UNIVERSIDADE FEDERAL DE UBERLÂNDIA
INSTITUTO DE BIOTECNOLOGIA
CURSO DE GRADUAÇÃO EM BIOTECNOLOGIA

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ANTIDEPRESSANTS DETERMINATION USING AN ELECTROANALYTICAL APPROACH: A REVIEW OF METHODS.

PATOS DE MINAS - MG

OUTUBRO DE 2020

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Artigo Científico apresentado ao Instituto de Biotecnologia da Universidade Federal de Uberlândia como requisito final para a obtenção do título de Bacharel em Biotecnologia.

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Graphical Abstract:

Highlights

- The classified of antidepressants allowed in Brazil with chemical structure.
- Main electrochemical techniques used in the determination of antidepressants.
- Main electrodes used in the analyses of antidepressants.
- Perspectives of antidepressants analyses using electrochemical techniques.

Abstract:

Some substances act in the nervous system central, which are used in the treatment in the depression diseases by control of the reactions to minimizing the disturbances generated, and they are classified as antidepressants. This class have been most used in all world, due to genetic factors, environmental problems, modern lifestyle. Nonetheless, the ingestion of inadequate concentrations can provoke adverse effects for the patient, because the antidepressants have toxicity concentrations. Therefore, each country has safety policies to control these compounds in different samples. In this review shows the classification of the antidepressants permitted in Brazil according to the mode of actuation in the nervous system and the description of actuation type them. In reason of the control of the concentration of these substances in the biologic sample, water, and pharmaceutical formulations was realized a brief bibliographic survey of the electrochemical techniques that can be employed to the determination of antidepressants. Thus, it was described in detail about the electrochemical techniques and electrodes used in the antidepressants determination and alterations to improve analytical parameters and follow the guidelines of Green Analytical Chemical.

Keywords: antidepressants, electroanalytical techniques, pharmaceuticals compounds, carbon-based electrode, chemical modified electrode.

1. General considerations

Some chemical compounds are employed to improve the operation of the human body with therapeutics functions and diseases control, which are used in the pharmaceutical formulation that should have source synthetic or natural. These substances can be utilized in the treatment and prevention of symptoms of different diseases, such as degenerative disorders, infectious processes, mental disorders, among other diseases [1,2]. The benefits that the pharmaceuticals provide to the treatment of the patients and all society enable their applicability and also the magnification of the knowledge with new researches in the development and application of new drugs [3].

The pharmaceuticals compounds can be classified according to specific use in analgesics, antacids, antianxiety drugs, antiarrhythmics, antibacterials, antibiotics, anticoagulants and thrombolytics, anticonvulsants, antidepressants, antidiarrheals, antiemetics, antifungals, antihistamines, antihypertensives, anti-inflammatories, antineoplastics, antipsychotics, antipyretics, barbiturates, Beta-blockers, bronchodilators, cold cures, corticosteroids, cough suppressants, cytotoxics, decongestants, diuretics, expectorant, hormones, hypoglycemic, immunosuppressives, laxatives, muscle relaxants, sedatives, sex hormones, sleeping drugs, tranquillizer and vitamins [2,4].

It considering the main pharmacological compounds, the antihypertensives (drugs that act in the treatment of cardiovascular diseases, mainly hypertension and in prevention of other diseases, such as kidney failure, stroke, myocardial infarction, among others), the anti-inflammatories (drugs that act in the relief of effects from the inflammation by suppression of inflammatory response mediators), the analgesics (class composed by substances that decrease the pain due to a stimulus in the nociceptive pathway by inhibition of neuronal transmission in the nociceptive pathway), the antibiotics (employed in the treatment of the diseases and infections caused by microorganisms) and the antidepressants (act in the nervous system central and used in the treatment of the depression, minimizing the effects of the disturbances generated, such as, feeling of sadness, apathy, insomnia and even in more severe stages of suicidal thoughts and actions) are the pharmacological class more employed in all world [1, 5 – 12].

