SUPPLEMENTARY INFORMATION

Wastewater-based epidemiology to assess pharmaceutical consumption. Spanish perspective

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Table S1. LC-MS/MS information of the studied pharmaceuticals.

Compound Name	Therapeutic class	Rt (min)	Precursor Ion (*m/z*)*	Product Ion (*m/z*)*	Cone Voltage. (V)	Colision. Energy (eV)	q/Q
4-acetomidoantipyrine	Nervous system Analgesics	12.57	**246.0**	**228.1** 104.1	150	10 20	0.31
Acetaminophen	Nervous system Analgesics	9.90	**152.0**	**110.0** 93.0	125	15 20	0.21
Atenolol	Cardiovascular B-Blockers	9.97	**267.2**	**190.1** 145.0	125	20 28	0.55
Bezafibrate	Cardiovascular system	25.63	**362.2**	**316.2** 276.2	125	10 10	0.43
Carbamazepine	Nervous system	21.26	**237.1**	**194.1** **179.1**	130	16 35	0.14
Codeine	Respiratory syst. Cough	11.43	**300.0**	**215.0** 199.0	150	30 30	0.83
Diazepam	Nervous system Anxiolytics	25.21	**285.0**	**222.0** 193.0	125	30 30	0.55
Diclofenac	Muscul-skeletal Anti-inflammatory	28.73	**296.0**	**250.0** 215.0	100	10 15	0.56
Hydrochlorothiazide	Cardiovascular Diuretics	13.07	296.0	269 205	150	20 20	0.95
Losartan	Cardiovascular Renin-angiotensin	22.77	**423.0**	**405.0** 207.0	130	10 10	0.53
Omeprazole	Alimentary track Drugs for peptic ulcer	17.70	**330.0**	**182.0** 120.0	100	20 20	0.16
Pentoxifylline	Cardiovascular Peripheral vasodilator	16.15	**279.0**	**181.0** 138.0	100	12 28	0.31
Quetiapine	Nervous system Antipsychotic	18.08	**384.0**	**253.0** 221.0	100	20 40	0.61
Tramadol	Nervous system Opioids	15.29	**264.0**	**58.2**	100	24	-
Trazodone	Nervous system Psych analeptics	17.87	**372.0**	**176.0** 148.0	100	24 40	0.73
Valsartan	Cardiovascular Renin-angio.	26.33	**436.0**	**418.0** 235.0	125	5 16	0.93
Venlafaxine	Nervous system Antidepressant	17.11	**278.0**	**260.3** 58.2	100	10 16	0.25

*Bold denotes the quantification transition.

Table S2. Main characteristics of the wastewater treatment plants (WWTPs) considered in this study.

WWTP	Sampling mode[a]	Population served (inhabitants)	Daily flow (m^3/day)						
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Madrid 1	T (450 mL/60 min)	352,188 COD	89,136	89,136	89,136	89,136	89,136	89,136	89,136
Madrid 2	T (100 mL/60 min)	727,176 BOD	80,957	80,957	80,957	80,957	80,957	80,957	80,957
Tarragona	T (400 mL/30 min)	146,498 Census	26,068	26,068	26,068	26,068	26,068	26,068	26,068
Reus	Flow	103,696 BOD	16,868	16,868	16,868	16,868	16,868	16,868	16,868

[a] Sampling mode: T = Time proportional (volume sampled/frequency of sampling), Flow = Flow proportional

COD: chemical oxygen deamand; BOD: biological oxygen demand.

Table S3. Validation parameters.

	IQLs (µg L^{-1})	IDLs (µg L^{-1})	$\%R_{app}$[a]	%ME[a]	MQL (ng L^{-1})	MDLs (ng L^{-1})	%Intraday precision (%RSD, n=5)	%Interday Precision (%RSD, n=5)
4-acetamidoantipyrine	0.1	0.05	98	22	10.2	5.1	3.2	5.3
Acetaminophen	1	0.1	105	26	54.3	10.9	3.9	8.2
Atenolol	0.5	0.1	92	3	95.2	9.5	4.8	8.5
Bezafibrate	1	0.2	35	-64	285.7	57.1	4.1	7.8
Carbamazepine	0.5	0.1	94	6	53.2	10.6	5.0	8.1
Codeine	0.2	0.1	87	2	23.0	11.5	4.1	7.2
Diazepam	0.5	0.1	86	1	58.1	11.6	4.2	8.5
Diclofenac	0.8	0.2	57	-23	140.4	35.1	4.3	8.5
Hydrochlorothiazide	2	1	85	4	235.3	117.6	6.7	11.0
Losartan	0.5	0.2	87	5	57.5	23.0	3.9	6.0
Omeprazole	1	0.5	140	47	71.4	35.7	5.8	10.2
Pentoxifylline	1	0.1	92	6	108.7	10.9	5.1	10.6
Quetiapine	0.5	0.05	74	-1	67.6	13.5	3.9	6.3
Tramadol	1	0.1	83	0	120.5	12.0	5.7	8.3
Trazadone	0.5	0.1	41	-19	122,0	24.4	4.5	8.5
Valsartan	0.5	0.1	66	-4	75.8	15.2	3.9	7.0
Venlafaxine	0.5	0.1	70	-12	71.4	14.3	4.6	9.0

