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Recent trends in wastewater-based epidemiology of pharmaceuticals. Methods and applications

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ABSTRACT

This review article discusses the latest research on wastewater-based epidemiology (WBE) of pharmaceuticals since 2020. It covers the analytical methods that have been used to measure pharmaceuticals and their metabolites, mostly relying on off-line solid-phase extraction followed by liquid chromatography-tandem mass spectrometry. Then, we focus on general considerations related to WBE, such as biomarkers stability or back-calculation of drug use by using correction factors. We found that over 130 drugs have been analyzed and their wastewater concentrations converted to pharmaceutical use estimations, of which those related with the nervous system (ATC level 1 code N) have been by far the most frequently investigated. Subsequently the review focusses on studies related to the spatio-temporal assessment of drug use, with a specific section devoted to the impact of COVID-19 pandemic. Then, it covers studies which contrast WBE estimations of drug use with pharmaceutical dispensing data and how they complement each other.

1. Introduction

The development of our society and improvement of the quality of life is clearly linked to the development of medicine and availability of pharmaceuticals to treat different pathologies and their symptoms. Actually, the global use of pharmaceuticals was estimated to be around 3.4 trillion of Defined Daily Doses (DDD) in 2023 and these figures are expected to keep growing [1]. It is equally crucial to acknowledge the growing issue of inappropriate medication use, which encompasses a wide range of concerns, including increased morbidity and mortality, unnecessary medicalization, adverse drug reactions, and the escalation of antimicrobial resistance. According to estimates by the World Health Organization (WHO), more than half of all medicines are prescribed, dispensed, or sold incorrectly, and approximately 50% of patients do not adhere to proper usage guidelines [2].

Furthermore, there is a potential for drug misuse or abuse, particularly in the case of psychoactive drugs, that may also result in societal costs [3,4]. This includes the consumption of a medication that has not been prescribed to the user, or that is consumed in a manner not intended by the prescriber (e.g. taking higher doses or using non-approved routes of administration). Moreover, it encompasses scenarios where the medication is procured illegally, such as through illicit dealers or online sources, or is obtained under false pretences, including feigning symptoms [5]. Lastly, the use of pharmaceuticals also entails environmental repercussions. In 2016, a global literature review of studies that measured environmental concentrations of pharmaceuticals detected a total of 631 different drugs or their metabolites and transformation products in the environment of 71 countries [6]. The German Federal Environment Agency (UBA) collects information on the presence of pharmaceuticals, metabolites and transformation products in different environmental matrices. The latest version of this database, which contains data available up to 2021, describes the presence of 992 different pharmaceuticals in the environment [7].

Because of this, the use of pharmaceuticals needs to be monitored.

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Extensive research on drug use has been conducted over the last few decades [8]. These studies are mainly based on data on sales, turnover, prescriptions and movements throughout the pharmaceutical product distribution chain. However, the use of these data may result in an inaccurate estimation, due to the concurrent dispensation of pharmaceuticals by public and private healthcare institutions, or even because of the (combined) use of over-the-counter (OTC) drugs or the illegal trade or clandestine manufacturing of pharmaceuticals.

In this context, wastewater-based epidemiology (WBE) is an interesting tool which can provide rapid and local information, which is more difficult to obtain in a cost-effective way by other classical epidemiological indicators. WBE relies on the determination of drug residues (either the drug itself or its metabolites) in untreated wastewater, which combined with data on wastewater flows and population data can produce a reliable estimation of drug use. Although WBE initially targeted illicit drugs [9–12], its scope has broadened to encompass pharmaceuticals, driven by their potential for misuse among other applications. An excellent review on the applications of WBE for estimating pharmaceutical use was published by Boogaerts et al. in early 2021 [13]. Given that such publication had already examined trends in pharmaceutical use for the period 2008–March 2021 [13], the present review has been restricted to the years 2020–2025. The inclusion of the year 2020 was considered essential to capture the spatio-temporal patterns associated with the onset and progression of the COVID-19 pandemic. The Web of Science database was used to conduct the literature search in September 2025 using the following items:

[[“Wastewater-based epidemiology”] OR [“surveillance” AND “wastewater”]] AND [“pharmaceuticals” OR “medicines”]

Document type “Article”

Publication years “2020-2025”.

After a preliminary screening against the eligibility criteria, 78 publications were selected for this review, including those focusing on analytical aspects and/or performing WBE calculations and interpretations. A summary of the pharmaceutical classes considered in those publications is presented in Table 1, where they are grouped according to their Level 1 ATC code, together with examples of the main subfamilies and target drugs.

In the following sections we discuss key topics related to the: analytical methodology used to extract, separate and quantify pharmaceuticals and their metabolites in wastewater; and selected WBE considerations and applications.

Table 1
Summary of pharmaceuticals for which references have been encountered according to the level 1 ATC code and examples of drugs considered.

Level 1 ATC code	Main subfamily groups	Examples of pharmaceuticals investigated
A - Alimentary tract and metabolism	Anti-diabetic agents, anti-obesity drugs, acid disorders drugs	Metformin, glipizide, atorvastatin, bezafibrate, omeprazole
C - Cardiovascular system	Beta-blockers, antihypertensives, angiotensin II receptor blockers, diuretics	Atenolol, metoprolol, valsartan, atorvastatin
G- Genito urinary system and sex hormones	Urologicals	Sildenafil
H - Systemic hormonal preparations, excluding sex hormones and insulins	Corticosteroids, thyroid hormone replacement	Dexamethasone, levothyroxine
J - Anti-infective for systemic use	Antivirals, antimicrobial and antibiotics	Acyclovir, ciprofloxacin, azithromycin, sulfamethoxazole, darunavir, ritonavir
L - Antineoplastic and immunomodulating agents	Antineoplastic agents	Tamoxifen, cyclophosphamide
M - Musculo-skeletal system	Non-steroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen, naproxen, diclofenac
N - Nervous system	Opioid or non-opioid analgesics, antipsychotics, anxiolytics, antiepileptics and antidepressants	Amisulpride, carbamazepine, fluoxetine, sertraline, acetaminophen, tramadol, venlafaxine, morphine, citalopram, diazepam, temazepam, nordiazepam, oxycodone, codeine
P- Antiparasitic products, insecticides and repellents	Antiprotozoals, anthelmintics	Hydroxychloroquine
R - Respiratory system	Anti-asthmatics and bronchodilators, antihistamines, cough and cold preparations	Salbutamol, salmeterol, fexofenadine, ephedrine,
S - Sensory organs	Antibiotics	Brinzolamide
V - Various	Contrast iodinated drugs	Iodixanol

2. Analytical methodologies

Table 2 and Fig. 1 summarize the most relevant features of the analytical methodologies published in the last years. Several of the methods presented include analytes other than pharmaceuticals and their metabolites, as e.g. illicit drugs or other contaminants of emerging concern (for example personal care products), since both extraction and further determination methods are similar to those used for other substances, particularly for illicit drugs. A brief discussion on sampling and sample preparation and further determination is presented below.

