



Showcasing the potential of wastewater-based epidemiology to track pharmaceuticals consumption in cities: Comparison against prescription data collected at fine spatial resolution

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ABSTRACT

While the extent of pharmaceutical consumption within a society/community is of high relevance to its health, economy and general wellbeing, this data is often not readily available. Herein, we strengthen a wastewater-based epidemiology (WBE) approach as a way to track the consumption of pharmaceuticals within the sampled community. This method is less laborious than established questionnaire or databases approaches and allows a higher temporal and spatial resolution. The WBE approach was conducted by sampling influent wastewater from two wastewater treatment plants of different size. A total of 39 targeted compounds were quantified by liquid chromatography coupled with tandem mass spectrometry. The number of prescriptions and the defined daily doses for each prescription was obtained from the reference database of The Catalan Health System to validate the wastewater-based approach. The wastewater sampling and the data inquiry were both executed during the same period (October 2019) and standardised for comparison to treatments per 1,000 inhabitants per day. The back-calculation parameters were improved from previous studies by including the faecal excretion rate of the pharmaceuticals. For prescription only pharmaceuticals, where prescription numbers are expected to be a good estimate of consumption, our WBE approach agreed with 27 out of 32 (<0.7 order of magnitude). Common over-the-counter pharmaceuticals such as acetaminophen, ibuprofen and naproxen showed much higher values for treatments per day per 1,000 inhabitant in wastewater than prescribed, reflecting the usefulness of WBE in obtaining an estimate of the total consumption i.e. with and without a prescription.

1. Introduction

Global sale values of pharmaceuticals have increased from about \$350 billion in 2000 to \$800 billion in 2013 (inflation adjusted: \$593 billion in 2000 USD) (Belloni et al., 2016; Busfield, 2010). The evaluation of the consumption of pharmaceuticals in developed countries over the past couple of decades shows a substantial increase, both in terms of inflation adjusted expenditure per capita, as well as in defined daily doses (DDD) per capita for the majority of therapeutic classes (Busfield,

2010; OECD, 2019, 2020). Major increases (>50–100%) in consumptions of some classes of pharmaceuticals such as anti-hypertensives, lipid lowering agents, anti-diabetics and antidepressants between 2000 and 2013 have been reported (Belloni et al., 2016; OECD, 2019). However, it is noteworthy that during the same period the consumption of antibiotics in a number of western countries did in fact decrease, probably due to governmental efforts to reduce consumption as a way to mitigate antibiotic resistance (Van Boeckel et al., 2014).

The increase in pharmaceutical consumption is attributed to a

Abbreviations: R_{ex} , excretion rate; WW, wastewater; ATC, Anatomical Therapeutic Chemical; DDD, Defined Daily Dose; BCN, Barcelona; GRN, Girona; MC, measurement-based consumption; PC, prescription-based consumption; ABS, basic health area; OTC, over-the-counter; WWTPs, wastewater treatment plants; WBE, wastewater-based epidemiology; AC, actual consumption; PDF, uniform probability density functions; Acc, sample preparation accuracy.

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multitude of factors. In developed countries, the aging demographics are known to increase consumption due to age-correlated conditions and longer lives with chronic conditions (OECD, 2019). Changing societal attitudes towards consumption of pharmaceuticals are also relevant. The latter is subject to different factors such as an increase in influence of the pharmaceutical industry, higher standard of living and improved access to medicines (Busfield, 2010). Pharmaceutical utilisation research, at a societal level, has been around for multiple decades, and was defined by the WHO back in 1977 as the study of *marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences* (World Health Organization, 2003). In conjunction to this, standardised reporting methods on pharmaceutical use such as the Anatomical Therapeutic Chemical (ATC) classification system and the DDD system have been laid out. The ATC system groups pharmaceuticals based on the organ or system they act upon and on their chemical, pharmacological and therapeutic properties (World Health Organization, 2003). The DDD system assigns an average quantity in mass for a dosage an adult receives per day for the main indication of that pharmaceutical (World Health Organization, 2003). This harmonised system simplifies comparisons both between countries and their different health systems but also over time and with the introduction of new pharmaceuticals to the market.

Despite pharmaceutical utilisation research is such an essential part of our understanding of how the use of pharmaceuticals affects communities in, medical, societal, and economic terms (Elseviers et al., 2016), the statistics on frequency and distribution of pharmaceutical use are not easily collectable or available. Large scale pharmaceutical use data is mainly collected via (i) agglomerated medical prescription data and (ii) sales data from pharmaceutical suppliers, pharmacies or specialised companies such as Intercontinental Marketing Services (Elseviers et al., 2016), both of which have their limitations and some advantages as outlined in Table 1.

While other methods (e.g. patient questionnaire-based) are used, they are not feasible in order to obtain a good spatial and temporal breakdown of data per pharmaceutical and are mostly used for specific investigations rather than for an extensive overview of pharmaceutical consumption.

With these limitations in mind, an alternative method to estimate pharmaceutical consumption is desirable. The implementation of wastewater-based epidemiology (WBE) allows the measurement of pharmaceuticals consumption with very high temporal and spatial resolution. WBE is based on analysing concentrations of compounds of interest in wastewater. Back-calculations and correction factors can thus be employed to obtain the per capita consumption of the analysed pharmaceutical or other relevant compound, since the total volume of

wastewater can be measured within a catchment area as well as the number of inhabitants generating this wastewater.