[a] Spiked at 10 µg L^{-1}. See the text for the rest of conditions.

a

Table S4. Correction factor and source used to calculate measured consumption of the studied pharmaceuticals.

Pharmaceutical	Excretion (%)	CF	Reference
Acetaminophen	5	20	(Escolà Casas et al., 2021)
Atenolol	92	1.08	(Ceolotto et al., 2024; González-Mariño et al., 2021)
Bezafibrate	50	2	(Gómez-Canela et al., 2019)
Carbamazepine	72	1.38	(Lacorte et al., 2021)
Codeine	29	3.45	(Rice et al., 2020)
Diazepam	50	2	(Gómez-Canela et al., 2019)
Diclofenac	65	1.54	(Gómez-Canela et al., 2019)
Hydrochlorothiazide	95	1.052	(Escolà Casas et al., 2021)
Losartan	3,5	28.9	(Riva et al., 2020)
Metamizole	50	2	(Gómez-Canela et al., 2019)
Omeprazole	23	4.35	(Gómez-Canela et al., 2019)
Pentoxifylline	1	100	(Gómez-Canela et al., 2019)
Quetiapine	1	100	(Escolà Casas et al., 2021)
Tramadol	30	3.3	(Rice et al., 2020)
Trazodone	21	4.76	(Lacorte et al., 2021)
Valsartan	13	7.69	(Escolà Casas et al., 2021)
Venlafaxine	5	20	(Escolà Casas et al., 2021; Rice et al., 2020)

For those pharmaceuticals whose values could not be found (i.e., diazepam and metamizole), a default value of 0.5 was applied considering that a pharmaceutical will not be fully excreted as parent compound.

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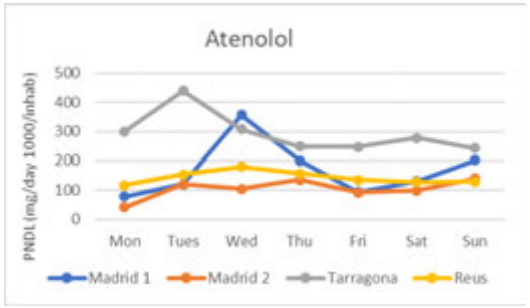
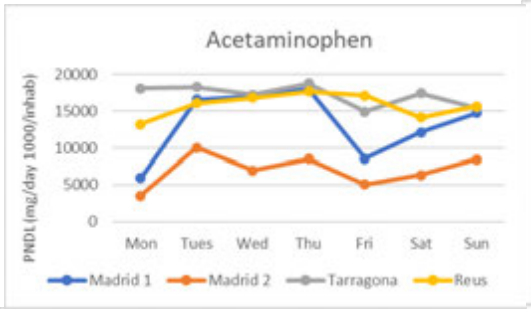
Table S5. Therapeutic class, ATC code (www.drug bank) and dose (ATC/DDD index 2023; https://www.whocc.no/atc_ddd_index/).