2.1. Sampling and sample pretreatment

The commonest way to obtain a representative sample is to collect 24-h composite samples with autosamplers, performing both flow-proportional [41,43] or time-proportional [26,36,77] sampling. Some studies combine the two sampling methods, as covering a large number of wastewater treatment plants (WWTPs) require different approaches [30]. Spot sampling was performed only in one study, but in this specific case samples were used for screening purposes only [17]. Alternatively, some authors used passive samplers such as Polar Organic Chemical Integrative Sampler (POCIS) [83], Speedisks [82], and microporous polyethylene tubes (MPT) [84,72], all of them containing polar reversed-phase solid-phase extraction (SPE) sorbents (Table 2). The results of passive samplers show, however, an underestimation of concentration level compared with the SPE procedures when samples were collected at the same time [72]. There is also an on-line SPE-liquid chromatography-mass spectrometry (LC-MS) analysis procedure established *in situ* at the WWTP with satisfactory results [81].

The first step in sample preparation usually corresponds to the elimination of suspended particulate matter. This is most of the times achieved by filtration, where glass fiber (GF), with different porous sizes [28,48,62,85], is the most popular material. Yet, some authors prefer the use of centrifugation as an alternative to filtration [30,72,48,27,33,51,60,64,71,74]. The addition of internal standards is also a common step that may be done before [30,62,33,19,20,35,37,38,47,50,57,59,65,73,75] or after [81,85,28,27,14,34,42,46,66,67,70,76,80,86] the filtration or centrifugation step. At this point, although most pharmaceuticals are polar, it has been shown that some analytes (e.g. some antidepressants) may be partially lost during the filtration step [87]. In such cases, this can be minimized by selecting the appropriate filter material (GF seems to be less prone to this issue) or adding methanol to the sample, while the addition of the surrogate internal standards prior filtration is a must.

Once the particulate matter has been eliminated, most published methods rely on SPE for sample preconcentration, followed by methods based on the direct injection of the filtered sample (Fig. 1). Obviously, direct injection is only feasible when the concentrations are high enough and/or a high-sensitivity LC-tandem mass spectrometry (LC-MS/MS) instrumentation is available. Thus, even both approaches can be

Table 2
Overview of methodologies published in the last 5 years for the determination of pharmaceuticals and their metabolites in wastewater.

Sample preparation[a]	Determination technique[a]	Therapeutic family[b]	Reference
Direct injection	LC- QqQ	N	[14]
Direct injection	LC-QTRAP	N, J, R, S, C	[15]
Direct injection	LC-QTRAP	C, N, M	[16]
Direct injection	LC-Orbitrap	J, L, N, R, C, A, S, V	[17]
Direct injection	LC-QqQ	N, C, A, R	[18]
Direct injection	LC-QTRAP	J, N	[19]
Direct injection	LC-QqQ	A, C, G, J, L, M, N, R, V	[20]
Direct injection	LC-QqQ	A, C, G, J, M, N, R	[21]
Direct injection	LC-QqQ	C, J, N	[22]
Direct injection	LC-QqQ	J	[23]
Direct Injection and SPE with StrataX	LC-LC-QqQ	A, N, J, C, M, G, R, L, S, H	[24,25]
SPE with Oasis HLB	LC-QqQ	N, C, G, R	[26]
SPE with Oasis HLB	LC-QqQ	N, C	[27]
SPE with Oasis HLB	LC-QTRAP	M	[28]
SPE with Oasis HLB	LC-QTRAP	A, C, J, M, N	[29]
SPE with Oasis HLB	LC-QqQ	N	[30,31]
SPE with Oasis HLB	LC-QqQ	N, C, M	[32]
SPE with Oasis HLB	LC-QqQ	N, C, M, G, J, S	[33]
SPE with Oasis HLB	LC-QqQ	J, G, H, M, S	[34]
SPE with Oasis HLB	LC-QqQ	J, A, S, M	[35]
SPE with Oasis HLB	LC-QqQ	J	[36,37,38,39,40]
SPE with Oasis HLB	LC-QqQ	M, N	[41]
SPE with Oasis HLB	LC-QqQ	C, M, N	[42]
SPE with Oasis HLB	LC-QqQ	A, C, L, N, R	[43]
SPE with Oasis HLB	LC-QqQ	A, C, M, N, R	[44]
SPE with Oasis HLB	LC-QqQ	N, M	[45]
SPE with Oasis HLB	LC-QqQ	A	[46]
SPE with Oasis HLB	LC-QqQ	M	[47]
SPE with Oasis HLB	LC-QqQ	A, C, G, J, M, N, R	[48]
SPE with Oasis HLB	LC-Orbitrap	N	[49]
SPE with Oasis HLB	LC-QqQ	A, M, N, R	[50]
SPE with Oasis HLB	LC-QqQ	A, C, J, M, N, R	[51]
SPE with Oasis HLB	LC-QqQ	N, C, A, R, S	[52]
SPE with Oasis HLB	LC-QqQ	C, G, J, M, N	[53]
SPE with Oasis HLB	LC-Orbitrap	A, C, H, J, M, N, R	[54]
SPE with Oasis HLB	LC-Orbitrap	N	[55]
SPE with PRiME HLB	LC-QqQ	N	[56]
SPE with PRiME HLB	LC-QqQ	R	[57]
SPE with Oasis MCX	LC-QqQ	N	[58]
SPE with Oasis MCX	LC-QqQ	N	[59]
SPE with Oasis MCX	LC-QqQ	M, N	[60]
SPE with Oasis MCX	LC-QTRAP	R	[61]
SPE with Oasis MCX	LC-QqQ	G, N, C, A	[62]
SPE with Oasis MCX	LC-QqQ	A, C, M, N, V	[63]
SPE with Oasis MCX 96-well plate	LC-QqQ	N	[64,65]
SPE with Oasis WCX	LC-QqQ	A	[66]
SPE with Strata-X-CW + Derivatization	GC-Q	A	[67]
SPE with Strata-X-CW	LC-QqQ	N	[68]
SPE with Cleanert PCX	LC-QqQ	N	[69]
SPE with Thermo PEP	LC-QqQ	J	[70]
SPE with Cleanert PEP-2	LC-QqQ	R, C, A, J, G, M, N, S	[71]
SPE with UCT XRADH 506	LC-QTRAP	N	[72]
SPE with Oasis HLB and MCX	LC-QqQ and LC-QTOF	A, C, G, H, J, L, M, N, R, S	[73]
SPE with Oasis HLB and MCX	LC-QqQ	N	[74,75]
SPE with Oasis HLB and MCX	LC-Orbitrap	A, C, J, M, N, R	[76]
SPE with Oasis HLB, PRiME HLB and MAX	LC-QqQ	A, C, M	[77]
Tandem SPE with Oasis HLB and ENVI–CARB	LC-QqQ	A, C	[78]
SPE with cartridges: Oasis HLB + Isolute ENV+ + Strata-X-AW + Strata-X-CW	LC-QTOF	A, C, G, H, J, L, M, N, R, S	[79]
On-line SPE with Hypersil Gold aQ C18 column	LC-QqQ	A, C, G, J, M, N, R	[80]
On-line SPE with Oasis HLB	LC-QTRAP	N, J, C, A, V	[81]
Passive sampling- Speedisk with DVB-HLB	LC-QqQ	C, G, J, M, N, V	[82]
Passive sampling - POCIS with Oasis HLB	LC-QqQ	N, C	[83]
Passive sampling - Microporous Polyethylene Tube with Strata-X	LC-QTRAP	A, C, J, M, N	[84]

