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Electrochemical nanosensors in therapeutic pharmaceutical monitoring: from drug following to clinical protocols

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ABSTRACT

Therapeutic monitoring (TDM) combines the quantification of drug concentrations in the blood, pharmacological interpretation, and treatment guidance, introducing a valuable tool in precision medicine. However, quantifying drug concentrations requires expensive techniques, specialized laboratories, and trained personnel. A plausible alternative to solve this limitation is quantifying pharmaceutical compounds using nanosensors. This review starts by describing the standard methodology used in TDM to emphasize further how to explore electrochemical nanosensors for this purpose. It points out the advantages of electrochemical nanosensors compared to conventional methodologies based on their analytical features, potential for point-of-care applications, fast response, miniaturization, convenient operation, and portability. The review concludes by summarizing the patented work and discussing important points to consider in developing electrochemical nanosensors in clinical settings, as well as challenges and gaps that must be filled to introduce such new technological innovations in TDM and personalized therapy.

1. Introduction

The concept of therapeutic drug monitoring (TDM) started in 1970 with the basic principle based on the fact that some drugs show a close relationship between the plasma level of the drug and its clinical effect [1]. Medical doctors usually monitor the pharmacodynamics of medicines by directly measuring the physiological indices of therapeutic response, e.g., lipid concentrations, blood glucose, blood pressure, and coagulation tests. In other cases, it is difficult to distinguish between disease progression and the pharmacological effects of a drug. In these situations, TDM is an essential part of clinical management, which process is based on the assumption that there is a definable relationship between the dose and the concentration of the drug in plasma or blood and between the latter and the pharmacodynamic effects [2–4].

TDM is typically indicated in the following circumstances; coadministration of other drugs and genetic and/or environmental variations that alter the absorption, distribution, metabolism, and excretion of the drug, for example, drugs with saturable metabolism may lead to rapid accumulation of drugs to toxic concentrations (e.g., Phenytoin, Phenobarbital). Furthermore, in the context of precision medicine, TDM is crucial for managing drugs with a narrow therapeutic index, ensuring that serum concentrations remain within their therapeutic windows, and optimizing clinical outcomes, like prevention of adverse drug effects, another important fact, is the marked inter-individual pharmacokinetic variability, which increases the variability in the dose-plasma dose concentration relationship. Finally, noncompliance, low adherence to treatment and poorly defined clinical endpoint, severe toxicity coupled with a poorly defined or complex to detect clinical endpoint (e.g., Anticonvulsants and Cyclosporin) [5–7].

TDM is more than just analyzing a single drug concentration in a patient's blood and a measurement report. It also includes interpreting the measured value using mathematical (pharmacokinetic) principles, drawing the appropriate conclusions on the result, and advising the medical doctor who ordered the test on optimizing the treatment [7,8]. For example, when starting pharmacological therapy, the medical doctor may find it helpful to measure the plasma concentration of the drug and adjust the dose to the individual. It introduces a precision medicine tool in times of growing awareness about the need for personalized treatment, especially in the absence of clinical response in the therapeutic dose range, the evaluation of drug adherence, tolerability problems, pharmacological interactions, and the risk of producing resistance for some drugs. All of those mentioned above make it necessary to

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control drug serum concentrations due to the risk of undergoing intoxication [2]. Some drugs have high hepatic metabolism, interactions in the absorption and metabolism at the level of cytochrome P450, high plasma protein binding, frequent adverse effects, and difficulty adhering to treatment. Therefore, drug level measurements in plasma have been incorporated for many years to optimize patient use. They continue to be monitored toward personalized dosage, as the level obtained must always be interpreted concerning the therapeutic objective [3,9] (Table 1).

The need for fast, cost-affordable, and practical TDM methods is urgent to facilitate real-time monitoring in environments with limited access to equipped laboratories. Advances in electrochemical nanosensor technology offer a promising solution, with highly sensitive and specific devices allowing rapid and non-invasive sampling, providing trustable results at lower costs. Electrochemical sensing units can be easily miniaturized for point-of-care analysis [4]. In addition, modifying the sensing interface with nanomaterials and specific affinity layers may significantly improve the device's selectivity and sensitivity. Despite their features, implementing these nanosensors in clinical practice requires overcoming regulatory and logistical barriers and reaching a consensus between technology developers and medical personnel. Therefore, integrating these portable devices in real environments, such as hospitals and clinics, requires a joint effort with trained clinical staff, which is essential to ensure their effectiveness and accessibility [10]. We review recent progress in electrochemical nanosensors for monitoring therapeutic drugs, discussing their principles and transduction mechanisms, highlighting the analytical performance when monitoring various drugs, and mentioning practical biomedical applications. Finally, we highlight the last patents encompassing electrochemical sensors in drug analysis and essential points to consider in developing electrochemical nanosensors as a step forward to implementing these devices in clinical practice.

2. Current practice and recent advances

2.1. Conventional TDM

The measurement of plasma drug concentrations is only one of the steps in optimizing dosing. For example, when interpreting the plasma drug concentration, it is vital to match the treatment to the physiological needs of the patient, so not only the concentration but also other clinical characteristics that may affect the nuanced concentration-clinical effects relationship must be considered [5,6]. Conventionally, TDM establishes therapeutic ranges of exposure within the expected therapeutic range. This simple interpretation of the data allows for the dose adjustment with a "simple rule of three," which allows medical doctors to adjust the dose or the dosing interval. The most used strategy is Dettli's rules to keep the drug concentration in the therapeutic range based on creatinine clearance. In addition, an extension of these conventional therapeutic ranges is dosing nomograms to guide the adjustment of maintenance dose or dosing intervals [11,12].

When considering conventional TDM, some limitations have been identified. Sampling must be performed at a steady state. Quantification must be performed on the second or third day of treatment for drugs with a long half-life, hindering having immediate results for interpretation, which in the case of some pathologies is vital for directing treatment, e.g., infections [13]. Conventional TDM is a relatively passive approach that monitors and accepts the measured drug concentration as "therapeutic" if it is within the therapeutic range (sometimes quite broad), which can lead to a suboptimal achievement of the pharmacokinetic/pharmacodynamics (PK/PD) target. Finally, dose adjustment by the rule of three is not feasible for drugs whose pharmacokinetics are not linear as they are concentration- and/or time-dependent [14–16].

The adequate timing of blood sample collection is important in providing clinically valuable measurements regarding a patient's plasma drug concentration. Following the onset of treatment, plasma concentration values should be measured once the drug has reached a steady state concentration. A steady state occurs once equilibrium between administration and drug elimination has been established, after at least five half-lives when the drug is eliminated by 94–97 % [17]. For example, here are some recommendations for sample timing of some drugs to improve the TDM. (i) Carbamazepine's half-life maybe 48 hours following a single dose. A thorough concentration taken just after a dose and a peak level three hours later is ideal. (ii) Digoxin, the measurement must be made at least six hours after a dose to avoid inappropriate high levels. (iii) Gentamicin, pre-dose peak; half hour after intravenous (I.V) and one hour after intramuscular (I.M) administration. (iv) Lithium, a twelve-hour sample, gives the most precise guide to dosage adjustment. (v) A sample of phenobarbitone at any time is sufficient. (vi) Phenytoin, since it has a long half-life, a single daily dose may be employed, so the timing of concentration monitoring is not critical. (ii) Theophylline has a narrow therapeutic index, and the sampling timing is not critical if the patient receives one of the slow-release formulations [2].

Table 1
Drug concentrations that require monitoring of treatment in biofluids.

Pharmacological group	Drug	Sample timing (h)	Concentration	Steady-state (days)	Sample
Anticonvulsivants	Valproic acid	3 to 7	50 to 100 mg/L	2 to 4	Plasma
	Carbamazepine	4 to 8	4 to 12 mg/L	2 to 4	Plasma
	Phenytoin	1to12	10 to 20 mg/L	6 to 21	Plasma
	Phenobarbital	2 to 4	10 to 40 mg/L	15 to 29	Plasma
Antibiotics	Amikacin	30 min after the end of the intravenous infusion	<1mg/L	Non reported (N.r)	Plasma or serum
	Gentamicin	30 min after the end of the intravenous infusion	<1mg/L	N.r	Plasma or serum
	Vancomicin	0.5 to 2	10 to 20 mg/L	1 to 2	Plasma or serum
	Voriconazole		1–5 mg/L		Plasma or serum
Immunosuppressors	Cyclosporin	1 to 4	150–2000 μg/L	3 to 5	Whole blood
	Methotrexate	0.5 to 5	24 h < 10 μmol/L 48 h < 1 μmol/L 72 h < 0.1μmol/L	4 to 5	Plasma
	Sirolimus	1 to 2	5 to 10 μg/L	12 to 17	Whole blood
	Tacrolimus	0.5 to 6	5 to 20 μg/ml	8 to 10	Whole blood
	Mycophenolic acid	1 to 1.5	1 to 4 mg/L	3 to 5	Whole blood
Cardioactive drugs	Digoxin	1 to1.5	0.8 to 1.8 ng/mL	20 to 35	Plasma
Antineoplastic	Irinotecan	1 to 3	Cmax < 10 mg/L	NA	Plasma
	5-fluorouracil	1	AUC: 20–25 or 20–30 mg·h/L	NA	Serum
	Tamoxifen	5	≥0.02 μM	NA	Serum

2.2. Dispensing based on TDM precision model

The leading causes of unexpected serum concentrations in patients are non-compliance, inadequate dosing, poor absorption, low bioavailability, pharmacological interactions, liver or kidney disease, altered protein binding, and genetic factors. Whether these factors cannot be eliminated, dose adjustment is required [14]. Using mathematical models individualized to the pharmacological group, considering the individual characteristics and populations that may affect PK/PD, has gained strength in recent years and involves several components: (i) concentration-time profile, whose model describes typical pharmacokinetics. (ii) A covariable submodel that defines the relationship between PK parameters and patient-specificity such as body weight, age, organic function markers, or combined medication, and (iii) a mathematical representation of the inter- and intra-individual variability of the PK parameter and the residual variation around the individually predicted drug concentration-time profiles that explain the differences with observed concentrations [17–19]. Another model is Bayesian statistics, where a maximum *a posteriori* probability (MAP) estimate relies on estimating an unknown quantity that equals the mode of the posterior distribution. The PK model population provides this *a priori* parameter distribution to estimate the most likely PK parameters for one individual given a set of patient-related data (i.e., observed concentrations and covariates). An individualized dose can then be calculated based on the patient's *a posteriori* parameters [17]. Assistance in dosage adjustment model-informed precision dosing platforms already exist, e.g., DoseMe (https://doseme-rx.com/ (accessed on 8 July 2024), BestDose (https://bestdose.software.informer.com/ (accessed on 8 July 2024), TUCUXI software (http://www.tucuxi.ch/ (accessed on 8 July 2024), InsightRx (https://www.insight-rx.com/ (accessed on 8 July 2024).

