the variance and complexity of the wastewater matrix and the semi-continuous nature of WWTP process. Continuous monitoring as well as grab sampling may have provided additional insights.

Pharmaceutical loads entering WWTPs are dependent on community size and the origin of the wastewater (e.g., domestic, hospital, industry discharges), with larger communities (generally with more hospitals, healthcare facilities and homes) producing more heavily polluted wastewater compared to small, rural communities (Huber et al., 2016; Nebot et al., 2015; Verlicchi et al., 2012a). However, in comparing pharmaceutical concentrations at the Wick WWTP to those in the literature from urban sites in the UK (Ashton et al., 2004; Baker and Kasprzyk-Hordern, 2013; Gardner et al., 2013; Kasprzyk-Hordern et al., 2009; Kay et al., 2017), Spain (Santos et al., 2009), Portugal (Santos et al., 2013), Sweden (Göbel et al., 2007) and China (Liu and Wong, 2013), pharmaceuticals concentrations were comparable. A population will produce wastewater proportional to its size, but it may be that the presence of certain industries which dispose of large quantities of water to municipal sewers (e.g., fish processing plants, textile manufacturers) will effectively dilute pharmaceutical levels entering a WWTP. The Wick WWTP receives wastewater from approx. 7000 inhabitants, and several non-domestic sites including an elderly care facility, a distillery and other local businesses (in addition to CGH). There are therefore multiple sources which may introduce pharmaceuticals into wastewater, and effect wastewater volumes entering the WWTP.

4.2.4. Pharmaceutical change within Wick WWTP

In the Wick WWTP, appreciable removal of NSAIDs and analgesics seemed to occur, while clarithromycin and carbamazepine concentrations increased during treatment. Fluoxetine and trimethoprim were largely unaffected by the WWTP process (with average removal <30%). These results are in good agreement with literature, particularly for paracetamol (87%, our study), carbamazepine (−50%, our study) and fluoxetine (15%, our study). In literature, removal of paracetamol ranges 86–100% (Tran and Gin, 2017; Verlicchi et al., 2012a) and removal of carbamazepine ranges −20 to −40% (Kasprzyk-Hordern et al., 2009; Petrie et al., 2014). Fluoxetine removal is variable between studies, with reported values of 0% (Petrie et al., 2014), 40–60% (Baker and Kasprzyk-Hordern, 2013) and 33–100% (Comber et al., 2018). Additionally, diclofenac, ibuprofen and trimethoprim removal vary greatly across studies, ranging from −40–92% for diclofenac (Kasprzyk-Hordern et al., 2009; Petrie et al., 2014; Santos et al., 2013; Tran and Gin, 2017), −13–99% for ibuprofen (Clara et al., 2005; Gardner et al., 2013; Santos et al., 2013), and −40–70% for trimethoprim (Göbel et al., 2007; Gurke et al., 2015; Kasprzyk-Hordern et al., 2009; Lindberg et al., 2005; Santos et al., 2013).

Our results fell within these ranges, however clarithromycin removal in our study (−51%) was in poor agreement with most literature values e.g., −45–20% (Göbel et al., 2007), 50% (Ghosh et al., 2009), 82% (Singer et al., 2014) and 0–55% (Santos et al., 2013). Increased clarithromycin concentrations in solution after wastewater treatment was observed by Guerra et al. (2014), and this may due to desorption, as other macrolide antibiotics (i.e., erythromycin and roxithromycin) are released into solution during biological treatment (Verlicchi et al., 2012a). Macrolide loads entering WWTPs may be underestimated, as they are mainly excreted within faeces, and so enter the WWTP bound within the solid-phase (Göbel et al., 2007; Verlicchi et al., 2012a), but latterly desorb.

Biodegradation and adsorption to solid phases that ultimately precipitate to become WWTP sludge are considered the dominant processes controlling micropollutant removal from wastewater (Petrie et al., 2014; Van Doorslaer et al., 2014). Our data suggests that carbamazepine is resistant to removal through these mechanisms. Carbamazepine was detected at statistically significantly higher concentrations in the Wick WWTP effluent than in influent. This may be due to enzymatic cleavage of transformation products/human metabolites during secondary treatment (Radjenovic et al., 2009; Petrie et al., 2014), or, repartitioning from the solid-phase/sludge back into the liquid phase (Mohapatra et al., 2014; Pérez-Estrada et al., 2005). These processes may occur simultaneously and will impact pharmaceutical behaviour during treatment.