[a] List of abbreviations: DVB: divinylbenzene; GC: gas chromatography; LC: liquid chromatography; Q: quadrupole; QqQ: triple quadrupole; QTOF: quadrupole-time of flight; QTRAP: quadrupole-linear ion trap.
[b] For brevity, the type of drugs analyzed are presented according to level 1 ATC codes (see Table 1 and S1).

combined for multiresidue methods which aim at covering different targets present at different concentrations [24,25]. In the case of SPE, the sorbent that has been, by far, the most popular one is Oasis HLB [41,43,26,30,36,28,74,51,27,33,37,35,73,38,34,47,50,46,42,29,31,39,40,44,45,49,52,54,55], followed by Oasis MCX [62,85,60,64,59,65,58,61,63] (Fig. 1). This is likely because Oasis HLB is a hydrophilic-lipophilic balance reversed-phase sorbent which works well for many compound polarities, while the mixed-mode Oasis MCX (which adds a strong cation exchanger to the structure of Oasis HLB) can improve the extraction efficiency or selectivity of basic analytes, as it is the case of many drugs. Other sorbents that have been used include Oasis PRiME HLB [57,56] for psychoactive drugs (many ATC level 1 code N) and beta-agonists; Strata-X or Strata-X-CW [67,24,68] for opioids, analgesics, antiepileptics, antihypertensives, the antidiabetic drug metformin, etc.; UCT XRADH 506 [72] for noroxycodone; PEP [71,70] for a wide range of pharmaceuticals; Oasis WCX [66] for metformin; and Cleanert PCX [69] for benzodiazepines. Yet, most of these sorbents are alternatives from manufacturers other than Waters or small modifications from this same manufacturer (e.g. Oasis PRiME HLB is very similar to Oasis HLB).

In some cases, where a wider range of polarities and acid-base properties are analyzed, several sorbents or even a mixed-bed cartridge are used. For instance, Galani et al. used a mixed-bed cartridge with up to four sorbents (Oasis HLB, Isolute ENV, Strata-X-CW and Strata-AW) for the extraction of a broad range of compounds, including antihypertensives, nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, antiepileptics, etc. [79]. Similarly, Yao et al. performed the SPE with two cartridges connected in tandem, Oasis HLB and ENVI-CARB, for chronic diseases treatment drugs [78] or for antidepressants, analgesics and antivirals [76]. In order to minimize sample intake and improve throughput, particularly when direct injection cannot suffice in terms of sensitivity, two alternatives have been proposed, the use of 96-well plates [64,65], for benzodiazepines, and on-line SPE, for a wide set of drugs [81,80], both of them requiring no more than 2 mL of sample.

2.2. Analytical determination

Several analytical methodologies have been developed over the years to determine pharmaceuticals in wastewater, however, most of them rely on similar principles, predominantly based on LC coupled with various mass spectrometric detection systems [81,74,68,32,88–90] (Table 2, Fig. 1). Regarding the chromatographic columns selected in studies over the last years, there is a clear preference for the use of ultra-high performance liquid chromatography (UHPLC) columns,

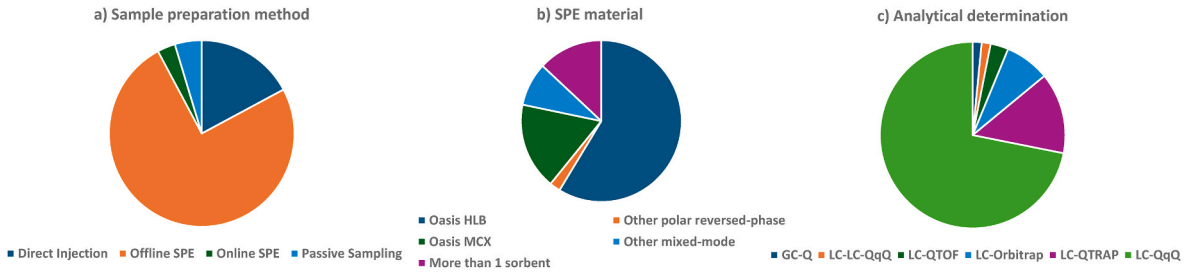

Fig. 1. Distribution of: a) sample preparation methods; b) sorbent used in those methods where off-line solid-phase extraction (SPE) is used; and c) analytical determination methodologies. GC: gas chromatography; LC: liquid chromatography; Q: quadrupole; QqQ: triple quadrupole; QTOF: quadrupole-time of flight; QTRAP: quadrupole-linear ion trap.

which allow for better chromatographic resolution, and for stationary phases working in reversed-phase mode, particularly C18. Yet, many authors opted for the use of polar endcapped or columns with an extended pH work range (such as Omega Polar C18 from Phenomenex, Zorbax Extend-C18 from Agilent, or BEH C18 from Waters, among others). This is due to the fact that many pharmaceuticals pose a basic character. For instance, in a work from González-Mariño et al. an extended-pH column was combined with a switch of pH across the gradient, when multiple illicit, drugs pharmaceuticals and metabolites were determined in a multiresidue method [87].