WBE has mostly been used to estimate the consumption of illicit drugs (Bishop et al., 2020; Du et al., 2020; Mastroianni et al., 2017; Mercan et al., 2019; O'Rourke & Subedi, 2020). The utility of the WBE approach for illicit drugs is evident since the data sources listed in Table 1 are not available for these compounds. Despite WBE being co-opted for illicit drug studies, it has a large potential to be a source of information on pharmaceutical use and epidemiological data (Thomaidis et al., 2016; Yan et al., 2014). For prescription pharmaceutical use, an additional advantage is that WBE based data can be validated against prescription-based data within the same area and the same time period.

Till present, only a few studies have related WBE derived pharmaceutical levels with prescription or sales indicators (predicted consumption). A major limitation in past studies has been the availability of the source data for the predicted concentrations. Carballa et al. (2008) used per capita annual consumption throughout Spain; similarly, Lai et al. (2011) used regional averaged annual values for Australia. Verlicchi et al. (2014) used national averages for Italy adjusted to match the population under study. All these methods assumed that temporal fluctuations in consumption within a year are minimal, as are minimal the differences in consumption between the regional (sample) population and the national statistics available in their respective countries. A study in which more specific consumption data (to the sampling population) is used was carried out by van Nuijs et al. (2015). Therein, they used annualised prescription data, that contained DDD values linked to a postal code matching the wastewater sampling areas. Eleven compounds were analysed and reported a good correlation between the prescription-based values and WBE measured values (6 of 11 compounds were within a 3-fold discrepancy and all but one within 1 order of magnitude). However, this study raises some methodological uncertainties since only one 24 h sample was used, and only urinary excretion of the pharmaceuticals is considered in the back calculation. In an effort to narrow down the gap between wastewater measured and prescription-based quantities, we used averaged values from five 24 h flow-proportional samples and incorporated faecal excretion rates in the back calculation. The quantity of the compound of interest excreted in faeces is relevant since human excreta is diluted around 100-fold in wastewater (Daughton, 2018), and even a somewhat hydrophobic compound excreted in faeces would still partition to a substantial degree in the aqueous phase. Additionally, we decided to investigate differences in the accuracy of our method in two different size cities from the same region: Barcelona (catchment area population 1,619,000) and Girona (catchment area population 151,000). In this way, it would be possible to evaluate the effects that city size might have on the congruency

Table 1
Methods to quantify pharmaceutical consumption at population level and their advantages and disadvantages.

Collection Method	Pros	Cons
<i>Agglomerated medical prescription data</i>	<ul style="list-style-type: none"> Currently the most reliable source for prescription pharmaceutical utilization data when temporal resolution is needed. Allows a high temporal resolution. 	<ul style="list-style-type: none"> Does not consider over the counter (OTC) pharmaceuticals. Requires a centralised effort to agglomerate individual prescriptions into a searchable database. Is only an estimation for the consumed dose, since not all the prescribed quantity is consumed by all patients.
<i>Sales data</i>	<ul style="list-style-type: none"> Considers prescription only pharmaceuticals as well as over-the-counter pharmaceuticals. Large multinational companies have the potential to provide sale data over multiple years and in numerous countries. Receipts of pharmaceutical sales to individuals could potentially be adapted to telemetrically transmit data on quantity, date of purchase, locality and other data to a centralised database. 	<ul style="list-style-type: none"> The data has commercial value and is very expensive to obtain. Data at supplier level is limited since a stock purchased in one month will be sold throughout several subsequent months, which hinders temporal resolution of data. Potential discrepancies on availability or how data is collected between countries or even regions. Spatial resolution is also limited by pharmacies operating multiple, geographically distinct, points of sale while purchasing their stock centrally. Rise of online pharmacies further increase spatial data uncertainty. Pharmaceutical producers are not legally obliged to make sale data of each pharmaceutical available for purchase. Not all the sold quantity is consumed.

between measured and predicted consumption values. To do so, analytical data and prescription data were obtained for the same period and from the same served population. The main objective of this study was to develop a more powerful WBE approach that allows reliable back-calculation of a wide variety of pharmaceuticals from different classes by (i) using highly spatially and temporally specific prescription data, (ii) accounting for wastewater levels of pharmaceuticals that result from both urinary and faecal excretion.

2. Materials and methods

Nowadays, chemical analyses are very accurate and the largest source of error of such studies is often either sampling or the back-calculations. With this in mind, 24 h composite samples (flow proportional) were taken for 5 consecutive days (Wednesday till Sunday). The parameters used for the back calculations, most importantly the excretion rate (R_{ex}), were thoroughly researched (see [supplementary information \(SI – Table S1\)](#)). Additionally, sampling was designed according to the suggested Sampling Guide by Ort et al. (2010). The R_{ex} employed herein was a combination of urinary and faecal excretion of the compound of interest unmetabolized nor conjugated. Faecal excretion was included because compounds excreted in faeces will be in contact with large bodies of wastewater while being continuously mixed along the wastewater network. Therefore, dissolution from faeces to the aqueous phase is highly probable.

Compounds of interest: The analysis herein includes some of the most consumed antibiotics in Europe according to a recent WHO study (World Health Organization, 2018). Included are also the most commonly detected antibiotics in wastewater from Spain and specifically Catalonia (Auguet et al., 2017; Gracia-Lor et al., 2012; Rodríguez-Mozaz et al., 2015) and some of the most dispensed antibiotics without prescription according to a study conducted in the neighbouring province (Tarragona) (Guinovart et al., 2018). The analytical method by Castaño-Trias et al. (2021) includes metabolites of some of the most commonly consumed pharmaceuticals and these were used to assess if metabolites are more suitable than the parent compound, for predicting prescribed loads. The full list of target compounds is presented in Table 2.