In the last decades, the use of antidepressants has a significant increase in all world due to modern lifestyle, environmental problems, and genetic factors. However, the antidepressants have concentrations that aid in the disease treatments, but the high concentration can provoke adverse effects in the human body or their low concentration can not assist in the reactions of human metabolism. With this, the scientists provide the researches to obtain the difference between malefic and beneficial concentrations and develop analytical methods for the determination of these compounds in the biological (blood, urine) and environmental (natural waters).

2. Antidepressants

The use of the antidepressants in inadequate concentrations can cause risk for the patient, in reason of the levels of the concentrations of toxicity of these substances ingested by people. Hence, each country has safety policies to make to control compounds permitted and their concentrations in the drugs, biologics and water samples. In Brazil is permitted this class 22 compounds that are normally sub-classified in classes according to the mode of actuation in the nervous system, as shown in Fig. 1. In Table 1 is presented this classification for all compounds and respectively chemical structure. Thus, it can observe that in their chemical structure have organic functions, double and triple bonds, heteroatoms, and aromatic rings [7,11].

FIGURE 1

TABLE 1

Thus, the classes that have a greater amount of substances are selective serotonin reuptake inhibitor and tricyclic antidepressants, that own more than 50% of the substances [11,13]. The serotonin reuptake inhibitors, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, and norephephrine and dopamine reuptake inhibitors act in the increase of the bioavailability of neurotransmitters in the synaptic cleft, which found in low concentration [12]. While the monoamine oxidase inhibitors have action mechanism based in the inhibition of reversible or irreversible character of the monoaminoxidase enzyme, exercising the function in the nervous system central of inactivating neurotransmitters present in high concentrations in the synaptic cleft [12].

Already, the atypical antidepressants possess the action based in the block of transport of the neurotransmitters dopamine, serotonin, and norephephrine allowed the increase of the concentration of these on synaptic cleft, minimizing the depression effects [12,14]. There was an increase in the commercialization of the antidepressants and also the index of utilization inadequate their of accidentally or at high doses ingested. However, the ingestion of these substances in high concentrations provides adverse and collateral effects, due to toxicological degree to people, such as seizures caused by an overdose of citalopram [15] and cardiotoxicity due to high doses of venlafaxine [1,16].

This way, according to the National Pharmacological Toxic Information System in 2017 about 27 000 cases of human poisoning by drugs were registered in Brazil, and their 25% stands for use inadequate of drugs [17,18]. In accordance with the National Health Surveillance Agency (ANVISA,

of the Portuguese Agência Nacional de Vigilância Sanitária) the class with a higher usage rate in Brazil is the antidepressants, which is responsible by 15.3% of the pharmaceutical market billing in 2017 [13]. Furthermore, there is a trend to the increase in the growth of the pharmaceutical market worldwide since the discovery, registration and commercial availability of new medicated inputs [19]. Hence, there was a significant increase by analytical methodologies in the determination and quantification of the new antidepressives, so, their use is released with most quickly [20–22].

Recent researches of the Henrique Duarte et. al [23]and Mohammadi et. al show [24] that the methodologies to the determination of the antidepressants have prioritized the minimization of the cost and sample preparation steps, increase in the analytical frequency and adequacy in the guidelines of the Green Analytical Chemistry [25]. Besides this, it is necessary for the identification and quantification of these substances in the water, biological and pure drugs samples in low concentration, due to toxicological effects, such as endocrine disruptors in snails, fish and crustaceans [26–30].

Therefore, the determination of these compounds aid in the adjustment of the therapeutic doses to minimize the error of the concentration ingested through the drug metabolization. Furthermore, the evaluation of the efficiency of the drugs treatment already on the market, drug analyses that found in the process of drug registration, and still, in the quality control in the complex sample. In order to, the measure of the antidepressant residues that can provoke endocrine deregulation in animals and humans [15,21,30].

Furthermore, some researches show the mechanism of antidepressants that are directly related to redox reactions, which occur with interactions in the living cells. In specific cases, the electroanalytical techniques can be used in the investigation of the possible redox reactions, products, and generated metabolites, according to the relationship between the antidepressants and voltammetry. Thus, the electroanalytical techniques are adequate to supply the insights on these compounds properties redox and their metabolism [31].