2.3. Analytical methodology

Determining complex active substances in the body is challenging because matrices such as body fluids, tissues, and organs can be very variable when quantifying body drugs. Therefore, the analytical methodology to be used for this purpose should [2,15]: (i) distinguish between compounds of similar structure, unmodified drugs, and metabolites. (ii) Detect small amounts. (iii) Minimize the matrix effect. (iv) Not be affected by other drugs administered simultaneously. It distinguishes several clinical analytical methods to determine medicines in TDM, including the chromatographic method and immunological analysis. The main differences between the methods relate to the differential detection of metabolites, as spectrometric tests are more specific than immunological analyses [20].

Chromatographic analysis refers to various techniques that leverage differences in component distribution between stationary and mobile phases to separate and identify mixtures of compounds. The chromatography used in TDM for some pharmacological groups includes high performance liquid chromatography (HPLC), ultra-performance liquid chromatography-mass spectrometry (UPLC-MS), and gas chromatography (GC) [21–23]. HPLC with various detectors is one of the most widely used analytical methods for TDM in clinical laboratories because this technique can simultaneously measure multiple drugs in a single sample. Also, it can separate metabolites from the parent compound. Limitations of these chromatography methods include high purchase and maintenance costs, the need for specifically trained staff, complex method validation, limited robustness, minimal automation, limited manufacturer technical support, and a dedicated laboratory. In addition, sample pretreatment and separation can be complicated and time-consuming, and batch testing and establishing universal laboratory standards can be challenging [21].

Immunoassays have been widely used for drug tracking. The basic principle depends on detecting an analyte by binding to specific antibodies, making them useful for detecting and quantitating analytes in complex sample matrices such as body fluids, including blood, urine, saliva, sweat, or vitreous humor. This methodology has low sample volume requirements and high-performance adaptability; it is simple and low-cost [1]. The test design can be classified into competitive and sandwich-like modes, mainly used for analytics with small or large molecular weights. For example, chemiluminescent enzyme immunoassay (CLIA), chemiluminescent microparticle immunoassay (CMIA), enzyme-linked immunosorbent assay (ELISA), fluorescence polarization immunoassay (FPIA), microparticle enzyme immunoassay (MEIA); antibody conjugated magnetic immunoassay (ACMIA) and cloned enzyme donor immunoassay (CEDIA) [21–25]. However, the specificity of these methods is sometimes restricted due to the structural similarity of the drugs to each other or their metabolites. Then, the prevailing limitation of immunoassay is cross-reactivity with metabolites of the parent drug.

In summary, TDM is a clinical decision-making tool that enables dosage regimen adjustments based on clinical and laboratory measurements, typically drug blood concentrations, to reach drug exposure associated with the highest possible response rate. Therefore, many laboratory bioanalysis tests considered standard in developed countries are excessively costly and inaccessible to medical doctors in low-income countries. Therefore, the development of precise dosing requires a new generation of decentralized and user-friendly analytical tools capable of supporting efficient, more accurate, and faster TDM [26,27]. On-site testing, known as "point of care," ensures rapid detection close to patients. It refers to analytical tests conducted outside the laboratory and can be located within a hospital to complement the central laboratory or in primary care outside the hospital setting [10] . Fig. 1 describes all the workflows involved in TDM with electrochemical nanosensors.

3. Electrochemical nanosensors for therapeutic drug biosensing

The World Health Organization (WHO) has called for new bioanalysis methods to work in environments with limited access to an equipped laboratory. Attention Point Bioanalysis based on Point-of-Care Testing (POCT) systems can be completed at or near the attention site or other low-resource environments and provides instant results without waiting days for sample transport and laboratory processing [28–31]. Nanosensors have been one of the strategies that, in recent years, have been positioned as simple, low-cost, highly sensitive, and specific tools with the potential to overcome the limitations of routine methods. The International Union of Pure and Applied Chemistry defines a biosensor as a device that uses specific biochemical reactions mediated by isolated enzymes, immune systems, tissues, and organelles (or entire cells) to detect chemical compounds, usually from electrical, thermal, or optical signals [32]. Nanosensors enable rapid and continuous detection of targets in vitro *and* in vivo. They can be classified into several different categories according to their detection method (optical, electrochemical, thermometric, magnetic, or mechanical), sensing mechanism (direct/label-free or indirect/labeled), functionality (single- or multi-user), or degree of invasiveness. When the transducer platform is modified with nanomaterials and biomolecules, the device is called nanobiosensor [29,33,34].

Nanomaterials are characterized by at least one structural dimension of 100 nanometers or less. At this scale, materials exhibit unique properties that distinguish them from macroscopic materials [35]. Although the overall dimensions of nanosensors are often on the millimeter scale, they are defined by the nanosensor-containing nanoscale materials' enhanced magnetic, mechanical, thermal, and chemical properties [36,37]. In this context, remarkable properties of nanomaterials have been taken advantage of in designing a myriad of nanosensor architectures for TDM. For example, the high surface-area-to-volume ratios of nanomaterials increase binding sites for drug molecules, thus improving sensor sensitivity. Signal amplification strategies based on catalytic materials and nanozymes, i.e., enzyme-like nanomaterials, can also enhance sensitivity. The unique advantages of nanomaterials contribute

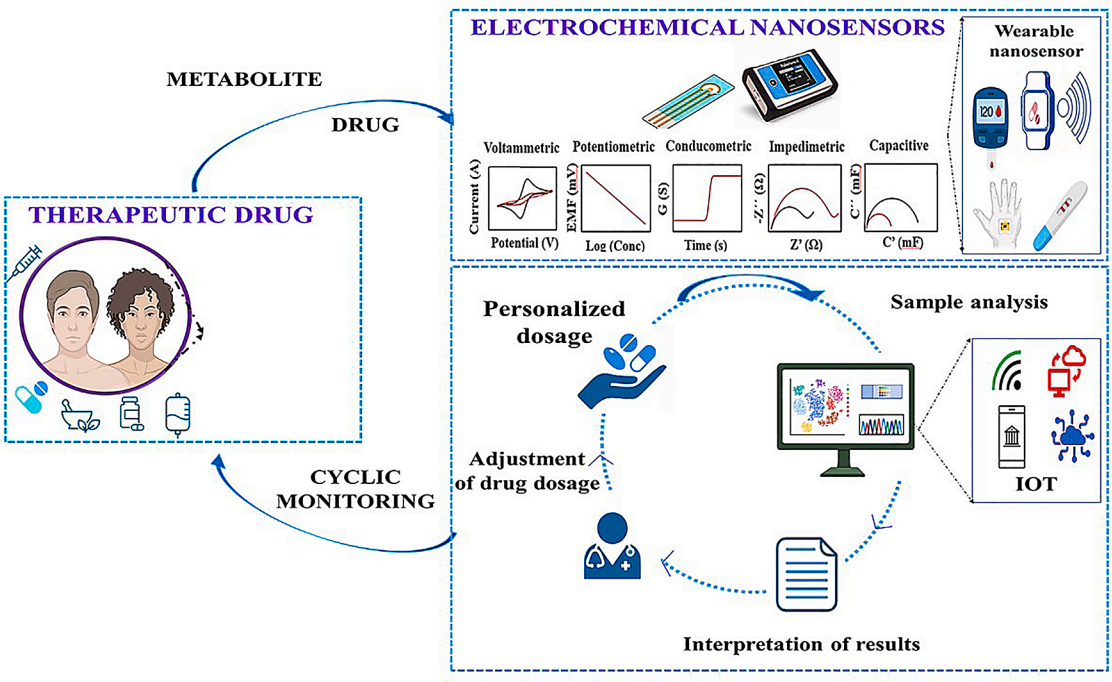

Fig. 1. Workflow for TDM using electrochemical nanosensors. It is a cyclic process that starts with the need of the patient for a therapeutic drug, whose levels are detected usually in blood samples but eventually in urine and saliva samples by electrochemical nanosensors using voltammetric, potentiometric, conductometric, impedimetric, or capacitive measurements. Nanobiosensors can be designed to be wearable, and their values, after sample analysis and interpretation of results, can be used by the medical doctor to adjust the dose and prescribe a personalized dosage plan in a cyclic monitoring manner.

to solving the challenges and limitations of conventional TDM monitoring methods, often related to low drug concentrations, complex biological matrices, and the need for rapid detection in clinical settings [38].