Prescription-based consumption data (PC): For all parent compounds analysed in wastewater, the corresponding data from medical prescriptions in the same time period and geographical area was used. Pharmaceuticals prescriptions were obtained already aggregated at a monthly scale (October 2019; the finest possible source) and at the spatial level of *Basic Health Area (ABS)*, which is the elementary territorial unit through which the primary health care services of Catalonia are organised; an ABS covers between 5,000 and 25,000 inhabitants. In the case of Barcelona, the wastewater treatment plant (WWTP) collects wastewater from the inhabitants residing in a total of 71–77 ABS units (information obtained from the public company managing the wastewater system of Barcelona (BCASA)). While it is certain that these 71 ABS units drain exclusively to this specific Barcelona WWTP, an additional six ABS units only drain there partially with an unknown proportion; this source of uncertainty was included in the analysis of the results. In the case of Girona, the wastewater (WW) received comes entirely from the 6 selected ABS units and hence no uncertainty in the prescription-based consumption (PC) data is shown. This PC data was provided by the Observatory of The Catalan Health System (*Observatori del Sistema de Salut de Catalunya*). This prescription data consisted in the number of prescriptions per person of each specific pharmaceutical, organised by ABS and ATC; for each prescription, the prescribed amount as DDD was listed. The observatory includes prescriptions from the public medical sector only (i.e. excluding prescriptions from the private health sector) (Idescat-Statistical Institute of Catalonia, 2020). SQL queries were used to filter the data and obtain the summed number of DDDs – for each compound analysed in WW – over the entire month of October 2019. Using the population size of the specific area (Idescat-

Table 2

Classification and abbreviation of each target compound.

Classification	Drug	Abbr.
Analgesics	Acetaminophen	ACE
	Ibuprofen	IBU
	2-OH ibuprofen*	
	Naproxen	NAP
Antibiotics	Azithromycin	AZI
	Cefalexin	CEF
	Ciprofloxacin	CIP
	Clarithromycin	CLA
	Clindamycin	CLI
	Erythromycin	ERY
	Metronidazole	MEZ
	OH-metronidazole*	
	Sulfamethoxazole	SMX
	N-Acetyl-sulfamethoxazole*	
Trimethoprim	TRI	
Antihypertensives <i>Calcium-channel blockers</i>	Diltiazem	DIL
	Irbesartan	IRB
	Losartan	LOS
	Valsartan	VAL
	Furosemide	FUR
<i>Diuretics</i>	Hydrochlorothiazide	HYD
	Atenolol	ATE
<i>β-blocking agents</i>	Metoprolol	
	Metoprolol acid*	MET
	Propranolol	PRO
	Sotalol	SOT
Sedatives <i>Antiepileptic</i>	Carbamazepine	CAR
	2-OH carbamazepine*	
<i>Antidepressants</i>	Citalopram	CIT
	Fluoxetine	FLU
	Norfluoxetine*	
	Venlafaxine	VEN
<i>Opioid</i> <i>Benzodiazepine</i>	O-Desmethyl venlafaxine*	
	Codeine	COD
H2-receptor antagonist	Lorazepam	LOR
	Ranitidine	RAN
Lipid-lowering agents	Bezafibrate	BEZ
	Gemfibrozil	GEM
	Pravastatin	PRA

* Metabolites are mentioned right under their corresponding parent compound; metoprolol was measured but only found as its metabolite metoprolol acid.

Statistical Institute of Catalonia, 2020), which matches the population generating WW in the sampled WWTPs, the data for each analyte, was normalised as treatments per 1,000 inhabitants per day according to Eq. (1) below.

$$PC = \frac{\sum DDD_{\text{October}}}{31} \frac{1000}{P_{\text{served}}} \quad (1)$$

WW sampling location and method: The influent WW of two WWTPs of different size were sampled; one in Barcelona (BCN) serving about 65% of the city of Barcelona and part of the wider metropolitan area (prescription population served = 1,619,602) and one in Girona (GRN) which serves the entire city of Girona and surrounding villages (prescription population served = 151,076) (Idescat-Statistical Institute of Catalonia, 2020). The goal was to compare two cities of different size but with similar pharmaceuticals consumption/prescription habits. Yet, the goal was not to extract conclusions from the influence of the size, but to verify that the outcomes of the paper are valid and consistent in two cities of different size.

Further information on the sampling points is provided in SI – Table S2. Sampling inflow WW at the WWTPs was carried out simultaneously and using identical methods and instruments in both sites for five consecutive days (16th–20th of October 2019). This was done by

installing a refrigerated autosamplers (Bühler 2000, Hach UK) in each of the WWTPs. The autosamplers pooled 900 mL of water every hour by collecting 300 mL of water every 20 min (3 samples per hour) for a total duration of 24 h. Each hourly sample (3 samples, 20 min apart) was stored in separate containers and using the hourly WW influent flow data of each WWTP, specific volumes from these hourly samples were combined to produce a 24 h flow-proportional composite sample. A total of 10 samples were collected, one for each sampling day (5 days) and from each WWTP (2 locations). Samples were stored in amber polyethylene terephthalate (PET) bottles and immediately frozen. The coefficient of variation (CV) of all pharmaceuticals mass loads was calculated for the two cities (2–27% in Girona, and 4–18% in Barcelona), and was compared against the CV in previous studies (5–55%) which assessed variability in pharmaceuticals mass loads (Baker et al., 2014; Pouzol et al., 2020). Since the CV was within the range in literature we assumed the 5 days sampling was a reasonable estimate of the variability within a month.