Pharmaceutical	Therapeutical class			ATC code	dose (mg)
Acetaminophen	Nervous system	Other analgesics and antipyretics	Anilides	N02BE01	3000
Atenolol	Cardiovascular system	Beta blocking agents	Beta blocking agents, selective	C07AB03	75
Bezafibrate	Cardiovascular system	Lipid modifying agents	Fibrates	C10AB02	600
Carbamazepine	Nervous system	Antiepileptics	Carboxamide derivatives	N03AF01	1000
Codeine	Respiratory system	Cough suppressants	Opium alkaloids and derivatives	R05DA04	100
Diazepam	Nervous system	Anxiolytics	Benzodiazepine derivatives	N05BA01	10
Diclofenac	Musculo-skeletal system	Anti-inflammatory and antirheumatic products, non-steroids	Acetic acid derivatives and related substances	M01AB05	100
Hydrochlorothiazide	Cardiovascular system	Low-ceiling diuretics, thiazides	Thiazides, plain	C03AA03	25
Losartan	Cardiovascular system	Agents acting on the renin-angiotensin system	Angiotensin II receptor blockers (ARBs), plain	C09CA01	50
Metamizole	Nervous system	Other analgesics and antipyretics	Pyrazolones	N02BB02	3000
Omeprazole	Alimentary track and metabolism	Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	Proton pump inhibitors	A02BC01	20
Pentoxifylline	Cardiovascular system	Peripheral vasodilators	Purine derivatives	C04AD03	30
Quetiapine	Nervous system	Antipsychotics	Diazepines, oxazepines, thiazepines and oxepines	N05AH04	40
Tramadol	Nervous system	Opioids	Other opioids	N02AX02	30
Trazodone	Nervous system	Psych analeptics	Other antidepressants	N06AX05	300
Valsartan	Cardiovascular system	Agents acting on the renin-angiotensin system	Angiotensin II receptor blockers (arbs), plain	C09CA03	80
Venlafaxine	Nervous system	Antidepressants	Other antidepressants	N06AX16	100

Table S6. Population-normalized daily loads for the studied pharmaceuticals per WWTP mg day^{-1} 1000 inh^{-1}).

	Population normalized daily load (mg day^{-1} 1000 inh^{-1})							
	Madrid 1		Madrid 2		Tarragona		Reus	
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
4-acetamidoantipyrine	1226 - 3275	2365 ± 696	658 - 1875	1371 ± 469	1630 - 2186	1963 ± 220	1967 - 2689	2429 ± 263
Acetaminophen	5911 - 17985	13259 ± 4598	3539-10029	6984 ± 2220	15453 - 18264	17162 ± 1457	13224 - 17660	15807 ± 1624
Atenolol	78 - 357	169 ± 96	42 - 135	105 ± 33	242 - 440	294 ± 69	116 - 181	143 ± 22
Bezafibrate	<MDL - 104	36 ± 36	6 - 39	26 ± 12	<MDL - 38	15 ± 14	151 - 214	182 ± 24
Carbamazepine	4 - 20	11 ± 6	2 - 16	8 ± 5	12 - 15	14 ± 1	11 - 23	17 ± 4
Codeine	27 - 68	46 ± 17	11 - 56	37 ± 14	51 - 75	60 ± 9	46 - 67	53 ± 7
Diazepam	4 - 44	14 ± 15	9 - 56	24 ± 16	3 - 16	6 ± 5	5 - 8	6 ± 1
Diclofenac	106 - 423	240 ± 119	65 - 677	326 ± 200	120 - 473	236 ± 125	186 - 744	325 ± 190
Hydrochlorothiazide	319 - 978	638 ± 242	160 - 521	363 ± 110	598 - 837	706 ± 97	646 - 847	764 ± 70
Losartan	174 - 338	271 ± 78	85 - 281	192 ± 63	182 - 283	250 ± 45	242 - 327	281 ± 33
Omeprazole	33 - 138	93 ± 38	16 - 190	106 ± 60	79 - 127	101 ± 20	65 - 130	96 ± 24
Pentoxifylline	8 - 21	15 ± 5	7 - 13	9 ± 3	7 - 19	13 ± 5	40 - 48	43 ± 3
Quetiapine	35 - 65	51 ± 11	34 - 87	64 ± 19	17 - 24	21 ± 3	54 - 78	67 ± 9
Tramadol	110 - 362	241 ± 101	67 - 384	236 ± 95	204 - 321	267 ± 43	353 - 455	394 ± 43
Trazodone	44 - 78	66 ± 13	19 - 94	57 ± 25	27 - 34	31 ± 2	30 - 41	35 ± 4
Valsartan	1177 - 2677	2006 ± 541	579 - 1609	1139 ± 406	571 - 1773	1196 ± 427	1605 - 2626	2041 ± 352
Venlafaxine	58 - 225	143 ± 66	42 - 358	191 ± 100	446 - 530	479 ± 32	218 - 346	259 ± 43