Now, nanosensors' sensitivity, specificity, cost-effectiveness, and portability are recognized; they do not require specialized laboratory or trained personnel, and a medical doctor could potentially take and analyze samples next to the patient's bed, allowing for faster and more

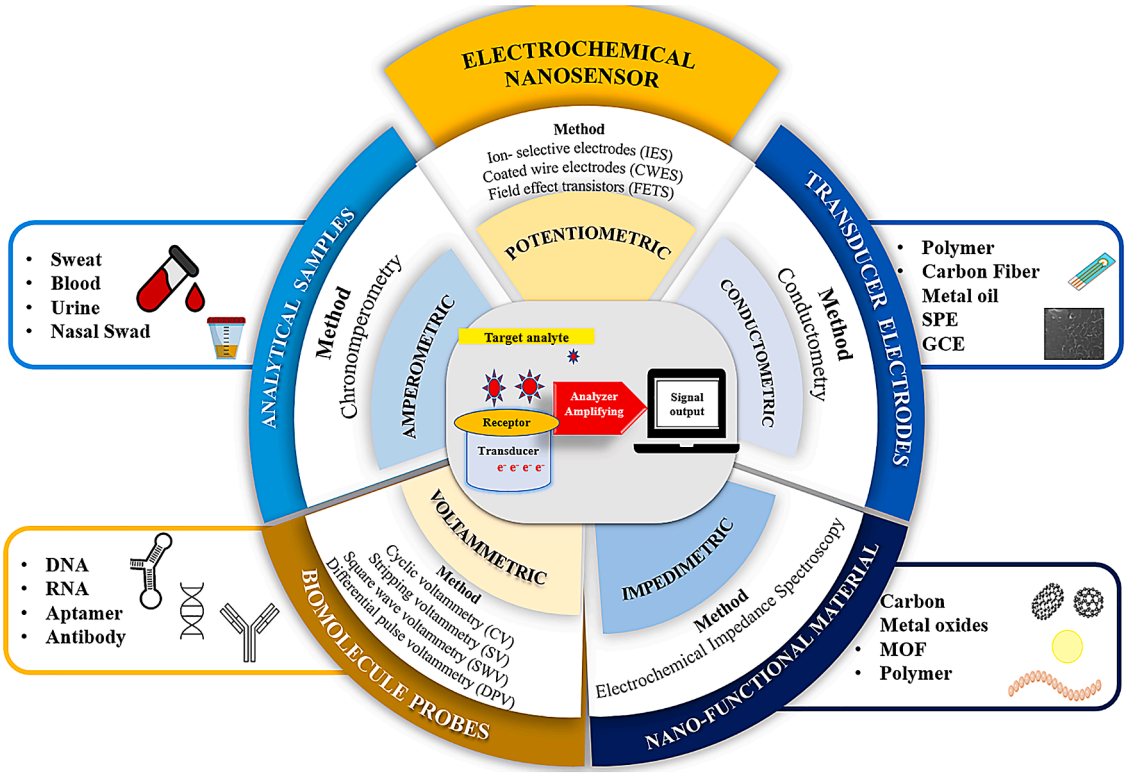

Fig. 2. Classification of electrochemical and signal transduction methods in nano(bio)sensors: voltammetric, potentiometric, conductometric, impedimetric, and capacitive.

accurate decision-making. Therefore, they represent one of the most promising methods for analyzing and quantifying drugs in body fluids within the advanced personalized medicine concept [22]. Since Clark developed the 1st version of an electrochemical biosensor for blood glucose [39], various nanosensors have continuously been developed for the detection of different targets, including viruses, bacteria, parasites, and biomarkers [28–31,40], with some introduced and commercialized for diverse applications [22]. A sensor comprises a biorecognition unit in direct spatial contact with a transducer unit, which converts the analyte-transducer platform interaction into a measurable analytical signal [32,41].

An electrochemical sensor is a standalone integrated tool that translates the information associated with electrochemical reactions into analysis-ready signals, and they can be subclassified into four categories (Fig. 2): potentiometric, amperometric, conductometric, and impedimetric [41,42]. For example, in voltammetric bionanosensors, analytes in the solution interact with the electrode surface, where the potential can be controlled, undergoing charge transfer (oxidation or reduction), which produces the measured current [42] with two components, the faradaic current and capacitive (non-faradaic) current. The faradaic current originates from electron transfer at the electrode surface-electrolyte interface and is target molecule concentration-dependent [41]. The non-faradaic current is formed when the double layer at the working electrode charges or discharges due to changes in the electrode potential but is not the analytical signal. Different voltammetric techniques are used, such as cyclic voltammetry (CV), chronoamperometry (CA), differential pulse voltammetry (DPV), and linear sweep voltammetry (LSV) [43,44]. Finally, impedimetric biosensor measurements using electrochemical impedance spectroscopy (EIS) or electrochemical capacitance spectroscopy (ECS) are also worth mentioning [33,45].

Electrochemical detection involves an auxiliary or counter electrode, a reference electrode, and a detection electrode, also known as working electrodes. The reference electrode, commonly made of Ag/AgCl, is kept at a distance from the reaction site to maintain a known and stable potential [34]. The working electrode serves as a transduction element in the biochemical reaction, while the counter electrode establishes a connection with the electrolytic solution so that a current can be applied to the working electrode and close the circuit. Several signal amplification strategies have been tested, such as the use of nanomaterials with unique physicochemical properties, i.e., compounds of platinum, gold, carbon (e.g., graphite), and silicon, depending on the analyte [34,46]. The active layer of the sensor can be composed of several types of materials and is designed to interact with the target analyte to produce a measurable signal once connected, enhancing the electrochemical output. Among the common nanomaterials, metal nanomaterials (e.g., gold and silver nanomaterials), carbon nanomaterials, quantum dots, and metal-organic frameworks can be directly used as electroactive platforms to achieve signal amplification in nano(bio)sensors (Table 2) [29].

The electrochemical cell modified with the nanomaterials mentioned in Table 2 provides a proper ‘nanoenvironment’ for anchoring a bioreceptor. Thus, the bio-receptor is also an essential component for designing electrochemical biosensors that provide selectivity and specificity to the device. Bioreceptors for which the analyte has a particular binding affinity commonly involve antibodies, lectins, peptides, deoxyribonucleic acid (DNA), peptide nucleic acids (PNAs), aptamers, and molecularly imprinted polymers (MIPs). Various sensors modified with nanocomposites have been used for TDM due to their high specific surface area, biocompatibility, ability to accelerate electrical conductivity, catalytic activity [62]. Additionally, it is sought to take advantage of the fact that the nanometric dimensions of these objects are similar to the size of the target biomolecules, potentially increasing the probability and kinetic of interactions, decreasing diffusion barriers, and enhancing the sensitivity of the measurements [63].

4. TDM by electrochemical nanosensors

4.1. Neuropsychopharmacology

TDM has gained increasing interest in various clinical settings, including treating psychiatric and neurological patients. For instance, more than 200 medicines have been discovered and developed over the last 60 years, and the follow-up strategy is part of the therapeutic scheme, determining an individualized dose of prescribed medicines to maximize clinical effectiveness and reduce toxicity [64]. In anticonvulsant drugs [65], tricyclic antidepressants [14], first- and second-generation antipsychotics or "atypical" [66,67] and mood-stabilizing drugs [68] there is clear evidence of its benefits. In recent decades, the Working Group on Neuropsychopharmacology and Pharmacopsychopathy (AGNP) defined the TDM consensus guidelines, initially published in 2004 and updated in 2018, which establish four

Table 2
Comparison of nanomaterials, highlighting benefits in electrochemical nanosensors.

Nanomaterial	Types	Advantages	Comments	Ref
Metal nanoparticles	Metal nanoparticles (AuNPs, AgNPs, and PdNPs), metal oxide nanoparticles (CeO_2 NPs and CuO NPs), polymetallic nanoparticles, and metal sulfide nanoparticles	Larger active surfaces promote the transfer of electrons. It enables signal amplification used as redox trackers and catalytic markers.	High electrical conductivity, biocompatibility, and chemical inertness. Limitations imposed by thermal stability and differential environmental stability	[47–49]
Carbon Nanomaterials	Carbon nanotubes (CNTs), graphene (GR), graphene oxide (GO), carbon nanofibers, and carbon quantum dots (CQDs)	Superior hardness, remarkable mechanical properties, better thermal and electrical conductivity than other nanomaterials	GR and GO enjoy unique electronic properties, remarkable electrical conductivity, large specific surface area, and strong mechanical strength. Yet, it is challenging to control impurities of GR, as well as the diameter, chirality, and degree of agglomeration of CNTs	[50–54]
Quantum Dots (QDs)	Sulfur compounds: cadmium sulfide QDs (CdS), cadmium telluride QDs (CdTe), and lead sulfide QDs (PbS); graphene QDs (GQDs)	Fluorescent semiconductor nanostructures with a particle size between 1–10 nm. They have high quantum confinement, electron transfer efficiency, and surface reactivity.	QDs have good photochemical and optoelectronic properties. They are rich in carboxyl groups, making them easy to functionalize	[55,56]
Magnetic Nanoparticles	Magnetic core made of metal oxides such as iron or cobalt (e.g., Fe_3O_4)	Electrode surface modifiers amplify the electrochemical signals by increasing the rate of electron transfer	Paramagnetic advantages, biocompatibility, and ease of surface modification	[57,58]
Metal-Organic Framework Materials (MOFs)	Organic-inorganic hybrid materials combine metal ions or clusters and organic ligands as linkers.	They enjoy high porosity, large specific surface area, and high thermal stability and are well-suited for loading bioligand molecules based on various functional groups (e.g., NH_2, -COOH), pi–pi stacking, and other interactions.	Issues related to MOFs’ poor electrical conductivity and stability have made their development exceedingly challenging.	[59–61]

levels of evidence-based recommendation: Level 1 (very recommended), Level 2 (recommended), Level 3 (helpful) and Level 4 (probably useful), these guidelines and recommendations represent a high level of scientific evidence on their use in mental health, emphasizing their importance in dose optimization, safety, adherence assessment, treatment resistance, possible drug interactions and genetic alterations of drug metabolism [16,69,70].