Sample treatment and instrumental analysis: The variability of the extraction and analytical process was assessed by extracting the samples from the first day in triplicate. Approximately 50 mL of each sample was filtered first through a 1 µm glass-fibre filter (Whatman, Maidstone, UK) and then through a 0.45 µm polyvinylidene difluoride (PVDF) membrane filter (Merck, Germany). Precisely, 25 mL of this filtrate was taken; 750 µL of 0.1 M EDTA and 25 µL of a 400 ppb solution containing surrogate standards were added, and the sample extracted by solid phase extraction using Oasis HLB cartridges (Waters Corporation, MA USA) following the procedure by (Gros et al., 2012) under modification by (Castaño-Trias et al., 2021). Just before the analysis, sample extracts (1 mL methanol:water 15:85) were thawed and spiked with 20 µL of a 500-ppb internal standard solution (see SI – Table S3).

Determination and quantification of the target compounds was carried out by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) using the AB SCIEX QTRAP5500 LC-MS/MS System (Applied Biosystems, Foster City, CA, USA) in selected reaction monitoring (SRM) mode recording the two most intense transitions of each compound. The analysis was carried out in negative and positive ionisation mode. SCIEX Analyst Software 1.6.3. was used to evaluate the qualitative and quantitative analysis of the detected target compounds. Quantification was performed using linear regression curves with the internal standard approach. Integration values were relative to internal standards areas in order to correct matrix effects, since the calibration curve was performed in a mixture of MeOH/MilliQ®. Repeatability of the instrumental methodology was evaluated by the injection of quality control solutions at a concentration of 10 ppb every 10 samples in the LC-MS/MS system. This allowed to verify that each compound signal was appropriate along the analytical run so that we could quantify the compound accurately. The recovery rates ranged between 31% and 111% for the 38 pharmaceuticals, whereas the limits of detection (LOD) of the method ranged from 0.24 to 128 ng/L (see SI – Table S3). The values for daily - and average concentrations (C_A) and their standard deviation can be found in SI – Table S4 for Barcelona and in SI – Table S5 for Girona.

Data treatment to obtain the measured consumption (MC): MC was back-calculated from wastewater measured concentrations by using Eq. (2) (Gracia-Lor et al., 2017; Zuccato et al., 2008, 2005) as part of a Monte Carlo simulation.

$$MC = C_A \cdot V_{WW} \frac{M_p}{M_A} \frac{100}{R_{ex}} \frac{1000}{P_{served} \cdot DDD} Acc \quad (2)$$

where C_A is wastewater measured concentrations of each analyte; V_{WW} the total volume of wastewater generated in one day; P_{served} is the prescription population served by the WWTP; M_A the molecular mass of the analysed compound; M_p the molecular mass of the corresponding parent compound; R_{ex} the percentage of the analyte excreted in a chemically unchanged form (not conjugated nor metabolised); a factor

of 100 was used to convert the percentages of R_{ex} into decimals; a factor of 1,000 was used to normalise to thousand inhabitants and the mass of DDD, as per the WHO's ATC/DDD Index 2020, was used as standardised dose for each target compound (WHO, 2019). This makes the MC and PC values directly comparable.

The Monte Carlo simulation was conducted as follows. Uniform probability density functions (PDF) were estimated for the percentage of the analyte excreted (R_{ex}) (see SI – Table S1) and the sample preparation accuracy (Acc) (see SI – Table S6) for each of the 38 compounds. The minimum and maximum values for the PDFs applied to each compound were obtained from a literature review (see the values with the references in SI – Table S1). The Monte Carlo simulation included 1,000 runs. Each run contains one randomly selected value from each of the previously defined probability distributions. For each selection of R_{ex} and Acc the MC is computed with Eq. (2) in MatLab. The solution of the model, for all the input combinations, results in a PDF of MC. The median, 10th and 90th percentiles of this PDF were computed, and the values were used to plot MC and can be found in SI – Table S7 and SI – Table S8 for Barcelona and Girona, respectively.

3. Results

3.1. Prescriptions vs. Measurements

The MC of 28 out of the 38 pharmaceuticals were within 0.7 order of magnitude (factor of 7) to the PC, which was obtained from the prescription data (Fig. 1). Considering prescription-only compounds, 27 out of 32 (≈84%) fell within a factor of 7 difference, of which 7 out of 9 antibiotics were within a 0.3 order of magnitude. Four out of 9 antibiotics showed also less than 50% absolute deviation in between wastewater measured and prescription consumption values. These compounds are clindamycin, sulfamethoxazole, clarithromycin, metronidazole and ciprofloxacin (Girona) (Fig. 1–first row). As expected, the MC of prescription-only pharmaceuticals fitted better with the PC than OTC pharmaceuticals. A low deviation was also obtained for 2 out of 3 lipid-lowering agents (<log 0.2), 8 of the 10 antihypertensive (<log 0.7) and 5 out of 6 sedatives (<log 0.7).