Atenolol
PNDL (mg/day 1000/inhab)
500
400
300
200
100
0
Mon Tues Wed Thu Fri Sat Sun
Madrid 1 Madrid 2 Tarragona Reus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10000
5000
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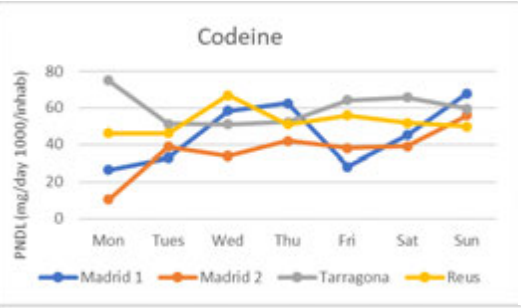
Madrid 1 Madrid 2 Tarragona Reus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40
20
0
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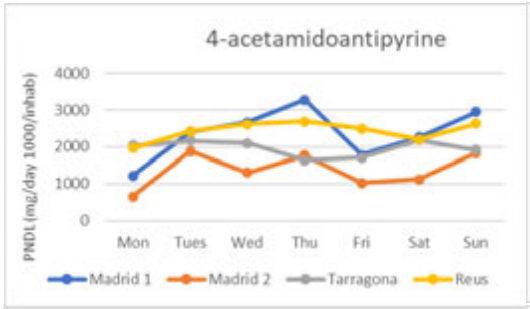
Madrid 1 Madrid 2 Tarragona Reus


4-acetamidoantipyrine
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3000
2000
1000
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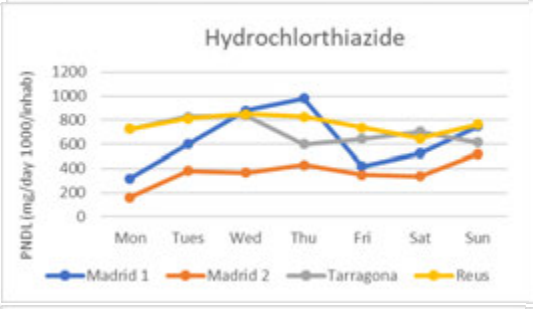
Madrid 1 Madrid 2 Tarragona Reus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600
400
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0
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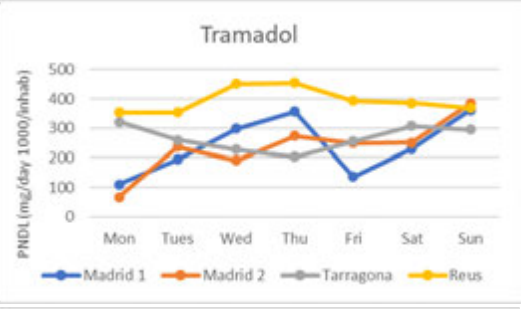
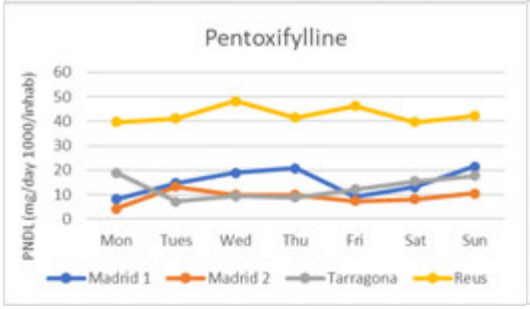
Madrid 1 Madrid 2 Tarragona Reus


Tramadol
PNDL (mg/day 1000/inhab)
500
400
300
200
100
0
Mon Tues Wed Thu Fri Sat Sun
Madrid 1 Madrid 2 Tarragona Reus


Pentoxifylline
PNDL (mg/day 1000/inhab)
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30
20
10
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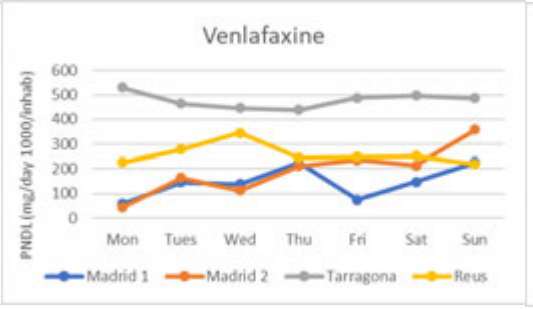
Venlafaxine
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500
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300
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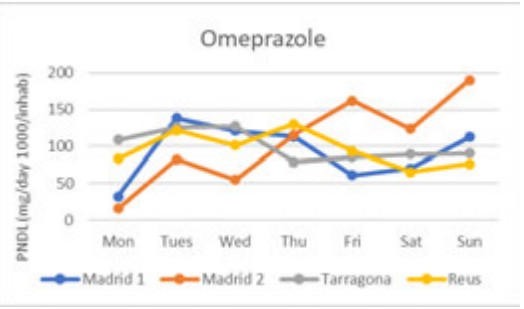
Madrid 1 Madrid 2 Tarragona Reus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PNDL (mg/day 1000/inhab)
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150
100
50
0
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Madrid 1 Madrid 2 Tarragona Reus