Also, because of this basic character, there is a general predominance of electrospray positive ionization mode that has prompted to use formic acid or ammonium acetate as modifiers in the LC mobile phases. As exceptional cases, it is important to highlight that two studies have employed two dimensional heart-cutting LC (LC-LC), combining a C18 and a polar-endcapped C12 columns to produce a multiresidue method [24,25] and, another study described the use of gas chromatography (GC) for the identification of more hydrophobic and volatile drugs [67] (Table 2).

All studies compiled in this review article have used MS techniques to identify and quantify pharmaceuticals in wastewater (Table 2). Depending on the objective of the study (target or screening), different mass analyzers have been used (Table 2, Fig. 1). The preference for target studies has led to the triple quadrupoles (QqQ) or the hybrid quadrupole-linear ion trap (QTRAP), normally used as a QqQ, as the most frequent analyzers.

3. WBE application

3.1. General considerations

As previously and widely described in the literature for illicit drugs, there are several factors that may influence the uncertainties related to the WBE process such as sampling, population estimation, stability of biomarkers in sewage water and back-calculation with the corresponding correction factors (CFs) [91]. Most of these aspects are independent of the target analytes and have been extensively discussed in the literature [91]. Thus, only some relevant developments will be commented here.

One relevant aspect is the stability of pharmaceutical biomarkers [91]. Stability may be evaluated in two different ways: in-sewer (through the sewage system) and in-sample (during the laboratory process). Most of the studies that evaluate in-sample stability focus on how the analytes degrade during different periods of time, temperatures and under different pH conditions. The temperature evaluation ranged from – 80 °C for antidepressant and antihypertensive drugs [85] to room temperature for a broad range of compounds (antidepressants, antihypertensives, opioids, beta-blockers, etc.) [43,77,30,85]. Also, intermediate temperature conditions, at – 20 °C and 4 °C stability conditions were evaluated, as they are the most frequent storage conditions prior to the analysis. In general terms, compounds showed a satisfactory stability under the selected storage conditions, including antidepressants [85], antihypertensives [77,85], antibiotics and their metabolites [70], psychoactive drugs [56], beta-agonists [77,57], metformin [66], etc. A clear exception are glucuronide metabolites, which are in most cases labile, but this is often considered when performing back-calculations, as discussed below.

Finally, pharmaceutical use estimation is based on CFs that take into consideration their urinary excretion profile [92]. Most CFs are calculated assuming that glucuronide metabolites are transformed into their free forms in sewage, yet a few benzodiazepine metabolite glucuronides have been shown to be partially stable in wastewater, and an enzymatic deconjugation has been recommended [93]. CFs can be calculated as presented in Eq. (1).

$$CF = \frac{1}{Excretion\ ratio} x \frac{MW_{drug}}{MW_{biomarker}} \quad \text{Eq. 1}$$

The excretion ratio is expressed as a fraction (not percentage) and MW refers to the molecular weight of the drug being investigated and its biomarker, i.e. metabolite or drug itself.

Details on the CFs that have been applied are presented in Table S1. In total 131 human pharmaceuticals have been translated into drug use by considering different CFs. It can be noted (Table S1) that different CFs have been used by different authors which may, or may not, have considered the former literature. This results in a lack of comparability. Furthermore, some studies use metabolites as biomarkers, while others make use of the parental drug. The first approach is typically preferred, as it reduces the risk of the interference on the results caused by eventual pharmaceuticals disposal of down the drain. However, this approach depends on the specific metabolic profile of each drug, the extent of existing knowledge, and the availability of appropriate standards. It is also remarkable that some studies employed different methods for obtaining the CF, as e.g., comparing WBE mass loads with prescriptions [14,16]; considering stability [94]; or accommodating the formula for incorporating excretion and the fraction lost in the sewer system [40,79]. Therefore, we recommend deeply investigating the available pharmacokinetic studies and former literature and also consider those publications which have already done so and provide curated CFs. Some examples are the publications from Ceolotto et al. which covers a wide range of drugs, such as analgesics, antiepileptics, antihistamines, etc. [43]; Yu et al. for NSAIDs, antihistamines, antibiotics, antivirals and antitussives [54]; and Sims et al. for antimicrobial agents [39].

Among the identified publications, the top-5 most studied pharmaceuticals (Fig. 2a) are nervous system (ATC level 1 N) drugs, including three antidepressant drugs (venlafaxine, citalopram and fluoxetine), an analgesic (tramadol), and the antiepileptic drug carbamazepine. Similarly, if we consider drug families, the most frequently studied class according to ATC level 1 code are nervous system drugs (N), which were converted to drug use in 20 of the 27 publications (Fig. 2b). It is also noteworthy that most of the publications considered several families together in multiresidue methods (Fig. 2c), where those families of drugs which are more frequently considered together include C