3. Analytical methods

The ingestion of the drugs in inadequate concentration should adverse effects on the human body, due to triggering of the undesirable reactions and toxicological effects. Beyond this, it is necessary the monitoring of type of these substances in the medicines and the dosage ingested by patients. Hence, the analytical techniques are employed in the control of the substances in the water, biological samples and medicines, which are spectroscopy, chromatography and electroanalytical [32].

So, these techniques obey the fundamental physical and chemical laws that influenced the analytical parameters due to different physical and chemical characteristic. The analytical techniques convert the information of the physical and chemical properties of the analyte in a signal electric, which will be used in the quantification and determination of the drugs. The technique used in the determination of the drugs is chosen mainly according to with chemical structure, sample quantity, physical and chemical proprieties of the sample, sample composition, and concentration range because this can influence the analytical signals [33].

Thus, the spectroscopic techniques are based in the interaction of matter with the radiation or energy fonts, that should provoke the absorption or emission of the energy by target compounds after of the incidence of the energy form. These techniques show high sensibility, accuracy, precision, and robustness that are advantages in the employed their. However, they need skilled labour, steps of sample preparation, low analytical frequency, and expensive cost. Furthermore, the spectroscopic techniques normally have low selectivity to organic compounds, because other compounds present in the sample can have chromophorous groups that absorption and/or emission radiation in the same wave-length [32,34].

The chromatography techniques are based in the separation of the substances across the interaction with mobile phase and stationary phase, being that some drugs stay retained in stationary phase, and others interact more strongly with the mobile phase. Thus, it occurs the separation of the bands or zones, which will be determinate by a detector. These techniques show high selectivity, accuracy, precision that are advantages in their use. However, they need skilled labour, steps of sample preparation to minimize interferences, the high time of analyses, and expensive cost. Furthermore, the chromatography techniques have low sensibility due to their detectors employed, needing to realize detector spectroscopy or electroanalytical [32,34,35].

While electroanalytical techniques are based on the electric properties of the target compounds that are used in the control of pharmaceutical industries and routine tests. These analyses need good analytical parameters, such as the sensibility, selectivity, quickly, and robustness, moreover, it enables the realization chemical speciation of the antidepressants [36].

4. Electroanalytical techniques for antidepressants analysis

Electroanalytical techniques are used redox reactions that employ electric properties of the analyte to its determination. Furthermore, these techniques should present low limit of detection and information of the electrochemical systems, for example, mass transfer velocity, stoichiometry, equilibrium constants, interfacial charge transfer velocity, velocities of chemical reactions, the extent

of adsorption and chemisorption. These electroanalytical techniques in antidepressants analysis need the equipment and electrochemical cell, that is composed of electric and ionic conductors. The ionic conductor is a supporting electrolyte solution, that aids keep constant the ionic force of solution and decrease system resistivity [36].

While the electrical conductor is composed of working, reference and auxiliary electrodes, which are responsible for generating an electrical current from of reaction that occurs in the electrolyte/working electrode interface. Hence, the analytical signals are influenced by electrolyte support and the working electrode, and consequently, the sensibility and selectivity of the methodology developed [36]. The signal obtained also is influenced by mass transfer of the analyte from the solution to the surface electrode, that can be diffusion, convection or migration [37].

4.1 Techniques

The sensibility of the electroanalytical techniques is directly related to the mode of application of potential or current in the working electrodes, which are classified in electrochemical impedance spectroscopy, stripping voltammetry, amperometric, voltammetry, chronoamperometry, and chronocoulometry. Besides this, the voltammetric methods are subdivided in Normal Pulse Voltammetry (NPV), Differential Pulse Voltammetry (DPV), and Square Wave Voltammetry (SWV) following the application of the potential [37]. In Fig. 2 shows the percentage of the researches that were published in the period from 1996 to 2020 with the determination antidepressants using electroanalytical techniques. With this were enabled perceive that the voltammetric methods have a high application in the determination of the antidepressants, which will be discussed below [21,38].

FIGURE 2

4.1.1 Cyclic voltammetric

The CV is based in the application of the potential, that is varied linearly with the time and measured the current, the sweep starts in the potential that occurs not reactions and going the potentials the provides the reduction and/or oxidation reactions. In this technique, the direction of sweep is inverted and the potential is returned to the beginning. The number cycle can be evaluated in a specific time, which provides potential and current signals in the anodic and cathodic directions [39].