The highest deviation recorded was for naproxen which MC was between 3.2 and 3.8 orders of magnitude higher than its PC in Barcelona and Girona, respectively. As analgesics are highly consumed OTC, rarely prescribed and the excretion rates are well known, the deviations are mainly explained by non-prescribed consumption. In contrast, other pharmaceuticals which are mostly prescription-only can be also sold in co-formulations or as an ingredient in other products. Such types of pharmaceuticals include, codeine – commonly sold in co-formulations and common cold treatment syrups – and erythromycin, which despite of being a prescription antibiotic it is commonly found in ointments and facial wipes for treating acne. While these acne treatments are also sold only by prescription, they would nonetheless not be recorded in our prescription data. From all three lipid lowering agents, the highest deviation was found for gemfibrozil with 0.85–0.64 orders of magnitude in Girona and Barcelona, respectively. In the case of the antidepressants fluoxetine or venlafaxine, it could be that it is being prescribed at a substantially higher rate by private psychiatrists, not part of the public sector database, and hence being found at higher levels in wastewater than their PC values suggest. Another potential reason is the fact that this medication is usually prescribed for long periods of time and the database would have a single prescription containing multiple DDDs to cover several months. This could result in a gap between PC and MC if the number of prescriptions is not more or less constant over the year. As for the lipid lowering agent gemfibrozil the reason for this large deviation is not known, speculatively it could be due to the fact that excretion rates are often obtained from healthy individuals while gemfibrozil is commonly prescribed to individuals who have conditions that can affect the excretion rate of the pharmaceutical. Two distinct cases are, the antibiotic cefalexin – which was 10 times more prescribed than

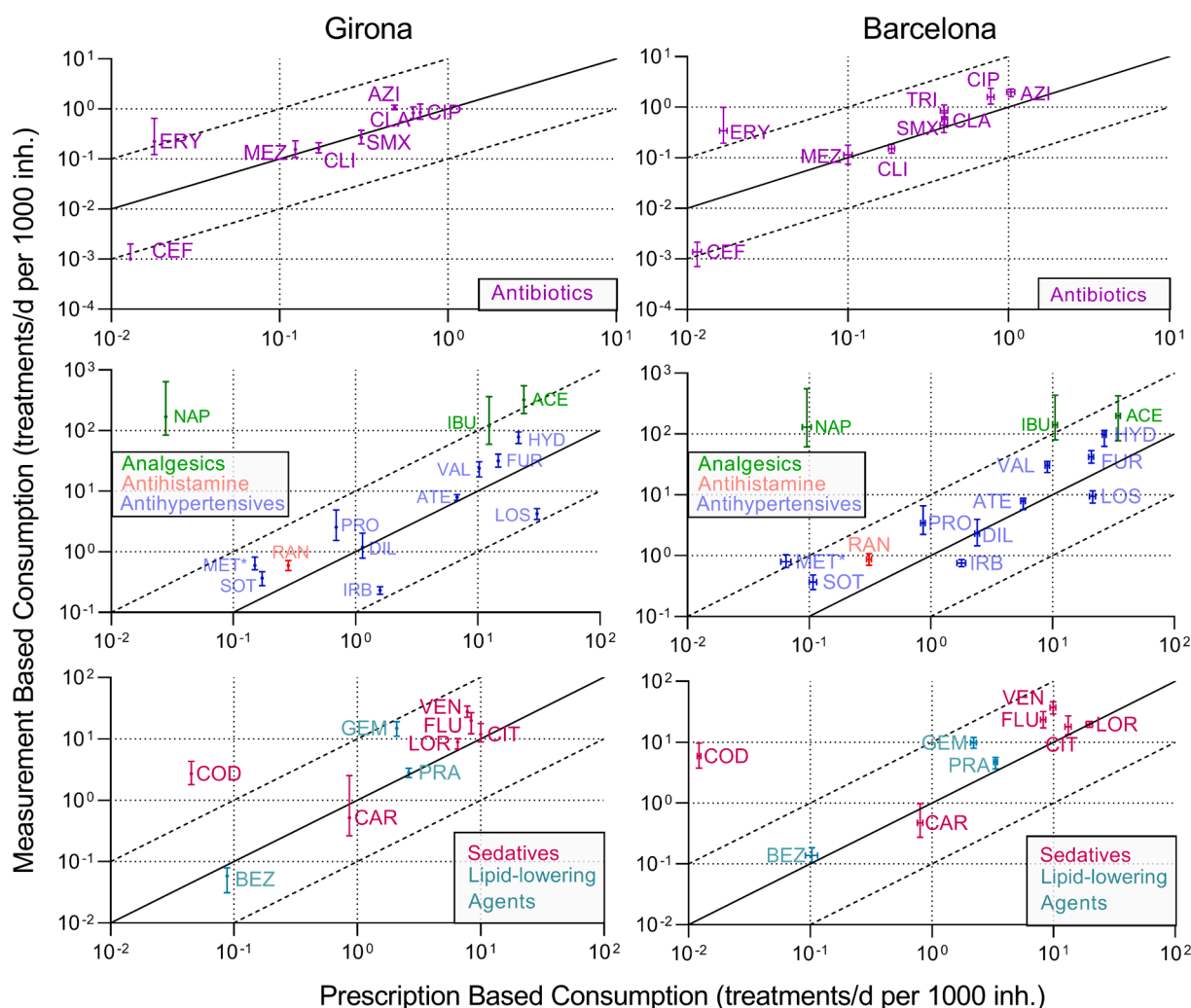


Fig. 1. The comparison of measured consumption (MC) (Eq. (2)) and prescription-based consumption (PC) (Eq. (1)) of pharmaceuticals grouped by class. The solid diagonal line indicates a perfect match between the MC and PC values, the dashed line indicates 1 order of magnitude difference.

measured – and ranitidine, which MC was 5 times higher than the PC. In the case of cefalexin, an explanation may be that it is prescribed in boxes that contain more pills than those needed for the treatment (personal communication from prescription-data providers). Ranitidine case instead, is different. This pharmaceutical was sold OTC until October 2019 (the month of sampling) when medications containing this pharmaceutical was withdrawn – due to the presence of a toxic impurity – by the Spanish Medicines Agency via a noticed dated 1st October 2019 (AEMPS, 2019). Therefore, the consumption mismatch could reflect that people were still consuming ranitidine, obtained in previous months and unaware of the notice, while new prescriptions were effectively curtailed by physicians aware of the issue.