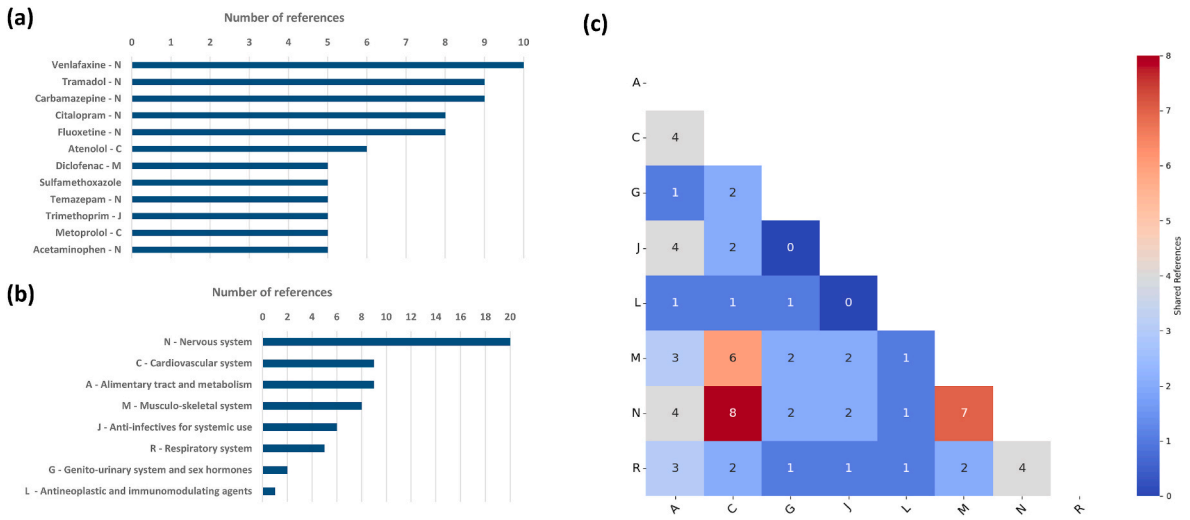

Fig. 2. Number of publications where biomarker concentrations were converted into drug use estimations by the use of CFs: (a) most frequently studied individual drugs, (b) most frequently studied families according to Level 1 ATC code, and (c) heatmap showing families that were considered together in a single study.

(Cardiovascular system), M (Musculo-skeletal system) and the previously cited N (Nervous system) ATC level 1 drugs. This is likely due to the fact that many drugs belonging to M and N classes can be prone to abuse or misuse (e.g. benzodiazepines, antidepressants, antipsychotics, opioid analgesics, etc.).

Between 2020 and 2025, a substantial number of scientific articles have examined pharmaceutical profiles, highlighting the need to identify emerging trends in order to better understand the future outlook of pharmaceutical use. Accordingly, from herein, this review section was further divided into the following overarching aspects: (i) the prevalence and evolution of pharmaceutical use through WBE, either from a general perspective (3.2), or evaluating the effect of the COVID-19 pandemic (3.3), and (ii) comparison with pharmaceutical dispensing data (3.4).

3.2. *Spatio-temporal trends*

To characterize WBE spatio-temporal variations, this review section focused on studies that explicitly investigated these patterns. Furthermore, general comparisons between studies were made when population-normalized daily loads (PNDLs) were available for the same family of target chemicals.

We selected the 11 longitudinal WBE studies that specifically analyzed pharmaceutical trends [41,26,60,33,71,20,76,25,39,44,22], excluding the studies related to trends during the COVID-19 period that will be specifically studied in Section 3.3. Such selected studies have covered spatio-temporal periods between 2014 and 2024 and were developed in different areas, such as Europe (United Kingdom (UK), Latvia, Spain …), China, the United States of America (USA) or South Africa (Table 3). In general terms, the most frequently studied pharmaceutical group in these papers was nervous system drugs (ATC level 1 code N), primarily analgesics and psycholeptic [41,26,60,33,71,20,76,25,44,22], followed by the musculo-skeletal system drugs (ATC level 1 code M), especially the NSAIDs [41,60,33,71,20,76,44], then, the cardiovascular system drugs (ATC level 1 code C), with a focus on beta-blockers [26,33,71,20,76,25,44,22] and finally, anti-infectives for systemic use (ATC level 1 code J), especially antimicrobial and antiviral agents [33,71,20,76,25,44,22] (Table 3), well in line with what has been overall found (see 3.1).

Wastewater levels over the countries confirm that the analgesic acetaminophen is the pharmaceutical drug more generally used by the population, with PNDLs ranging from 5 to 50 g/day/1000 inhabitants in many countries [41,71,44]. According to these investigations, the

Table 3
Summary of longitudinal studies conducted to estimate spatio-temporal variation of pharmaceuticals use through WBE, excluding those related to the COVID-19 pandemic (presented in Table 4).

Therapeutic family (ATC level 1 code)[a]	Period	Country	Ref.
N, G, R	2014-2018	UK	[26]
N, C, M, G, J, S	2018-2019	South Africa	[33]
N, A, J, C, D	2021	Latvia	[25]
R, C, A, J, G, M, N, S	2018-2019	China	[71]
M, N	2018-2019	UK	[41]
J	2018-2019	UK	[39]
A, C, G, J, L, M, N, R, V	2021-2022	Czech Republic	[20]
A, C, M, N, R	2022	Spain	[44]
C, J, N	2021-2022	Czech Republic	[22]
A, C, J, M, N, R	2022-2024	USA	[76]
M, N	Not disclosed	Belgium, Latvia, Lithuania and Rumania	[60]

[a] Please see Table 1.

substance has not experimented a notarial temporal variation over the studied periods, although a publication has reported a seasonal increase in use during winter [41]. Other pharmaceuticals which stand out for their widespread consumption are some NSAIDs, especially ibuprofen, with PNDLs rising to 30 g/day/1000 inhabitants in some Latvia regions [25], and diclofenac, showing levels around 0.5-2 g/day/1000 inhabitants [41,25,44]. Finally, some antihypertensives (such as valsartan) also showed high PNDLs in wastewater (around 1 g/day/1000 inhabitants) [25,44]. No clear long-term trend has been identified for those substances, excluding those reflected in Section 3.3 due to COVID-19 pandemic. However, seasonal variations have been observed in the case of NSAIDs. For instance, a study in the UK reports higher consumption during the winter months (Fig. 3) [41], whereas in Latvia, use tends to rise in both spring and summer time [25].