Furthermore, the same information can be used in the reaction mechanism of the antidepressants, such as half-peak potential and the half-wave potential values, to the evaluation of

the reversibility electrons transfer kinetic, the number of the electrons quantification through of the interface solution/electrode, identification of the adsorption process and others. Some researches used the CV also for the modification of the electrodes by electropolymerization of the surface electrodes with the formation of a thin polymeric film [32,39]. According to the bibliographic survey realized this technique is a technique more employed in the works published of quantification of antidepressants allowed in Brazil, as presented in Fig 2.

4.1.2 Differential pulse voltammetry

The DPV is based in the application of potential waveform with a potential pulses series with the constant amplitude in the linear ramp, and the current is measured at the potential pulse beginning and end. Thus, it is realized the difference between the two values of the current in the function of the potential applied. With this is generated the voltammogram characterized by analytical signal more sensibility than the CV and NPV, due to decrease of the background current and capacitive current [39]. Thus, the DPV is the second technique with the high applicability in the determination of the antidepressants permitted in Brazil according to Fig 2 [40].

4.1.3 Square wave voltammetry

The SWV is largely employed in the determination of the antidepressants, due to high sensibility, which is provided by the type of potential application in the working electrode. This technique is realized an amplitude pulse series with equal values in the staircase potential with the cathodic and anodic pulse. Thus, the analyte diffuses for the surface electrode and it is reduced or oxidized during the direct pulse. When the pulse has inverted the reduced/oxidized analyte, it can return the chemical structure initially that is considered a reversible reaction or the reaction occurs not that is considered an irreversible reaction [41].

The current values are measured before and end of each pulse, providing the improvement of the sensibility and selectivity permitting low detection limits. Furthermore, this technique still allows the verification of the electrochemical mechanism of the target compounds on the surface electrode. The SWV is the third electrochemical technique more used to the identification and quantification of the antidepressants in the diverse samples [41].

4.1.4 Stripping voltammetry

The stripping voltammetry is a step of the pre-concentration of the antidepressant in the electrode surface before the measured electroanalytical of the target compound, that posteriorly can be used CV, SWV, DPV. In Fig. 2 is shown its applicability in the pre-concentration of antidepressants permitted in Brazil coupled with other voltammetric technique, so, it provides the high of sensibility, selectivity and low detection limits. Normally, this step involves reactions, that are quick and irreversible or reversible [36].

Moreover, stripping voltammetry can be influenced by some factor, such as potential values, temperature, ionic strength, pH, electrode material, electrolyte support, among others. These techniques can be divided according to the manner that the antidepressants are stripped from the electrode and measured of the analytical signal, that can be potentiometric stripping analysis, adsorptive stripping voltammetry, cathodic stripping voltammetry, and anodic stripping voltammetry [36,38].

4.1.5 Electrochemical Impedance Spectroscopy

The electrochemical impedance spectroscopy is realized by application of the sinusoidal voltage in the electrochemical cell providing a current signal, which can be directly related to alteration impedimetric changes by the presence of the chemical or biological group into electrode surface. This way, this technique aids the determination of antidepressants according to the evaluated electric properties in the electrode surface, because the potentiostat software makes the conversion of current and potential measured in an impedance value. Thus, the electrochemical impedance spectroscopy analyses measure the capacitive and resistive properties of the electrode surface into a solution that have a relationship with the concentration of the antidepressants [36,42].

4.1.2 Chronoamperometry and chronocoulometry

Chronoamperometry and chronocoulometry normally are classified in the same group due to similarity in the measured in the analytical signals. The chronoamperometry is a technique directly dependent on the time, so, in the working electrode is applied potential as square-wave. Beyond this, this technique has low sensibility, which can be employed independently or coupled with other electroanalytical technique, such as CV. Thus, they can be used to measure the dependency of time-current in the diffusion processes in the working electrode [43].

Already, the chronocoulometry has some similarities to the chronoamperometry, but it is studying the relationship of the charge variation with time and the current is integrated. This integrated provokes the increase of signal with the time and provides the decrease of signal noise

aiding in the separation of the capacitive load of the faradaic load. So, the chronoamperometry and chronocoulometry have to be used as a detector in the chromatographic analyses [44].