TDM, as a clinical decision-making tool, enables dosage regimen adjustments based on clinical and laboratory measurements. Conventional electrochemical techniques for analyzing neuropsychopharmacology drugs include voltammetric techniques such as CV, DPV, SWV, and chronoamperometry [32,34]. In the following subsection, we will describe some groups of medications within the family of neuropsychodrugs and the most recent advances in detection through electrochemical nanosensors, highlighting their analytical features and advantages over other sensors and mentioning their potential for TDM.

4.1.1. Mood stabilizers

Lithium is one of the main mood stabilizers. According to AGNP recommendation, levels of lithium should be measured due to its narrow therapeutic margin, which can result in leading to sub-optimal dose situations, relapses, and the appearance of side effects during the therapy [71]. Despite the importance of their quantification, the reported nanosensors are limited [72]. Nevertheless, in 2018, a novel sensor to detect lithium ions in sweat was developed, which compared different nanostructured Solid-Contacts (SCs) in an Ion- Selective Electrode (ISE) with one-step electrodeposition of noble metals. Potentiometric measurements showed analytical qualities such as 10^{-3} to 10^{-1} M linear range, near-Nernstian behavior (57.6 ± 2.1 mV/decade) in the concentration range of interest, limit of detection (LOD) of 13.5 ± 2.1 × 10^{-4} M, a very short response time (15–30 s) and small potential drift. Although it was demonstrated that some parameters did not comply with what was reported in the literature, the sensor had enhanced analytical capabilities in aqueous solution, reversibility, and pH stability (pH 4–12) in sweat [73].

Singh 2020 reported a sensor based on a self-assembled monolayer and physically adsorbed 6,6′-dibenzyl-14-crown-4 ether as lithium-specific ionophore onto a disposable screen-printed gold sensor electrode to transduce the recognition of Li^+ ion employing hexaammineruthenium(III) chloride solution as a redox probe. The electrochemical behavior of the modified gold electrode was investigated by CV and EIS. The analytical signal was linear from 0.1to 2.5mM, with a LOD of 0.1 mM, of clinic relevance because it was in the therapeutic range of serum lithium. Finally, the selectivity over potassium was demonstrated [73].

Valproic acid (VPA) is another drug with a level 1 recommendation in this group. It is an inhibitor of cytochrome P450 that can increase the concentration and the effects of other concomitant drugs. Additionally, this drug has a narrow therapeutic window. Therefore, patients who take VPA are expected to be regularly followed up. In 2017, a voltammetric sensor was developed to detect this drug in human blood plasma samples using the cathodic peak current of VPA at -0.8 V. The authors immobilized magnetic nanoparticles (MNPs) coated with 3-aminopropyltriethoxysilane (APTES) on a pencil graphite electrode (PGE). This methodology was developed as a signal amplification strategy and characterized using EIS. The reduction peak current of VPA was found to be concentration-dependent in the range of 1.0 ± 0.2 to 100.0 ± 0.3 ppm with a LOD of 0.4 ± 0.1 ppm. According to the literature, this LOD is low, and the sensor has high specificity against similar drugs, such as carbamazepine, primidone, lamotrigine, ethosuximide, and phenytoin [74].

Another voltammetric sensor to quantify VPA was published in 2018 by Petit-Domínguez [75]. The drug is not electroactive, so the authors performed preliminary step derivatization with aminoethyl-substituted ferrocene as a redox group. As a second strategy to improve the sensor response, they deposited a first layer of molybdenum disulfide (MoS_2) platelet and a second layer of diamond nanoparticles (DNPs) on a glassy carbon electrode (GCE). Both nanomaterials in the transducer platform produced an enhanced linear response from 9.0×10^{-7} to 5.5×10^{-6} M, a high sensitivity of 740 μA/mM^1/cm^2, and a 0.27 μM LOD. Moreover, the device has a reproducibility of 8 % relative standard deviation (RSD) and retained 99 % of its initial response after 45 days of storage. In summary, the analytical performance of the drug-derivatized and the nanomaterial-modified device was better than that modified with only one nanomaterial, highlighting that MoS_2 and DNP enhanced the analytical performance towards VPA-Fc oxidation. Moreover, it was less expensive and time-consuming, requiring less sophisticated equipment, despite being worse than other techniques.

4.1.2. Antipsychotics

The electroactive nature of antipsychotics that enables their straightforward detection by electrochemical techniques has boosted the development of electrochemical nanosensors for this group of drugs, as extensively reviewed (Table 3) [75].

4.1.3. Antidepressants

Antidepressants are a wide pharmacological group that includes tricyclic molecules. According to the care and TDM guidelines, most of them fall into level 1 recommendation as selective serotonin reuptake inhibitors (SSRIs), level 2 (escitalopram, paroxetine, fluvoxamine, sertraline) or 3 (fluoxetine), and only one drug with level 1, citalopram. The serotonin-norepinephrine-reuptake (IRSNs), specifically venlafaxine and duloxetine, are included in the level 2 recommendation level [70].

Recent work showed one-step-developed sensors based on a plasticized polyvinyl chloride (PVC) membrane-coated glassy carbon (GC) electrode. A voltammetric method was used to quantify amitriptyline (AMI) and nortriptyline (NOT) tricyclic antidepressants in blood. Chronoamperometry experiments showed that the lineal range and the LOD were 0.25 to 0.50 μmol/L and 3 ± 3 nmol/L for AMI and 1.32 to 9.91 μmol/L 20 ± 20 nmol/L for NOT, respectively. Although the direct voltammetric methods did not permit the selective determination of both AMI and NOT in the same sample, they could measure them separately. Remarkably, the working range of the sensors covers the therapeutic range of the studied drugs, and the LOD is below the therapeutic level of the drugs [84].

In 2022, other authors described strategies for improving the detection and quantification of selective SSRIs, a sensor to quantify citalopram (CIT) and selegiline (SEL). The sensor was based on a CPE modified with zeolitic imidazolate frameworks of (ZIFs)-8/graphite carbon nitride (g-C_3N_4) /RGO nanocomposite for highly sensitive electrochemical target detection. The as-assembled electrode exhibited linearity from 0.009 to 900 μM with a LOD of 0.008 μM for CIT and 0.09–900 μM and 0.014 μM for SEL, respectively, when interrogated by CV. The results showed potential for quantification of the target analytes in real samples without pretreatment [85].

4.2. Immunosuppressants

TDM has proved crucial in daily clinical practice to optimize immunosuppressive treatments and reduce the incidence of organ rejection. For example, more than 100.000 solid organs, such as heart, kidney, lung, and liver, are transplanted worldwide. In this context, it is necessary to immediately translate information from the patient's immune status into clinical decisions near the patient to determine the effectiveness and safety of treatment and organ rejection incidence [26].

The adaptation and implementation of nanosensors in monitoring immunosuppressive drugs have been documented in recent years, highlighting their adaptability, immediate results, and follow-up at the care site, minimizing therapeutic failures [26,86]. For example, the zero electroactive activity of cyclosporin A (CSA) boosted the search for recognition alternatives, such as evaluating the electrochemical

Table 3
Antipsychotic sensors based on nanomaterials.

Nanomaterials	Sensor modifiers	Nanomaterial modifiers	Drugs	Characteristics	Ref.
Metal nanomaterials	**Noble metal NPs**	Ruthenium nanoparticles (Ru) and Safranin (Saf) as a modifier through a carbon paste electrochemical sensor platform	Amisulpride	Voltammetric: SWV method. Linearity: 9.8×10^{-8} to 7.0×10^{-5} M. LOD: 8.80×10^{-9} M.	[76]
	Transition metal sulfide	Flower-like cerium-ruthenium sulfide nanostructure (Ce–Ru–S NS)	Trifluoperazine	Amperometric. Linearity: 0.003 to 319 μM. LOD: 0.322 nM.	[77]
	Transition metal ferrite	Carbon nanofiber/copper ferrite nanoparticles composite modified carbon paste electrode (CNF-$CuFe_2O_4$/CPE)	Pimozide	Voltammetric: DPV. Linearity: 9×10^{-9} to 5×10^{-4} M. LOD: 2.3×10^{-10} M.	[78]
Carbon-based nanomaterials	**Quantum dots (QDs)**	Sulfur-doped carbon quantum dots (S-CQDs) chemically incorporated with iron oxide nanoparticles (S-CQDs/Fe_2O_3)	Olanzapine	Voltammetric: CV. Linearity: 0.1 to 35 μM. LOD: 0.006 μM.	[79]
		NH_2 functionalized multi-walled carbon nanotubes (NH_2*f*MWCNT) decorated with ZnO nanoparticles (ZnONPs) co-catalyzed by graphene quantum dots (GQDs)	Pimozide	Voltammetric: CV. Linearity: 6.25×10^{-11} to 1.20×10^{-7}M. LOD: 1.02×10^{-11}M.	[55]
		1, 4-bis(N-methyl)-benzene-bis(N-phenyl, N-benzoylphosphoramidate) (BMBPBP)/ CdS-QDs/ multi-walled carbon nanotubes (MWCNTs)) modified gold electrode	Olanzapine	Amperometric. Linearity: 20 nM to100 μM. LOD: 6 nM.	[80]
	Graphene	Nature of gold nanoparticles (GNPs), polydopamine (PDA), GNSs-@SiO_2 modified rGO stabilized on glassy carbon electrode.	Quetiapine	Voltammetric: SWV. Linearity: 500 μM to 3 mM. LOD: 500 μM.	[81]
Molecularly imprinted polymer (MIP)		MIP nanoparticles were synthesized via precipitation polymerization and incorporated into the carbon paste electrode (CPE)	Midazolam	Voltammetric: CV. Linearity: 5.0×10^{-1} to 1.0×10^{-7} M. LOD: 1.77 x10^{-10} M.	[82]
		MIP nanoparticles were synthesized by precipitation polymerization method in the composition of modified CPE	Quetiapine	Voltammetric: SWV. Linearity: 2.50×10^{-6} to $2.00 \times 10^{-5\mathbf{M}}$ LOD: 5.04×10^{-9} M.	[83]

oxidation capacity of alcohols in acetonitrile for various nitroxyl compounds. This concept was used to detect a CSA, a drug with a hydroxyl group in the molecule, by the most active nortropine-N-oxyl (NNO) (Fig. 3**A**). The signal was concentration-dependent from 1 to 100 μM (1202–120,261 ng/mL), with a LOD of 360.8 ng/mL when tested by CV [87].