One of the most important target families in WBE research in the last years is opioid analgesics [41,26,33,76], likely because of their potential illicit use. Temporal analyses within this pharmacological class demonstrated heterogeneous patterns of use. A significant increase in oxymorphone and hydrocodone consumption was observed between 2014 and 2018 in several UK cities [26], with 2018 PNDL levels being six-to ten-fold higher than those reported in 2014. In contrast, morphine exhibited an upward trend only during 2014–2015, rising from 160 mg/day/1000 inhabitants in 2014 to 300 mg/day/1000 inhabitants in 2015, while tramadol declined significantly over that period [26]. More

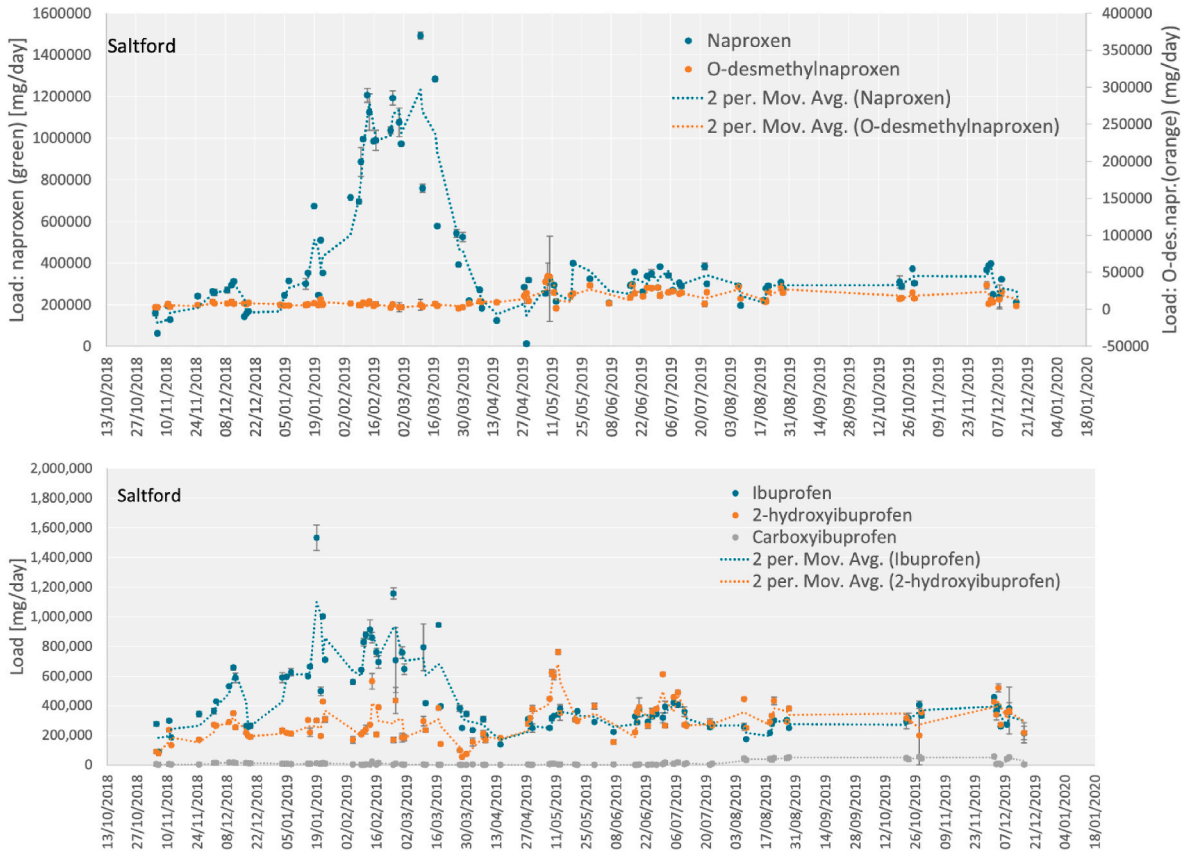

Fig. 3. Seasonal variation of the daily loads of naproxen, ibuprofen and their metabolites in Saltford (United Kingdom). Reproduced from Ref. [41].

recently, a parallel investigation conducted in the UK during 2021–2022 reported a stabilization in opioid consumption [41]. Nonetheless, this information contrasts with data obtained from a study conducted in the USA between 2022 and 2024, where the use of analgesic opioids has currently experienced an alarming increase [76]. Seasonal studies also show contrasts between countries, where, for example, opioids use increased during the warmer months in South Africa [33], while in the UK no clear seasonal variation was observed [41]. Thus, this reflects a very particular profile of opioid analgesic use depending on the country and time of the year.

Another example is related to benzodiazepine use, where trends also differ among countries [26,60,20]. PNDLs for diazepam metabolites, temazepam and nordiazepam, have experimented an increasing trend in UK over 2014-2018 (showing levels over 500 mg/day/1000 inhabitants and 100 mg/day/1000 inhabitants, respectively), while PNDLs in countries such as Belgium or Czech Republic were below 30 mg/day/1000 inhabitants for these biomarkers [60,20].

Finally, there is a group of drugs for which general seasonal trends have been detected in most countries: antibiotics and antivirals (Level 1 ATC codes S and J). A significant increasing consumption of these drugs in cold months, reflected in September-December months in countries in the northern hemisphere, has been determined [25,39,22]. This increase in consumption is mainly explained by the difference in temperature between the two seasons, which promotes respiratory tract infections. In addition, as many authors report, there is a widespread tendency to misuse antibiotics to treat viral diseases [95,96]. Curiously, a study carried out in South Africa showed no clear seasonal variation [33]. In the southern hemisphere, temperature contrasts between seasons are usually less extreme, which may explain why there is no clear increase in the colder months. The most commonly used and studied drug in this category is the antibiotic sulfamethoxazole, with PNDLs in wastewater ranging from 1 to 30 mg/day/1000 inhabitants [25,39]. Other seasonal trends observed in these studies were the upward trend in antihistamines use during May in China related to the increasing of allergies in spring season or the frequent use of alimentary tract and metabolism drugs (such as omeprazole) in Christmas time [71].

3.3. Impact of the COVID-19 pandemic on the use of pharmaceuticals

Prior to 2020, WBE studies typically focused on illicit substances and a limited range of pharmaceuticals; however, the emergence of COVID-19 rapidly expanded its application to encompass the monitoring of pharmaceuticals that included both OTC medications and drugs used specifically in COVID-19 treatment protocols. The global emergency created an unprecedented demand for rapid, community-level insights into health behaviors, treatment practices, and ultimately, emerging resistance patterns, making WBE an indispensable tool [97,98]. Table 4 summarizes the studies conducted to evaluate pharmaceuticals consumption during the pandemic situation in different regions.

Table 4
Summary of studies conducted to evaluate the COVID-19 pandemic influence on the use of pharmaceuticals by WBE.