3.2. Intercity variability

A noteworthy result that attests to the consistency of the method is the congruence showed for the same compound between cities (SI – Fig. S1). While a compound could deviate by up to 3.8 orders of magnitude between MC and PC, the variation between Barcelona and Girona for the same compound was only a fraction of this. No prescription data of trimethoprim was available but it was measured in Girona and therefore cannot be included here. Out of 37 compounds left for comparison, 24 had less than 0.15 orders of magnitude difference between cities and 33 of 37 compounds had less than a third of order of magnitude difference. In more visual terms, both cities showed similar

deviations from the $MC = PC$ line of Fig. 1. Due to the proximity of the two cities and the similarity of lifestyle and habits of their inhabitants, a similar behaviour of pharmaceutical use or misuse was expected and the WBE results support this view.

3.3. Parent vs metabolite

For a minority of compounds, both the parent pharmaceutical and a known human metabolite were quantified. Using the respective parameters for each compound, the corresponding MC to PC ratio was computed. This back-estimated value for the parent and metabolite was compared in order to investigate if there is a consistent trend in the proximity to the null line (Fig. 2, green solid line) for parent and metabolite of the same pharmaceutical.

The MC of 4 out of 6 metabolites were within 0.4 order of magnitude (factor of 4) to the PC, of which one was the metabolite of ibuprofen and therefore expected to exceed one order of magnitude due to OTC consumption. Besides the high similarity between the cities, no consistent trend was identified for carbamazepine, metronidazole and ibuprofen using either parent or metabolite. The venlafaxine metabolite was in better agreement with the prescription values than the parent compound, while this was not the case for sulfamethoxazole and fluoxetine. In summary, the comparison shows that the approach to estimate the consumption from either parent or metabolite produces similar uncertainties, which indicates the consistency of the back-estimation.

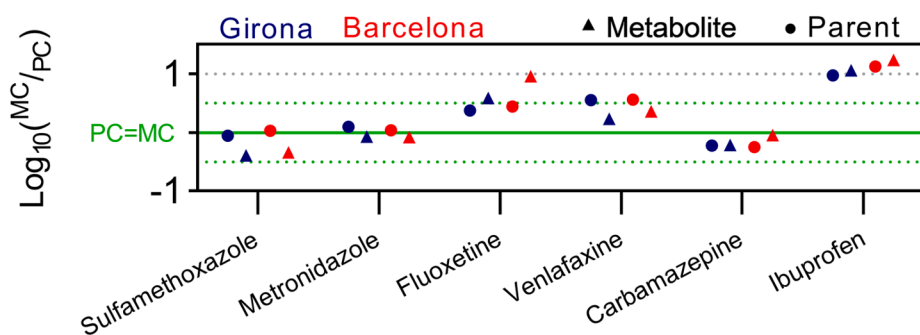


Fig. 2. Ratio between MC and PC. Comparison of using either the parent compound or a well-known metabolite. Solid Green PC = MC line corresponds to a perfect fit between PC and MC and the dotted green line half an order of magnitude difference. N-acetyl-sulfamethoxazole is the metabolite of sulfamethoxazole, OH-metronidazole of metronidazole, norfluoxetine of fluoxetine, O-desmethyl-venlafaxine of venlafaxine, 2-OH-carbamazepine of carbamazepine and 2-OH-ibuprofen of ibuprofen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In general, MC of pharmaceuticals in wastewater resulted in higher consumption estimates than the PC. This is in line with what is expected, since the contribution of OTC use of several pharmaceuticals (most notably, ibuprofen, naproxen, acetaminophen, but also to a lesser extent, codeine, ranitidine and erythromycin) is not included in prescription data. An additional contributor to the divergence is expected from the illicit use of controlled substances (e.g. codeine and benzodiazepines) and prescriptions from the private health sector, that are not part of the public sector database, as well as considered a minor contribution of hospitals and direct disposal. While several factors are identified for the observed divergence, this does not exclude that some parameters in the back calculation cannot be improved, most notably of which are probably the R_{ex} . We can see that R_{ex} are a major source of error as exemplified by the fact that different values are used in literature (see SI – Table S1). R_{ex} can have a major effect on the back calculation; for e.g. R_{ex} change from 10% to 20% will result in doubling of the back calculated value. For OTC available pharmaceuticals, the divergence between MC and PC is not an inherent flaw, since the real difference between the two would imply the proportion that is consumed OTC, information which is often not readily available.

4.1. Advancements in the WBE approach

While WBE has been employed multiple times for estimating pharmaceutical consumption within the sampled population (Mercan et al., 2019) to our knowledge, only five other studies (see (Baz-Lomba et al., 2016; Lai et al., 2011; Rice et al., 2020; Riva et al., 2020; van Nuijs et al., 2015)) have aimed to compare temporally and spatially matched measured and predicted concentrations. van Nuijs et al. (2015) matched WWTP inflow measurements with the corresponding prescriptions from the same population (filtered by postal code) being served by the WWTP. As it was the case herein, the van Nuijs et al. (2015) study also reported an overestimation of measured consumption of prescription-only pharmaceuticals. Therein 6 out of 11 pharmaceuticals showed higher levels in wastewater than predicted. A contributing reason for this could be that only urinary excretion was included in wastewater measured consumption. The importance of accounting for the faecal excretion of pharmaceutical was also noted in the same study (van Nuijs et al., 2015) but this issue was not addressed at that time. With this in mind, our consumption back-calculations integrated urinary and faecal excretion. Both van Nuijs et al. (2015) and our study, observed higher levels of pharmaceuticals in wastewater than predicted for citalopram, venlafaxine, valsartan and carbamazepine and with the same approximate range of deviations between measurements and prescriptions. For the other three compounds (atenolol, fluoxetine and losartan) we obtained different results which are probably due to the fact that different excretion rates were used. Recently, Rice et al. (2020) also published a WBE study in which prescription data from the same geographical area and month were used. While this study overwhelmingly dealt with illicit drugs, pharmaceuticals such as codeine showed a very good correlation