Continuing with strategies to improve the analytical profile for this group of immunosuppressant drugs, and due to the polymedication that patients often receive, some authors proposed a new sensor to detect mycophenolate mofetil (Mph) and tacrolimus (TAC) [88]. The sensor was based on the electropolymerization of multi-walled carbon nanotubes (MWCNTs) and a novel Cu-1*N*-allyl-2-(2,5-dimethoxy phenyl)-4, 5-diphenyl-1*H*-imidazole metal-organic framework (Cu-ADPPI MOF) on disposable pencil graphite electrode (dPGE) by DPV (Fig. 3**B**). The electrochemical behavior of Mph and TAC was investigated at the modified electrodes using DPV, within a linear range from 0.85 to 155 × 10^{-8} M and 1.1 to 170.0 × 10^{-8} M with LODs of 0.28 × 10^{-8} M and 0.36 × 10^{-8} M for Mph and TAC, respectively.

One device stands out for detecting the rapamycin drug with high sensitivity [89]. It consisted of a disposable screen-printed electrode based on ionic liquid/graphene composite (IL/G/SPCE) of high active surface area to detect the analyte by voltammetric signal (Fig. 3**C**). The disposable device was rapamycin concentration-dependent in the 0.1 to 100 μM range, and the LOD was 0.03 Mm. The proposed device could selectively detect rapamycin in the presence of commonly interfering compounds with previous purification of samples, and the sensitivity was similar to that of conventional methods [86].

4.3. Antimicrobial drugs

The impact of disease infections represents a challenge regarding the availability of pharmacological treatments and the progressive appearance of drug resistance. For example, out of 7.7 million deaths worldwide, 4.95 million are associated with drug-resistant pathogens [90] Several works report the benefits of TDM in antimicrobials because antibiotic tissue penetration can vary in critically or chronically ill patients, potentially leading to treatment failure. It can reduce antibiotic-resistant strains of bacteria because of exposure to suboptimal doses. Therefore, antimicrobial adjust doses through TDM should maximize microbial killing, minimize the development of resistance, and prevent drug overexposure-related adverse events [4,91–95].

One of the recommendations for drug monitoring is vancomycin (VAN) because it is the first line of treatment in infections caused by penicillin-resistant *Staphylococcus aureus* and an alternative for β-lactam antibiotic allergy [6]. For this medicine, the latest reports refer to aptamer-based (E-AB) sensors based on a single-step assembling sensing platform to measure it in plasma in real-time. E-AB sensors have electrode-bound redox-reporter-modified aptamer sequences whose binding with the target induced changes in electron transfer kinetics, which were easily monitored using SWV [96]. While the sensor was specific, the sensitivity was insufficient for what was expected in the treatment. Therefore, optimizing the sequence length of the binding aptamer expanded the dynamic range and detection limit up to those of clinical relevance [97].

The length of the vancomycin-binding aptamer sequence in the E-ABs was optimized to enable a broader dynamic range of the platform. The E-ABs were characterized at different levels: (i) the electrode, (ii) the self-assembled monolayer (SAM), (iii) the SAM-bound aptamer (which binds to the target, vancomycin), and (iv) the redox reporter. The voltammetry method had the following analytical parameters: serum 3trunc aptamer's KD in serum 11.7 ± 0.7 μM, nonlinear regression of the curve to a Hil model (red trace), obtaining a dissociation constant of

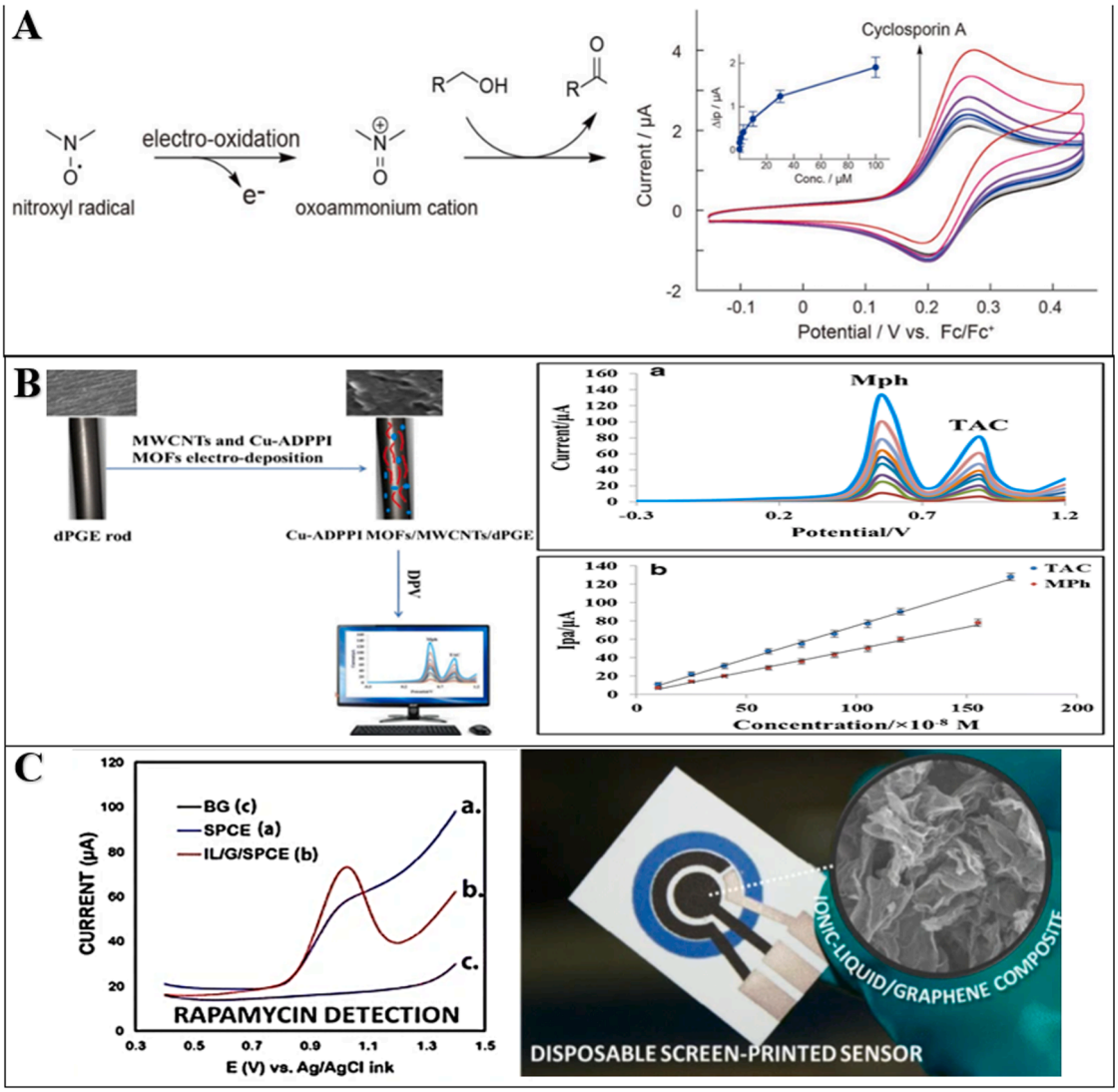

Fig. 3. Illustration of a three-electrode cell for detecting immunosuppressor drugs. A) Electrochemical detection of CSA, a drug with a hydroxyl group in the molecule, was carried out using the most active NNO. B) A combination of novel electropolymerized Cu-MOFs containing the allyl group and multi-walled carbon nanotubes (MWCNTs) to detect TAC and Mph in human plasma and urine samples. C) Screen-printed electrode modified with ionic liquid/graphene composite determination of rapamycin. Reprinted under the terms of the Creative Commons CC-BY.

11.7 ± 0.7 µM and a Hill coefficient of 0.66 ± 0.02. The clinically relevant range for serum vancomycin is 6–30 µM. This study demonstrated that 3trunc-functionalized E-ABs support reversible continuous sensing in flow systems in vitro and have superior performance in vivo compared to 4trunc sensors. In addition, this work reported for the first time the continuous monitoring of vancomycin penetration into the cortex of live mice following IV dosing in real time [98].

A recent report shows the usefulness of aptasensors in improving analytical capacity in the determination of vancomycin, in this case, the detection in different biological matrices, the electrochemical sensor was based on lab-printed carbon electrodes (C-PE) enriched with cauliflower-shaped gold nanostructures (AuNSs), on which VAN-specific aptamers were immobilized as biorecognition elements and short-chain thiols as blocking agents. Three electrochemical techniques were used, CV, DPV, and EIS, the linear correlation was of 5.0×10^{-8} to 1×10^{-6} M, the detection limit was 1.721×10^{-9} M, and LOQ calculated was 5.216×10^{-9} M. The aptasensor have acceptable selectivity in real samples especially with human serum comparte with milk [99].

In response to the need for improved methods for TDM, in the last years it has been developed different electrochemical nanosensors, many of them with the purpose of drug quantification in the patient's location or continuously monitoring concentrations within a patient's body, with finger-prick-scale volumes of whole blood; achieving seconds-resolved, performing high-precision feedback control over plasma levels of this historically difficult-to-dose drugs (Table 4) [94].