Therapeutic family (ATC level 1 code)[a]	Period	Country	Ref.
A, C, H, J, N	2022	South Africa	[99]
A, C, J, L, N, R, S, V	2020	Italy	[17]
C, J, N, R, S	2019-2020	Italy	[15]
A, C, G, H, J, L, M, N,P, R, S	2019-2020	Greece	[79]
A, C, G, J, M, N, R	2020-2022	USA	[48]
A, C, J, N	2020-2021	Latvia	[100]
A, C, H, J, M, N, R	2022-2023	China	[54]
N	2020	Mexico	[31]
N	2019-2021	Slovenia	[65]
M, N	2020-2022	UK	[45]

[a] Please see Table 1.

Thus, studies conducted in countries such as Greece [79], Italy [17] and the USA [48], revealed, as expected, a dramatic surge in the use of antivirals and other medications, particularly during the different waves of the pandemic. Different antivirals were administered and monitored in WBE approaches depending on the country (darunavir, remdesivir, ritonavir, etc.) and a significant increase in their use was observed in all cases. Alongside antivirals, significant increases in the use of analgesics [17,48], particularly acetaminophen, were observed reflecting the widespread use of this analgesic as a first-line symptom reliever for fever and pain associated with COVID-19 [17,79]. This was particularly true after vaccination when the delta and particularly omicron variants became dominant, where a clear correlation was observed (Fig. 4) [48], likely due to the effect of vaccination and milder effects of those variants, which could be treated with OTC medicines. In countries such as UK [45] and China [54], the use of analgesics such as acetaminophen and NSAIDs such as ibuprofen was recommended by health authorities in response to the onset of symptoms. This surge in usage was clearly reflected in the results obtained through WBE.

An increase in the consumption of antibiotics was also reported [15,100], a trend that appears to be associated with the prophylactic use of antibiotics to guard against secondary bacterial infections in patients with COVID-19. This practice also raised concerns about the potential amplification of antimicrobial resistance (AMR) in the environment in that period [15,99]. Another example is hydroxychloroquine (tested at the time and later on questioned) that was for example detected at levels 387% higher than its usage during pre-pandemic periods in Greece [79].

The pandemic's psychological impact was also been mirrored in wastewater profiles through altered trends in psychiatric medications, including benzodiazepines, antidepressants, etc. [65,31], which could be consistent with the reported elevated rates of anxiety, depression, and sleep disorders in the general population during periods of prolonged lockdown and social isolation [31,101], in some specific cases such as lorazepam in USA, the found loads pointed to an increase in the consumption which contradicted the official prescription data suggesting the illegal access or access through private insurance [31]. In other countries, such as Slovenia, an increase trend in use was observed for antidepressants, such as venlafaxine, using WBE approaches, however, the findings perfectly aligned with an increase in the prescription supported by official data [65].

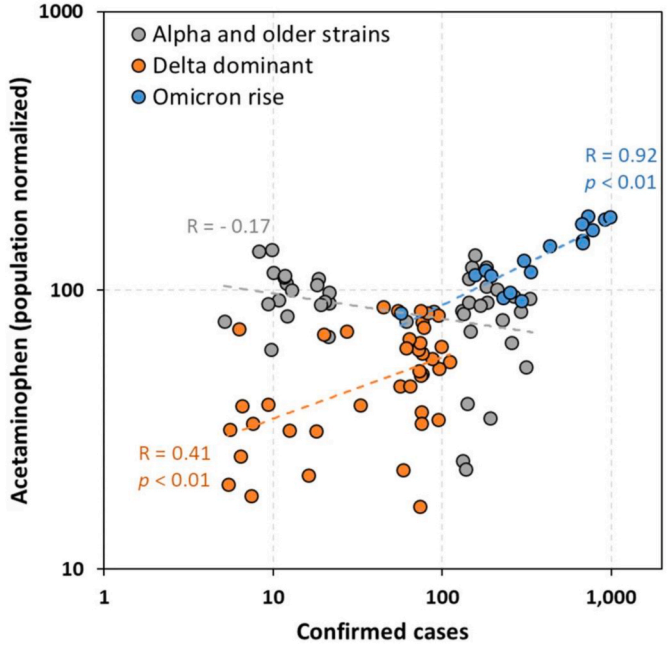

Fig. 4. Correlation of acetaminophen normalized loads compared to SARS-CoV-2 confirmed cases according to the dominant virus variant in Suffolk County, NY (USA). Reproduced from Ref. [48].

3.4. Dispensing data supplemented with WBE findings

Although WBE has proven to be a reliable approach for monitoring drug use, complementary sources of information are essential to reduce uncertainties and strengthen conclusions [91]. With this aim, pharmaceutical concentrations detected in wastewater can be compared with dispensing data reported by public health agencies. Some of the scientific studies included in this review performed such comparisons [43,26,85,27,38,29,44,22], the overall conclusions being presented here.

While these two methodologies are complementary, several factors must be considered when attempting to identify consistent trends. Prescription pharmaceuticals generally provide greater reliability when aligning WBE data with dispensing records, as their use typically follows regular patterns with higher levels of patient adherence. In contrast, non-prescription drugs are often purchased irregularly and may not be consumed immediately, or in some cases, at all. This distinction aligns with the results observed in WBE–dispensing data comparisons, where prescription drugs (e.g. antibiotics) usually exhibit strong correlations, whereas non-prescription drugs (e.g. many analgesics and NSAIDs) tend to show weak correlation and sometimes a totally different trend than the information obtained from wastewater (Fig. 5) [43,38,29]. Thus, WBE represents an advantage over dispensing data as true community use can be recorded at real time for both types of pharmaceuticals. Another key factor observed in those papers is related to the exclusivity of the biomarker. Pharmaceuticals that have an exclusive wastewater biomarker, either unchanged form or biotransformation product, will align better WBE with dispensing data. This problem has been observed for some benzodiazepines, such as diazepam, or morphine, where WBE levels are generally higher than dispensing data due to the cross-metabolism of several drugs [43,26]. In this case, complementation of both epidemiological indicators is essential to avoid overestimation in WBE results.

Considering both factors, studies that reveal similar trends from the two indicators but report low correlations between them can still provide valuable insights into the consumption of certain pharmaceuticals. In some cases, higher levels detected through WBE have suggested potential illicit use of specific substances (such in the case of ephedrine, codeine, or oxycodone) [26,27,44], reflected the uncertainties of the excretion rates employed in WBE-back calculations [43,16] or may advert on a direct discharges or incomplete dispensing data. On the contrary side, higher dispensing levels may also reflect uncertainties in the WBE methodology, such as the difficulty of aligning the medical area with the area covered by the WWTP [38] or lack of adherence to treatment.