between measured and predicted. Riva et al. (2020) have also recently published work in which they compared WW measured values to consumption values with annual temporal resolution and at a regional level. Only 2 of our measured compounds (losartan and citalopram) overlap with the 8 compounds measured by Riva et al. (2020). In both of our cities, both compounds had a better fit than in either of the 2 regions measured therein. As is also noted by Riva et al. (2020) a higher specificity of the PC data is expected to avoid selection bias and could explain the lower variation in our PC to MC ratio compared to theirs.

Our study takes the WBE approach a step further from these previous studies since (i) a larger number of compounds (38 including metabolites) were analysed; (ii) our data shows that the WBE approach is consistent since the variation between two cities with different wastewater-network size for the same compound was very low and (iii) the WBE approach is not only limited to pharmaceuticals that have a steady level of consumption within a population over time but also for pharmaceuticals administered for a short period of time, such as antibiotics.

This paper also provides, for the first time, a compendium of literature values of R_{ex} values in urine and faeces for all studied compounds (see SI – Table S1). The introduction of the faecal excretion-rates improved the fitting of 19 out of the 21 compounds where it has been included, though it worsened the fitting of two compounds. The improvement of including faecal excretion-rates was categorised as follows; for 90% of prescription-only drugs the fit to the 1:1 diagonal improved from 8% up to 2,500% in both cities (SI – Fig. S2). The inclusion of faecal excretion rates was especially relevant for compounds which are excreted in faeces more than in urine. Namely, azithromycin, clarithromycin, irbesartan, losartan and valsartan. However, in some cases, the inclusion of the faecal excretion rates, lead to underestimation of compounds; this underestimation was limited to highly hydrophobic compounds, since their hydrophobicity might prevent them from partitioning to the aqueous phase in the wastewater network conditions. This was probably the case of irbesartan ($\log K_{ow} = 5.31$), which was the only compound even more underestimated when the faecal excretion rate was included in the back calculation. The $\log K_{ow}$, $\log P$ and pK_a of each compound, with faecal excretion can be found in SI – Table S9. Herein, the concentration of pharmaceuticals present in the solid fraction of wastewater was not analysed. As for degradation of the compounds in the wastewater network, there was no obvious correlation between expected degradation rates and MC/PC ratio. Besides, the two cities, which have different sewer residence times, produced similar results for the same compound. Based on this experience, we would recommend that future WBE studies also assess if the inclusion of faecal excretion rates improves the fit between measured and prescription data.

With respect to the use of metabolites, while obtaining consumption data from the human metabolites of pharmaceuticals has its advantages, such as – the estimation is inextricably linked to actual administration of the pharmaceutical – the excretion data for metabolites is often less consistent than that for parent compounds and thus higher uncertainties can result. The way forward with metabolites in WBE studies, is

probably a case by case approach in order to select suitable metabolites. As for parent compounds, metabolites in WBE studies should have a well-studied excretion rate, not be very hydrophobic, not show a wide range of excretion rates that varies with common medical conditions and be chemically stable in wastewater. In addition, there is also benefit in being able to quantify both parent and metabolite since the difference in the values would be explained by improper disposal of non-administrated pharmaceuticals. In normal circumstances, this difference would be expected to be too small and not distinguishable by such an approach. It is also foreseeable that the accuracy of the back-calculation could be improved by using multiple compounds for each pharmaceutical, i.e. the back calculated value of each pharmaceutical is computed as a weighted average value for the parent and multiple metabolites. The advantage here is that an over-expression of the excretion rate of one parent/metabolite implies an under expression of another, in such a way that the overall error of the average value would be minimised.

4.2. Limitations of the approach

While PC is not a perfect proxy measure for actual consumption (AC) of pharmaceuticals it is the most consistent data available that allows the validation of a WBE-based approach (e.g. MC).

This study uses prescription data at a fine spatial and temporal scale, yet it has limitations. First, a substantial portion (28% of the population of Catalonia) has both public and private medical coverage (ESCA, 2019) but only the public prescription numbers were available. Second, only prescriptions for oral administration were counted (excluding parenteral, dermal and rectal administration). Third, the OTC is not accounted in the PC. Another factor which would have the opposite effect is the fact that the number of DDD per prescription might be different from the total DDD of one whole treatment (i.e. some medications are left over and not administered). These limitations might explain some of the differences between PC and MC. Yet, these differences (for the prescribed-only compounds) were up to 0.7 orders of magnitude (similar to former research studies) and cannot be only explained by uncertainties related to PC. We believe that the largest source of deviation comes from the excretion rates of pharmaceuticals reported in literature which are scarce and not up-to-date. While R_{ex} is often not too relevant to medical practitioners and thus mostly ignored in medical literature, for WBE, the excretion rate has a strong influence on the MC (as per Eq. (2)). Teaming up with the health sector and updating excretion rates for pharmaceuticals would be a relevant milestone for the WBE field. Besides excretion rates, another limitation of our approach would be related to uncertainties in the population estimates which has not been taken into account in our uncertainty analysis, and which has been estimated in literature to be between 7 and 55% relative standard deviation (RSD) (Castiglioni et al., 2013). Furthermore, MC may also be influenced by in-sewer stability of the compounds or sorption on the sewer biofilms. A former study (Jelic et al., 2015) which included some of the compounds included in this paper showed that the majority of the studied pharmaceuticals were stable in a pressurized sewer of 7.6 km with concentrations varying $\pm 10\%$. A correction factor for in-sewer transformation was not applied due to the lack of concluding studies on pharmaceuticals in-sewer stability; the fact that the differences were systematic in the two cities with varying sewer system characteristics reinforces the argument that the main source of deviations might not come from in-sewer stability issues. Further research in-line with McCall et al., 2016 studying in-sewer stability of illicit drugs would be needed for the pharmaceuticals. Besides, sample stability should also be considered, as some analytes might be lost between sampling and analysis. In our case, we took in account that storage and preservation time were crucial for sample stability according to previous research (Fedorova et al., 2014; Llorca et al., 2014) and our sampling and sample extraction was therefore performed in less than one week.