4.4. Anticancer drugs

Cancer is one of the leading causes of death worldwide, triggering in recent years an acceleration in the development of new therapeutic alternatives. More than 150 approved medicines are available in different categories: monoclonal antibodies, antimetabolites, DNA insertion drugs, anti-microtubulin, and biologically targeted [108–110]. The fine balance between effectiveness and safety is the key to the success of chemotherapy. There are some strategies to control dosages, such as those based on the patient's body weight (BW) or body surface area (BSA). However, this practice is complicated when using combined therapies within groups or the variation of the pharmacological response according to the type of cancer. Yet, some recent reviews have demonstrated the usefulness of TDM for therapeutics against cancer

Table 4
Electrochemical nanosensors developed for antibiotic quantification.

Monitored drug(s)	Biosensor technology	Recognition element(s), nanomaterial(s)	Characteristics	References
ß-lactam antibiotics (piperacillin, cefuroxime, cefazolin)	Enzyme-linked assay	Antibody	Amperometric. Linearity: 1.6 to 5.000 ng/mL. LODs: 2.07, 4.88, and 5.71 ng/mL for piperacillin, cefuroxime and cefazolin, respectively	[100]
Tetracycline, pristinamycin	Enzyme-linked assay	Antibody	Amperometric. Linearity: 1 to 1000 ng/mL. LODs: 6.33 and 9.22 ng/mL for tetracycline and pristinamycin, respectively.	[101]
ß-lactam antibiotics; penicillin	Microneedle-based	ß-lactam hydrolysis; Iridium	Potentiometric. Linearity: 25 to 125 mg/mL. LOD: 6.8±1.04 µM.	[102]
ß-lactam antibiotic (phenoxymethylpenicillin	Microneedle-based	ß-lactam hydrolysis; Iridium-oxide layer	Potentiometric. Linearity: 0 to 16 mg/L. LOD: 0.17 mg/L.	[103]
Vancomycin Tobramycin	Microneedle-based electrochemical	Aptamer biosensing patch (µNEAB-patch)	Voltammetric. Linearity: 0 to 100 µM. LOD: N.A	[104]
Piperacillin/tazobactam	Multiplexed microfluidics, sensor platform.	Antibody-free and highly sensitive ß-lactam assay	Amperometric. Linearity: 0–1000µg/mL. LOD: 56 ng/mL.	[105]
Ketoconazole	Nanocomposite	Glassy carbon electrode with carbon black (CB) and gold nanoparticles (AuNPs) within a crosslinked chitosan (CTS)	Voltammetric. Linearity: 0.10 to 2.9 µmol/L. LOD: 4.4 nmol/L.	[106]
Itraconazole (ITZ)		Glassy carbon electrode with carboxylated multi-walled carbon nanotubes (MWCNTs-COOH) and NiO-ZnO composite (NiO-ZnO/MWCNT-COOH/GCE)	Voltammetric: cyclic voltammetry. Linearity: 0.025 to 2.2 µM. LOD: 4.1 nM.	[107]

[111–113].

We will comment on recent advancements in nanodevices for TDM, introducing newly developed systems that aim to identify and quantify anticancer drugs in biological fluids. The oldest example of cytostatic chemotherapy subject to TDM is methotrexate (MTX), whose plasma concentration measurement was introduced almost fifty years ago. Some authors have recently compiled advances in detecting anticancer agents using portable sensors, highlighting different strategies. Significant progress has been achieved toward utilizing different bioreceptors and using various electrochemical detection methods, redox species, and signal amplification strategie [43,114,115].

Doxorubicin (DOX), or hydroxydaunorubicin, is globally recognized as an anti-cancer medication. Various electrochemical sensors based on carbon nanostructures and polymer structures have been reported to detect DOX [114]. An aptamer label-free biosensor was developed to determine DOX. Combining the aptamer with rigid tetrahedral DNA nanostructures (TDNs) and fixing them on the surface of a gold electrode (GE) improved the analytical performance of the biosensor. The response was DOX concentration-dependent from 10.0 to 100.0 nM, with a LOD of 3.0 nM [115]. Another sensor of manganese tetraphenylporphyrin-decorated reduced graphene oxide (Mn-TPP/RGO), compared to the concomitant tetraphenylporphyrin decorated reduced graphene oxide (TPP/RGO) and reduced graphene oxide nanostructures coating a glassy carbon electrode were assembled for the detection of DOX by CV and DPV. The modified electrode showed a linear response range of 0.1–0.6 mM, sensitivity of 112.09 µA m/M/cm^2, LOD of 63.5 µM, and excellent stability [116].

As the literature in this regard is extensive, Table 5 summarizes descriptions of anticancer medications and recent electrochemical sensors reported in the last five years to provide an overview of recent progress.

Table 5
Electrochemical nanosensors for anticancer drug quantification.

Drug class	Antineoplastic drug	Reference
Alkylating agents	Cyclophosphamide	[117,118]
	Dacarbazine	[119,120]
Antimetabolites	5-Flourouracil	[121–128]
	Methotrexate	[129–132]
	6-Mercaptopurine	[133,134]
	Irinotecan	[124,135]
Cytotoxy antibiotics	Daunorubicin	[136–138]
	Doxorubicin	[44,47,139–143]
Endocrine Therapy	Tamoxifen	[144,145]
Alkaloids and other natural products	Cisplatin	[145–147]
	Praxitacel	[148,149]
Other	flutamide	[150–153]

5. Technological prospecting

Several analysis platforms based on electrochemical nanosensors have emerged in recent years, showing that the subject has been gaining prominence. However, significant challenges must be addressed to establish reliable and effective TDM systems. Herein, a technological prospection was made based on the reported patents encompassing the use of electrochemical sensors and nanosensors in the analysis of drugs. The search was limited to patents filed between January 1st 2020, and August 31st, 2024, using The Lens database (www.lens.org). This database includes Espacenet, Instituto Nacional de Propriedad Industrial (INPI), European Patent Office (EPO), World Intellectual Property Organization (WIPO), United States Patent and Trademark Office (USPTO), Free Patents Online (FPO), and Australian patent databases. The following search string filling in the "Query Text Editor" field: (title:(electrochemical sensor) OR abstract:(electrochemical sensor) OR claim:(electrochemical sensor)) AND (title:(drug*) OR abstract:(drug*) OR claim:(drug*)). This analysis assumes that patents that share similar keywords are related 173 patents were found from different statuses: pending, active, discontinued, inactive, and without status. The active ones were then selected, totaling 84 patents, with the United States holding the most significant number (62), followed by China with 13, the European Union with 8, and Canada with 1. From the most identified patent holders within the International Patent Classification (IPCR), 69 were classified in A61B5/00 (Human necessities: measuring for diagnostic purposes), 49 in A61B5/145 (Human necessities: measuring characteristics of blood in vivo), 38 in A61B5/1473 (Human necessities: invasive), finally, 42 in the classification of G01N27/327 (Physics:

biochemical electrodes).

As mentioned at the beginning of this review, there are different quantification methodologies, but they have some limitations, including prolonged processing times, hindering the ability to obtain immediate results necessary for on-site decision-making. Therefore, significant factors are required to successfully develop POCTs based on electrochemical nanosensors as an alternative to the gold standard methodologies. Table 6 gathers all the critical points in the POCT clinical validation process, guiding the developer to some questions that arise during the design, creation, production, and implementation of the sensing strategy, especially considering cost-effective factors.

Table 6
Important points to consider when developing electrochemical sensors in clinical settings.

Critical points	To consider
How does the clinical use of the POCT test be performed?	-Phenomenon to be measured. -Frequency, range, and change over time. -Heterogeneous patient profile. -Multiple sampling necessity. -Minimal sample preparation. -Hazardous waste management. -Manufacturer independent evaluations. -To perform basic maintenance procedures.
Is there any regulatory issue and laboratory accreditation requirement?	-Regulatory. -Normative values. -Comparison of outcome with gold standard. -Ethical Considerations. -Data privacy.
How do you describe the POCT method?	-Physical properties of the device and its application, as well as the conditions in which the device is expected to be used. -Factors that may confuse the measurements. -Selection of biological matrices based on analytical performance and usability. -Relevant clinical information for precision-dosing suggestions. -Energy efficiency. -Decision support system.
How to test a quality assurance sample?	-Validity/precision/accuracy: between-run imprecision $\leq$ 10 %, total error $\leq$ 15 %, validation of assay precision compared to available methods. -Sensitivity/specificity. -Calibration, autonomous self-calibration, or oversight by POCT coordinators.
How will the data be acquired, stored, scored, and analyzed?	-Interoperability, electronic communication with the laboratory information system and other electronic health records. -Software and secure information communication protocol and cyber security measures. -Scoring algorithms/programming. -Handling missing data. -Access to raw data visualization. -Prevent data alteration and manipulation. - Compatible with AI (artificial intelligence) and cloud technologies, where mass data are key
How do we perform the POCT test on a patient sample to impact the patient's adherence to the monitoring and treatment system?	-Basic user training on assay performance and quality control (QC) requirements. -Characteristics of the researcher, knowledge/experience, time, and effort. -Cost-effectiveness improved compared to the current analysis. -Reduction of the clinician's workload. - Self-efficacy, the ability of patients and doctors to respond to information obtained from POCT.

6. Challenges

The electrochemical sensors have demonstrated excellent prospects for biosensing in healthcare. This review highlights the most compelling and promising prospects in encompassing electrochemical sensors in drug analysis and the challenges in translating these technologies into valuable products for disease management and optimizing human performance. Table 7 compares conventional methodology for quantifying biological samples with some current electrochemical sensors developed to monitor certain medications. We highlight that some electrochemical sensors were less sensitive than conventional methodologies; however, the significant difference is that the sample preparation process was unnecessary in electrochemical nanosensors. That advantage minimizes using other equipment, reagents, and time and could impact the cost, staff qualifications, and the time needed to obtain the result. Despite the importance of clinical validation of these methodologies, comparing them in terms of their analytical capacity has not been easy because the reports from each author were not homogeneous, as observed in the table. Most electrochemical techniques report sensitivity by determining the detection limit, but conventional techniques only report the quantification limit.