Variability in removal could also be due to WWTP working parameters (e.g., sludge and hydraulic retention times, flow rate), the WWTP configuration (e.g., primary settlement/screening processes, CAS/membrane bioreactor, advanced tertiary treatment) and external factors (e.g., rain events, season/temperature, wastewater origin; Comber et al., 2018; Kosma et al., 2019; Petrie et al., 2014). The efficacy of micropollutant removal by CAS is particularly susceptible to precipitation and decreased hydraulic retention times; and, wastewater dilution by rain and road-runoff may reduce the time/degree of interaction between biological flocculants and pollutants (Joss et al., 2005). Reduced pharmaceutical removal during wet periods has also been reported elsewhere for carbamazepine, ibuprofen and diclofenac (Kasprzyk-Hordern et al., 2009). During this study, local rainfall data indicated mostly dry conditions during the sampling period (apart from two rain events in the first and fourth weeks), with 52 mm of total rainfall recorded over 4 weeks and a daily average of 2 mm (SEPA, 2018). However, due to our sampling methodology, correlations between the flow and day-to-day pharmaceutical removal could not be determined.

4.3. Water quality characterisation

Scottish Water regularly monitors drinking WQ at its source treatment facilities, and conductivity, turbidity, chloride, TON, sulphate, aluminium, copper, iron, manganese and sodium levels observed in this study were within Scottish Water quality standard ranges (Table S8, Supplementary Material). Several of the metals monitored were observed at higher concentrations in the Loch source water as compared to the CGH tap water (i.e., Al, Fe, Mg, Mn) indicating that the drinking water treatment process removes these. However, comparable levels of Zn, S, Na, K and Ca were observed in the CGH tap water and Loch source water, suggesting limited removal for these. Increased Na, Ca, sulphate, SRP and pH (in CGH tap water) were most likely due to the addition of ammonium sulphate and sodium hypochlorite for dechlorination, and lime for pH correction (Bateman, 2003).

As would be expected, CGH discharge was chemically very distinct from the Loch water source and CGH tap water. Conductivity, turbidity, TSS, COD, DOC, Cl, Al, Fe, Na and Zn concentrations were up to several orders of magnitude higher in the CGH discharge when compared to the corresponding tap water. For comparative purposes, literature values for these WQ parameters are listed against data from this study in Table S8. COD, DOC, TSS, K and Zn concentrations were highest in the CGH discharge, and were statistically different from the other water types. Indeed, hospitals generally have turbidity, COD and TSS levels that are 2–3 times higher than municipal effluents (Verlicchi et al., 2010).

There was a notable reduction in several WQ parameters between the WWTP influent and effluent. Limited change was observed (between WWTP influent and effluent) for conductivity, DOC, Cl, sulphate, SRP, ammonium, Ca, Na, K, Ni, Zn, Pb, As, S, Mn and Mg. Based on a survey of >160 WWTPs across the UK, Gardner et al., (2012) also reported that sulphate, Ca, Na, Cl, K and Ni were unaffected by wastewater treatment. The effluent values presented in this work were largely comparable to the values from Gardner et al. (2012; Table S8), with only Cl, Na, Zn, Pb and Mg higher than expected in the Wick effluent. The Wick WWTP is required to treat its effluent to meet the Urban Wastewater Treatment regulations for coastal discharge, and meets these standards (i.e., COD <125 mg/L, total phosphorus <2 mg/L, and total nitrogen <15 mg/L; Samson, 2003).

4.4. Pharmaceutical and water quality relationships

Statistical analysis demonstrated some significant correlations at the 95% confidence level between pharmaceuticals and WQ. Strong correlations ($r > 0.9$) were only observed between certain WQ parameters (Na,