4.3. Applicability of the approach

While being aware of the limitations is crucial, the comparison of MC and PC is still very informative since it allows the identification of outlier compounds, i.e. compounds that have a much larger divergence between MC and PC which warrants either a refinement in the back calculation or, with that excluded, demonstrates OTC use or improper use. This is not possible with illicit drugs, where the closest estimates for consumption are surveys or records of drug seizures by law enforcement, thus making it very hard to estimate the discrepancy between AC and MC. The comparison of MC and PC (as a proxy for AC) herein has elucidated the fact that both cities have very similar numbers for the same compound. The very small divergence between cities suggest that while an error between MC and AC is present to some degree it is very systematic and allows a WBE based approach to be used to compare different localities and at different times.

It is highly laborious to collect and compare pharmaceutical consumption amongst different nations. Not every country might collect the same information, the frequency of reporting might be different, privacy concerns might make it hard to obtain the data, some countries might not have statistics divided in smaller geographical units and many other limitations. A WBE based approach circumvents these limitations, the temporal and spatial resolution is only limited by the number of samples taken and the availability of wastewater networks from which to collect the sample. Differences in the way countries report pharmaceutical consumption is also avoided since a WBE method, utilising the same parameters in its back calculation, would be equivalent. Privacy concerns are also not an issue since the data is collective in nature and cannot be used to ascribe consumption to single individuals. A WBE based approach is also very practical (given a wastewater network is available) for low-medium income countries which might not have a robust health IT database collecting prescription data. Setting up such a campaign would simply involve employing flow-proportional auto sampling units and chemical analysis that could even be done in commercial labs.

While a WBE based approach could, in some situations, replace a PC approach to obtain consumption data of a whole population, there are also benefits from having both data sets. Since WBE measures directly what has been consumed by an entire population and PC measures what has been prescribed to single individuals, differences in these values could, for example, elucidate patterns in OTC pharmaceuticals use amongst a population over time. Such information is typically obtained from surveys (such as (Stosic et al., 2011)), which rely on individuals accurate reporting how frequently they use a specific pharmaceutical and is highly laborious to collect, notwithstanding that it is very impractical to collect for a large number of different compounds. With a WBE based approach and a database of prescribed OTC pharmaceuticals, only a few WW samples are required to be able to estimate the OTC of a very large number of pharmaceuticals. Likewise, this approach could be applied for pharmaceuticals that are regulated (not OTC) but that are often illegally available to willing individuals, such as benzodiazepines, opioid analgesics or amphetamines. The discrepancy between MC and PC would be of interest to health, social services and law enforcement since they indicate abusive consumption of licit drugs.

5. Conclusion

This study showcases the utility and limitations of applying wastewater-based epidemiology to quantify pharmaceutical consumption by presenting the most temporally and spatially specific comparison between wastewater measured (MC) and prescription based (PC) consumptions.

The main conclusions are:

- Differences between MC and PC for 27 out of the 32 pharmaceuticals which are only sold with prescription were within 0.7 orders of

magnitude. From these, 21 compounds were within half an order of magnitude difference.

- Using both the urinary and faecal excretion rates in the back calculation improves the fitting of pharmaceuticals that are excreted in faeces and not extremely hydrophobic.
- Antibiotics were the compounds showing the smallest differences between MC and PC.
- Compounds sold OTC showed large differences with much higher values measured than prescribed, meaning that WBE is a good approach to estimate total consumption (prescribed and non-prescribed).
- The reported differences were highly consistent in the two studied cities.

Future applications: Studies reporting pharmaceuticals consumption have relied on compiling statistics to produce yearly reports or databases with restricted access. Due to its high temporal resolution and relative low person-hours required, WBE applicability can be extended to numerous investigations. To name a few examples, to estimate OTC consumption by subtracting prescription data from WBE data, to monitor the progress of public health campaigns aimed at reducing illegal OTC sells and self-medication with pain killers, sedatives and antibiotics in order to prevent e.g. antibiotic resistance dissemination; to follow disease outbreaks such as COVID-19 by monitoring specific pharmaceuticals or biomarkers related to the outbreak (antibiotics, antivirals, antipyretics, etc.) and to develop customised prevention campaigns for non-communicable diseases.

CRediT authorship contribution statement

M. Escolà Casas: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **N.S. Schröter:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **I. Zammit:** Visualization, Writing - original draft, Writing - review & editing. **M. Castaño-Trias:** Formal analysis, Software, Validation, Methodology. **S. Rodríguez-Mozaz:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing - review & editing. **P. Gago-Ferrero:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing - review & editing. **Ll. Corominas:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Software, 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 material

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