However, achieving successful clinical practice requires multiple considerations:

1. Multianalyte sensing will be a promising approach for thorough TDM evaluation. It would be ideal for patients prescribed multiple drugs, and in particular for determining drug interactions. In clinical practice, a high percentage of polypharmacy patients favor interactions between molecules in a synergistic or antagonistic manner to the therapeutic effect. In recent years, efforts have been made to develop devices for this purpose. For pharmacological groups that are prescribed at the same time anti-epileptic drugs, researchers developed a disposable sensor chip based on molecularly imprinted polymer-modified carbon paste electrodes (MIP-CPs) for phenobarbital, carbamazepine, and levetiracetam. They used a single sensor chip for each operation interrogated by DPV, whose response was linear from 0–60 μg/mL for PB and LEV and from 0–12 μg/mL for CBZ. Although this work focused on the phenobarbital sensor, other work shows preliminary work on levetiracetam and carbamazepine sensors [179]. Although this is an example of progress in determining three medications, the analytical capacity is better for phenobarbital, and improvement actions are proposed for the other two medications. This situation has been repeated in several publications with similar aims, suggesting that individualized quantification is better than multianalyte [180,181].
2. Conventional sensors encounter limitations in data analysis; however, their small size enables them to navigate restricted spaces and collect vast amounts of data from different settings, yielding insights into chemical reactions, shifts in temperature, and other dynamic nanoscale processes [182]. For that reason, integrating artificial intelligence strategies and machine learning helps interpret extensive sensing data. Habibi et al., in 2024 [183] developed a sensor based on a graphitic carbon nitride (g-C_3N_4) and CNTs composite integrated into a glassy carbon electrode to improve the determination of morphine, methadone, and uric acid. They adopted a multivariable calibration methodology for addressing the overlapping signals from these analytes through partial least squares regression, effectively disentangling the signals. The authors reported that machine learning-enhanced using complete response-profile data to construct a predictive model was effective in detecting the drugs. Despite these, there are still several challenges to address. AI applications require intensive computational resources and time, and their development and implementation outside laboratory environments or by non-professional users is still not viable. Accessing datasets and computational resources can be costly [184].

Table 7
TDM by conventional methodologies compared to electrochemical nanosensors.

Drug	Clinical concentration	Method	Pretreatment Sample	Dynamic Range	Sensitivity	Ref
Valproic acid	50 to 100 μg/mL	Voltammetry and differential pulse voltammetry.	N/R	5 to 75 μg/mL	LOQ: N.R LOD: 2.91 μg/mL	[154]
		LC-ESI-MS/MS	Yes	5 to 300 μg/mL	LOQ: 5.00 μg/mL. LOD: N.R	[155]
Carbamazepine	4 to12 mg/L	SWV	No	0.01 to 100 μM	LOQ: N.R LOD: 0.001μM	[156]
		LC-MS/MS	Yes	4.2 to 169.3 μM	LOQ: N.R LOD: 105.81 μM	[156]
Phenytoin	10 to 20 μg/mL	CV	No	0.01 to 0.2 μg/mL	LOQ: 53.0 ng/mL. LOD: 12.9 ng/mL.	[157]
		Single reference high-performance liquid chromatographic (SR-HPLC)	Yes	1 to 50 μg/mL	LOQ: N.R LOD: 1.56 μg/mL	[158]
Phenobarbital	10 to 40 mg/L	Potentiometric	No	0.25 to 254 mg/mL	LOQ: N.R LOD: 0.12 mg/L	[159]
		Electromembrane extraction (EME) -HPLC-UV	No	0.025 to 1 mg/L	LOQ: 0.025 mg/L LOD: 0.0075 mg/L	[160]
Amikacin	<1mg/L	CV	Yes	0.039 to 11.72 mg/L	LOQ: N.R LOD: 0.029 mg/L	[161]
		UPLC MS/MS	Yes	0.5 to 100 mg/L	LOQ: 0.5 mg/L LOD: N.R	[162]
Gentamicin	<1mg/L	CV	No	1 pM to 100 μM	LOQ: N.R LOD 0.424 pM	[163]
		LC-MS/MS	Yes	0.2 to 19.5mg/L	LOQ 0.07 mg/L LOD: N.R	[164]
Vancomicin	10 to 20 mg/L	SWV	No	0.14 to 1485 mg/L	LOQ N.R LOD: N.R	[165]
		UPLC-MS/MS	Yes	0.5 to 50 mg/L	LOQ: 0.5 mg/L LOD: N.R	[166]
Cyclosporin	150 to 2000 ng/mL	CV	No	1202 to 120,261 ng/mL	LOQ: N.R LOD: 360.8 ng/mL	[167]
		LC/MS/M	N.R	0.2 to 20 ng/mL	LOQ: 0.2 ng/mL LOD: N.R	[168]
Tacrolimus	5 to 20 μg/mL	DPV	NR for biological simples	0.14 to 75.43 nM	LOQ was found to be 0.091 nM. LOD: 0.03 nM	[169]
		LC-MS/MS	Yes	0.2 to 20 ng/mL	LOQ: N.R LOD:0.2 ng/mL	[170]
Mycophenolic acid	1 to 4 mg/L	CV	No	0.32 to 32.0 mg/L	LOQ: N.R LOD:0.016 mg/L	[171]
		UHPLC-MS/MS	Yes	0.10 to 15 mg/L	LOQ: 0 0.10 mg/L LOD: N.R	[172]
Digoxin	0.8 to 1.8 ng/mL	Surface Enhanced Raman Scattering (SERS-ELISA)		0.8 to 2.0 ng mL^{-1}	LOQ: N.R LOD: 0.4 ng/mL	[173]
		UPLC–MS/MS method	Yes	0.25 to 5 ng/mL	LOQ: 0.08 ng/ml LOD: N.R	[174]
5-Fluorouracil	AUC: 20–25 or 20–30 mg·h/L	CV	Yes	1 to 9 mg/L	LOQ: 0.91 mg/L LOD: 0.35 mg/L	[175]
		UHPLC-MS/MS		0.1 to 2 mg/L	LOQ: 0.1mg/L LOD: N.R	[176]
Tamoxifen	≥0.02 μM	LSV		0.8 to 85 μM	LOD: N.R LOD: 0.1 μM	[177]
		UPLC–MS/MS		0.0026 to 1.34 μM	LOQ: 0.00013 μM LOD: N.R	[178]

3. Integrating sensors into the next generation of Internet of Things (IoT) sensors for TDM practice and advancing personalized healthcare through real-time monitoring and treatment. Currentley, IoT wearables are smart devices connected to the Internet to collect, send data, and receive information for decision-making [183,185]. They can be used with external accessories, tattooed, or even adhered to the skin. Their use in medicine is becoming increasingly common to monitor biological variables such as heart rate, temperature, and oxygen. In the case of electrochemical sensors, improvements have been described; however, barriers such as portability, data acquisition, communications, power supply, safety, degree of biocompatibility, and long-term functionality are some points that continue to be challenging [184–186].
4. Electrochemical sensors in TDM are medical devices and, therefore, must comply with national and international regulatory standards. Due to the critical nature of these devices' results, the regulatory processes are complex [187]. To solve this situation and achieve harmonization, the WHO has provided REASSURED guidelines (Real connectivity, Easy sampling, Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Deliverable to end-users) [188]. However, some comparative studies have demonstrated certain shortcomings in the available nanosensors to meet these standards, and it becomes more complex when implementing them in developing countries. Therefore, in their review, Mitra and Sharma highlighted the study of Chin et al. and indicated the minimum compliance levels [189].

- There is a shortage of qualified personnel trained in POCT methods, so the test must be autonomous and automated, allowing the use of unprocessed samples.
- Antibodies, enzymes, aptamers, and molecularly imprinted polymers require a high production level, standardization, control, and validation.

- Robust operation without the need for constant (re)calibration and to provide easy-to-interpret results.

5. Wearable electrochemical biosensors. Despite the recent advancements and available technologies, TDM still relies on the invasive collection of blood samples and analysis in centralized laboratories. However, the recent emergence of wearable biosensors capable of analyzing drugs in alternative biological fluids such as sweat has opened up a wide range of possibilities, i.e., real-time signal transmission to help patients adjust their medication dosage and reduce the risk of pharmacological toxicity [190,191]. These biosensors offer great versatility by easily integrating into the body through everyday clothing and accessories such as glasses, gloves, and watches. Moreover, they allow simple control through smartphones with Bluetooth or remote servers [37].

Due to the new advancements and significant challenges this type of strategy offers, recent reviews have been reported on this topic when conducting minimally invasive monitoring [37,190,192–194]. Regarding electrochemical sensors, the latest reports have focused on medications such as levodopa, antibiotics, and analgesics, whose metabolites can be detected in minimally invasive samples [37,194–196]. Some of the available strategies have advanced in ex vivo trials [197]. For example, Wu et al. [198](ISF) using microneedles adapted with electrochemical, aptamer-based (E-AB) sensors, achieving continuous, real-time drug monitoring in mice (Fig. 4**B**). Additionally, the authors highlighted the creation of a cleaning protocol to regenerate the surface of these microneedles for reuse. It evaluated the detection performance through tobramycin calibration curves ranging from 100 μM to 5 mM, and by measuring its response using SWV, the LOD was 1 μM.

In the face of clinical validation, two strategies have validated their use. A group of researchers conducted a proof-of-concept and subsequent human exploration of a β-lactam microneedle biosensor for monitoring phenoxymethylpenicillin (Fig. 4**C**), a commonly used antibiotic. They aimed to demonstrate the reliability and potential of a minimally invasive microneedle biosensor for continuous drug monitoring in extracellular fluid [199]. Previous studies demonstrated the development of a potentiometric biosensor coated with a pH-sensitive iridium oxide layer, which detects changes in local pH resulting from the hydrolysis of β-lactams by β-lactamase immobilized on the electrode surface, achieving a detection limit of 6.8 μM and whose reliability was compared to the gold standard measurement method, demonstrating its utility in real-time measurement of this group of drugs [200].