Cl, SS, turbidity, COD, Mg, Ca and S) as previously reported by Gardner et al. (2012) and Verlicchi et al. (2012a). Moderate correlations (r = 0.5 to 0.9) between pharmaceuticals and WQ were observed which might indicate interactions. Upon excluding "clean" water samples, both PCA and correlation matrix identified relationships between paracetamol and turbidity, and carbamazepine and Ca, Mn, Mg, S, sulphate, ammonium and DIC; plus, negative relationships between carbamazepine and DOC and Cu. This may point to certain interactions related to the presence (or absence) of these pharmaceuticals in solution. More specifically, that these compounds may associate with the aqueous phase under certain WQ conditions, as controlled by their physicochemical properties (e.g., acid dissociation constant, octanol-water partition coefficient and sorption capacity; Guerra et al., 2014; Petrie et al., 2014; Verlicchi et al., 2012a). Gardner et al. (2012) also observed weak correlations between ibuprofen, 17α-ethynylestradiol and certain sanitary parameters (biological oxygen demand, TSS and ammonium); and, diclofenac, erythromycin and fluoxetine and DOC in effluents. Significant correlations between fluoxetine, erythromycin, ofloxacin and propranolol were also reported in wastewater effluent (Gardner et al., 2012), most likely due to the fact that these pharmaceuticals are largely from the same source (human use-excretion) and co-administered. Co-administration may also account for the weak correlation observed here between diclofenac and paracetamol.

5. Conclusions

The objective of this research was to determine the impact of a rural hospital on pharmaceutical levels in relation to a source-to-sink assessment of water quality. This included monitoring pharmaceutical introduction into municipal wastewater and assessing WWTP removal efficiency. No pharmaceuticals were detected in the untreated source water or the treated tap water, indicating lack of pollution in the raw water source. Seven of the eight pharmaceuticals targeted were detected in the CGH discharge and Wick WWTP influent and effluent, with paracetamol and carbamazepine the only compounds with a 100% detection rate in all wastewater samples. Comparisons between the three wastewater types revealed that paracetamol, diclofenac, clarithromycin and trimethoprim were detected at maximum concentrations in the CGH discharge. This is reflective of the general medicine/A&E services provided at this hospital, and future work should monitor hospital impact on these compounds (and additional macrolide antibiotics). Overall, this study indicates that hospital impact on pharmaceutical loads in municipal wastewater is highly variable, as hospitals are only one of several important pharmaceutical sources (e.g., households, elderly care facilities, businesses, etc.) and their contribution is dependent on multiple factors (e.g., hospital services, prescribing practices, wastewater management, dilution effects, etc.).

Pharmaceutical removal at the WWTP varied depending on compound, with paracetamol most efficiently removed (87%) and carbamazepine and clarithromycin least so (−50% and − 51%, respectively). This work highlights the ongoing pharmaceutical micropollutant burden entering and being discharged from rural WWTPs. This is only set to increase as WWTP infrastructure ages, populations grow and age, and pharmaceutical use and diversity increases within, and beyond, the clinical setting. Rural WWTPs (such as that studied here), are failing to entirely remove pharmaceutical contaminants which enter their facilities in the mid-high ng/L range, and these compounds are now increasingly impacting receiving surface waters. Wick WWTP releases effluent into the North Sea, and tidal zones and harbours are reportedly acting as sinks for organic pollutants, including pharmaceuticals (Letsinger et al., 2019). This study supports previous work showing that rural communities with low population densities also produce wastewater with significant concentrations of pharmaceuticals (Nebot et al., 2015). However, their wastewater infrastructure is often less advanced (as compared to advanced tertiary systems that may be present in urban settings). Results here indicate that the persistence and wider lifecycle of these compounds should be further investigated, particularly their stability and degradation in wastewater and receiving surface waters (to seek to prevent adverse environmental effects). Further work in this field will hopefully act to inform government legislators, healthcare practitioners, and water regulators regarding pharmaceutical fate and behaviour in the wastewater system – and ultimately lead to potential improvements in hospital wastewater management.

CRediT authorship contribution statement

Lydia Niemi: Conceptualization, Investigation, Methodology, Formal analysis, Software, Visualization, Writing - original draft.**Mark Taggart:** Supervision, Conceptualization, Methodology, Validation, Resources, Writing - review & editing.**Kenneth Boyd:**Supervision, Writing - review & editing.**Zulin Zhang:**Funding acquisition, Conceptualization, Supervision, Writing - review & editing.**Paul P.J. Gaffney:**Investigation, Methodology, Validation, Resources, Formal analysis, Software, Writing - review & editing.**Sharon Pfleger:**Funding acquisition, Project administration, Writing - review & editing.**Stuart Gibb:**Funding acquisition, Project administration, Conceptualization, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.139618.

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