Finally, another advantage of this comparison is the possibility of establishing disease prevalence correlations, because pharmaceuticals are excellent markers for the population health status [63]. This is reflected, for example, in the correlation of the use of hypertension (such as sotalol) or diabetes drugs (such as metformin) with the unhealthy lifestyle in some countries [77] or in the development of respiratory diseases or allergies linked to excessive use of tobacco or chemical products [61].

4. Conclusions and outlook

Several WBE applications have been developed over the last years, as this methodology has been fostered by the COVID-19 pandemic due to its popularity in following the viral load, but also because of its utility to track changes in pharmaceutical use. In these applications, WBE has shown its potential in assessing the actual amount of pharmaceuticals being used, complementing dispensing data by providing easy to achieve information on small time and spatial scales for a multitude of drug families. This was possible because of the knowledge gained for illicit drugs years monitoring by WBE in the former years, as methods can be

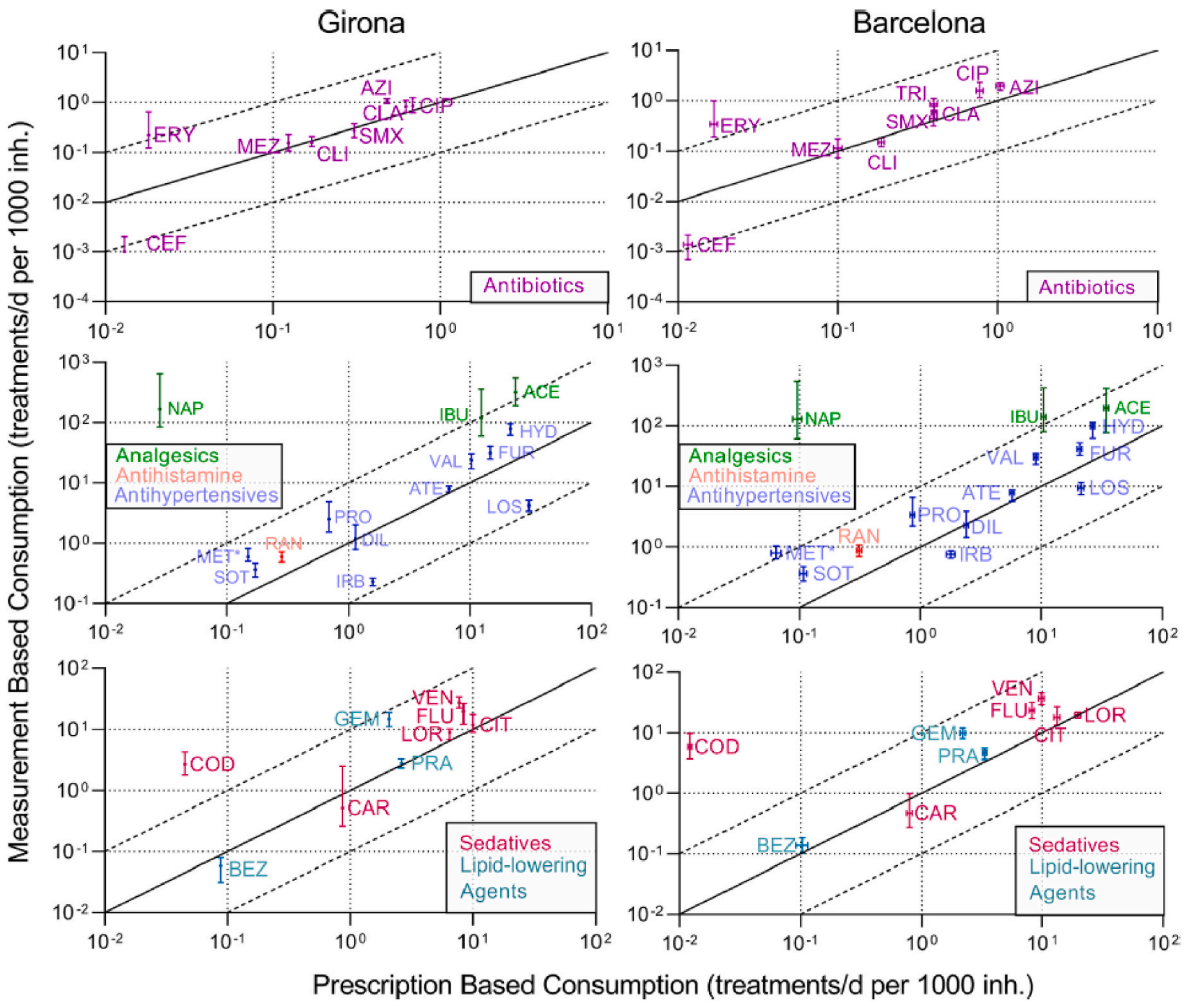

Fig. 5. Comparison of measured (by WBE) Vs. prescription-based pharmaceutical consumption in two Spanish cities. Reproduced from Ref. [29].

easily adapted in many cases and surrogate isotopically labelled standards are available.

A relevant challenge that still remains in some cases is the lack of extensive and publicly available pharmacokinetic studies [82] to properly assess the magnitude of pharmaceuticals use, though PNDLs can still be useful to follow trends.

CRediT authorship contribution statement

Carlos Pernas-Fraguela: Writing – original draft, Investigation, Conceptualization. **Rosa Montes:** Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Conceptualization. **Rosario Rodil:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Verónica Castro:** Writing – review & editing, Investigation. **José Benito Quintana:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Andrea Estévez-Danta:** Writing – original draft, Visualization, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: José Benito Quintana reports financial support was provided by Carlos III Health Institute. Andrea Estevez-Danta reports financial support was provided by Government of Galicia Department of Education Science Universities and Professional Training. Carlos Pernas-Fraguela reports financial support was provided by Spain Ministry of Education Vocational Training and Sports. Rosario Rodil & Rosa Montes reports financial support was provided by the Spain State Research Agency. All auhtors declare that no known furhter 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.trac.2026.118746.

Data availability

No data was used for the research described in the article.

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