Levodopa, a crucial drug in the treatment of Parkinson's disease, has been extensively researched for monitoring using wearable sensors [201,202]. In this context, a non-invasive sensor was developed to measure levodopa in sweat through amperometric responses between 5 and 30 μM. This innovative sensor integrated a porous hydrogel, designed to efficiently absorb sweat, with a printed biosensor electrode (Fig. 4**D**). This configuration facilitated rapid transfer of the biofluid to the surface of the electrode, which was enzymatically modified. As a result, the sensor exhibited well-defined linearity within the physiological concentration range of levodopa, allowing for the detection of concentrations as low as 1 μM and with an estimated detection limit of 300 nM. The efficacy of this sensor was successfully validated in a trial with healthy volunteers after oral administration of an L-Dopa/C-Dopa tablet, demonstrating a significant pharmacokinetic correlation between levodopa concentrations measured in fingertip sweat obtained by touch and corresponding capillary blood samples [203].

Finally, to provide a stable working environment for electrodes, including using flexible electrodes and conductive hydrogels to enhance electrode-skin adhesion, the sensors must be more robust against physiological parameters, such as pH and buffer strength, which can vary within the same biological fluid. Cost-effective technologies and scalable manufacturing procedures are required. The added effects of inconsistencies in biosensor preparation, the limited shelf-life of biomolecules, and changes in the testing environment also contribute to

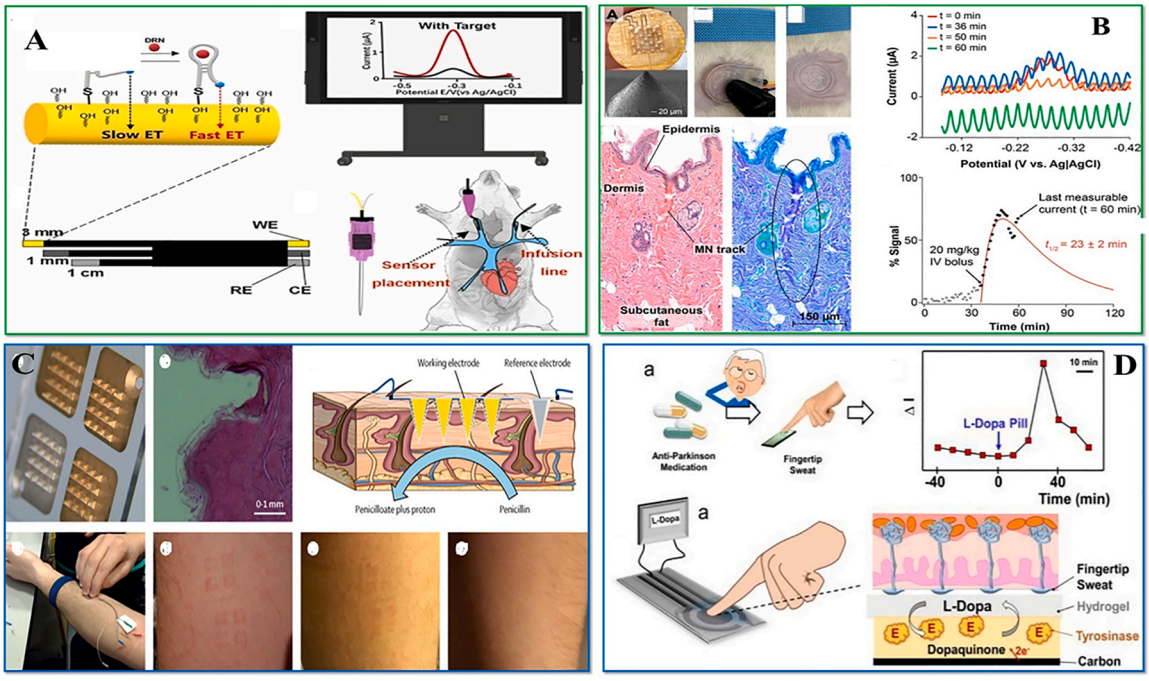

Fig. 4. Wearable sensor for ex-vivo and real-time measurement of drugs. **A)** monitoring of daunorubicin pharmacokinetics with nanoporous electrochemical aptamer-based nanosensor reprinted from [197]with permission from Elsevier. **B)** Measurement of the antibiotic tobramycin sulfate in interstitial fluid (ISF) using microneedles adapted with electrochemical, aptamer-based (E-AB) sensors, achieving continuous, real-time drug monitoring in mice [198], reprinted under the terms of the Creative Commons CC-BY. **C)** First exploration of a β-lactam microneedle array biosensor in humans for monitoringhenoxymethylpenicillin [199] reprinted under the terms of the Creative Commons CC-BY. **D)** Working principle of the touch-based non-invasive detection method relies on instantaneous collection of fingertip sweat on a highly permeable hydrogel that transports the sweat to a biocatalytic tyrosinase-modified electrode [203] reprinted under the terms of the Creative Commons CC-BY.

widely variable data that are difficult to compare adequately.

7. Conclusion

Although plasma level measurements have been used for years to optimize drug use by allowing personalized dosing, chromatographic methods and immunoassays have been at the forefront of methods for this purpose. However, they require expensive equipment and specialized personnel, which limits their mass accessibility. Adopting innovative technologies such as electrochemical nanosensors offers rapid, sensitive, and economical methods for measuring drug concentrations in blood, saliva, or urine, with great potential to revolutionize this field. Notably, the proposed electrochemical nanosensors are analytical instruments with significant achievements in the precise and sensitive determination of drugs in TDM. Their proximity to the patient and the speed of analysis are important and can make a difference in a patient's health status and the course of their treatment. However, challenges remain in their development and implementation, such as the integrated approach for analysis, data management, interoperability, and clinical decision-making. The combination of these strategies can lead to a universal point-of-care system. Therefore, more efforts are needed to reduce costs and make these technologies more reliable and accessible to a broader audience. More research is required to optimize the dosing regimen for TDM.

Abbreviation

3-aminopropyltriethoxysilane (APTES)
Amitriptyline (AMI)
Antibody conjugated magnetic immunoassay (ACMIA)
Aptamer-based (E-AB)
Body surface area (BSA)
Body weight (BW)
Cadmium sulfide QDs (CdS)
Carbon nanotubes (CNTs)
Carbon paste electrode (CPE)
Carbon quantum dots (CQDs)
Chemiluminescent enzyme immunoassay (CLIA)
Chemiluminescent microparticle immunoassay (CMIA)
Chronoamperometry (CA)
Citalopram (CIT)
Cloned enzyme donor immunoassay (CEDIA)
Cyclic voltammetry (CV)
Cyclosporin A (CSA)
Deoxyribonucleic acid (DNA)
Diamond nanoparticles (DNPs)
Differential pulse voltammetry (DPV)
Disposable pencil graphite electrode (dPGE)
Doxorubicin (DOX)
Electrochemical capacitance spectroscopy (ECS)
Electrochemical impedance spectroscopy (EIS)
Electromembrane extraction (EME)
Enzyme-linked immunosorbent assay (ELISA)
European Patent Office (EPO)
Fluorescence polarization immunoassay (FPIA)
Free Patents Online (FPO)
Gas chromatography (GC)
Glassy carbon electrode (GCE)
Gold electrode (GE)
Graphene (GR)
Graphene oxide (GO)
Instituto Nacional de Propriedad de Industrial (INPI)
International Patent Classification (IPCR)
Internet of Things (IoT)
Interstitial fluid (ISF)
Intramuscular (I.M)
Intravenous (I.V)
Ion- Selective Electrode (ISE)
Limited of detection (LOD)
Linear sweep voltammetry (LSV)
Magnetic nanoparticles (MNPs)
Manganese tetraphenylporphyrin-decorated reduced graphene oxide (Mn-TPP/RGO)
Maximum a posteriori probability (MAP)
Metal-Organic Framework Materials (MOFs)
Methotrexate (MTX)
Microparticle enzyme immunoassay (MEIA)
Molecularly imprinted polymer-modified carbon paste electrodes (MIP-CPs)
Molecularly imprinted polymers (MIPs)
Molybdenum disulfide (MoS2)
Multi-walled carbon nanotubes (MWCNTs)
Multi-walled carbon nanotubes (MWCNTs))
Mycophenolate mofetil (Mph)
Neuropsycho-pharmacology and Pharmacopsychopathy (AGNP)
Nortriptyline (NOT)
Nortropine-N-oxyl (NNO)
Pencil graphite electrode (PGE)
Peptide nucleic acids (PNAs)
Pharmacokinetic-pharmacodynamics (PK/PD)
Point-of-Care Testing (POCT)
Polyvinyl chloride (PVC)
Quality control (QC)
REASSURED (Real connectivity, Easy sampling, Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Deliverable to end-users)
High-performance liquid chromatography (HPLC)
Selective serotonin reuptake inhibitors (SSRIs)
Selegiline (SEL)
Serotonin-norepinephrine-reuptake (IRSNs)
Single reference high-performance liquid chromatographic (SR-HPLC)
Solid-Contacts (SCs)
Sulfur-doped carbon quantum dots (S-CQDs)
Surface Enhanced Raman Scattering (SERS-ELISA)
Tacrolimus (TAC)
Tetrahedral DNA nanostructures (TDNs)
Tetraphenylporphyrin decorated reduced graphene oxide (TPP/RGO)
Therapeutic monitoring (TDM)
Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS)
United States Patent and Trademark Office (USPTO)
Valproic acid (VPA)
Vancomycin (VAN)
World Health Organization (WHO)
World Intellectual Property Organization (WIPO)

CRediT authorship contribution statement

Maritza Fernández: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Jahir Orozco:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jahir Orozco Holguin reports financial support was provided by Colombia Ministry of Science Technology and Innovation. If there are other authors, they 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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Data availability

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

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