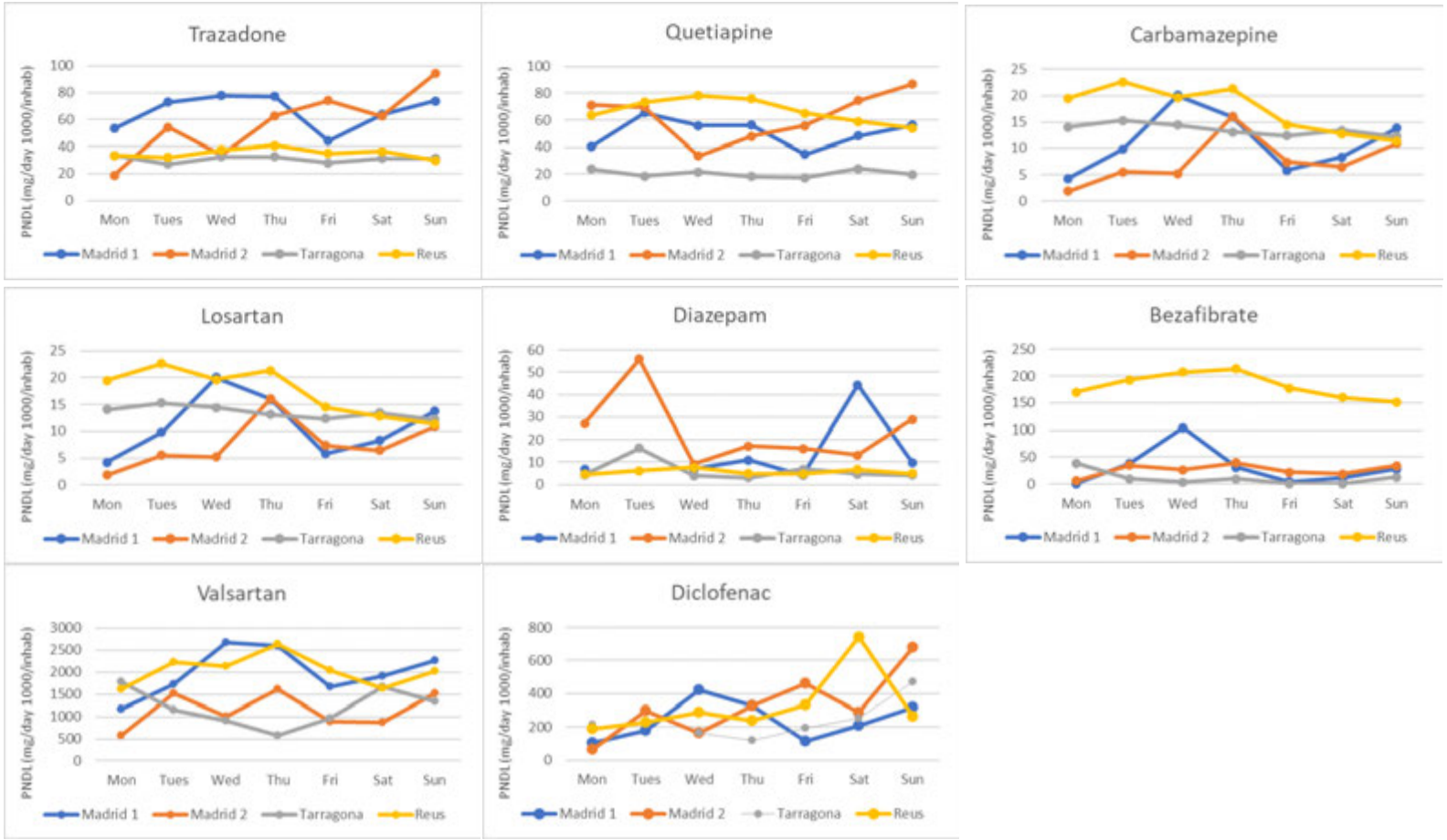

Figure S1. Plots showing the week trends of the PNDLs of each studied pharmaceutical for the four WWTPs.