4.3 Materials employed in the working electrode preparations

Normally, the electrochemical cell has working, reference and auxiliary electrodes, but when it has low current the electrochemical system can be modified and it used only two electrodes (working and reference electrodes). Thus, the working electrode is responsible by interest reaction happens. Already, the reference electrode makes the manutention of the potential of the working electrode employing a potentiostat, and the counter electrode is responsible by current-carrying, which also known as the auxiliary electrode [36,37,45].

The working electrode is directly responsible by an analytical signal obtained in the determination of the antidepressant. Hence, the chosen of the electrode composition must be evaluated considering the reproducible responses and relationship of the signal-to-noise. Others factors also must be considered, such as the toxicity of the material, easy availability of material, low cost, mechanical stability, reproducibility in the electrode surface, electrical conductivity, and mainly the potential interval that happens oxidation and/or reduction reaction of the antidepressants [37,38].

Nonetheless, it is many hard to have a working electrode that shows all characteristics mentioned above. Because of this has various materials of the working electrode available commercially or in laboratories, which can have a different chemical composition [38]. In Fig. 3 is shown the percentage of the article published from 1996 to 2020 according to the type of the electrode used in the determination of the antidepressants. Besides this, the chemically modified electrodes were more employed in the antidepressants determination, due to their selectivity, sensibility and follow the guidelines of Green Analytical Chemistry.

FIGURE 3

The second type of electrode used in the analyses of the antidepressants was the carbon-based electrode, because of different forms and origins of the carbon used in the electrode surface, that can provide good analytical parameters, and it is friendly to the environment. Already, the mercury-based electrode is used in the determination antidepressants in reason of the excellent analytical signals and parameters obtained, but the reduced number of the article published is because of the toxicity of waste generated in the analyses. Moreover, some researches used the metals electrodes made to the determination of the antidepressants.

4.2.1 Mercury-based electrodes

The use of mercury electrodes had great applicability until the implementation of the Green Chemistry in the early 1990s, due to its toxicity degree to the environment. Nonetheless, these electrodes have a wide potential range cathodic, good electrical conductivity, sensibility, reproducibility in the chemical analyses, and low cost. The mercury has chemistry and physical properties that aid the getting of the analytical signals, such as, hydrophobic surface, it shows high interfacial tension, and the liquid state in room temperature [36,39].

The mercury-based electrodes can have different formats, which are classified into liquid electrodes (hanging mercury drop electrode and mercury film electrode) and solid electrodes (amalgams). The use of a system composed of the pressure of the inert gas or electrical discharge coupled with specific software and potentiostat/galvanostat enables the control of the drop size used in the hanging mercury drop electrode. This system is responsible to control the drop dislodgment, dispensing and size, oxygen remotion from solution, and also the technique employed. With this, it enables the excellent surface renovation, and consequently, good reproducibility in mercury drop size, minimization of residue generation and quickly in the analyses [46,47].

While the mercury film electrodes are made by deposition of a liquid mercury thin layer under metal-based, amalgams and carbon-based electrodes. The use of these films minimize the residue generation and still have similar properties with the mercury traditional electrode. Nonetheless, the metal-based electrodes can have low reproducibility, because some metals in contact with mercury react and produce the amalgams, such as silver, gold, and platinum. Thus, one alternative is the utilization of the carbon-based electrode, which have low cost, wide potential interval, easy surface renovation, and chemical inertness [38,46,47].

However, the mercury liquid electrodes have one disadvantage in the electrochemical analyses, that is their instability inflows systems and toxicity degree. Hence, new studies have searched by other materials for electrodes with similar properties of the mercury liquid electrode, providing the use of the amalgam electrodes to the determination of the antidepressants. So, these amalgam electrodes can be classified in the paste and solid form, which are made from the mixture of other metal with mercury in adequate proportion, which can be bismuth, gold, copper, and silver [46,48,49].

The solid amalgam electrodes do not have in its chemical structure liquid mercury and also have excellent reproducibility on the surface, electrical conductivity, and chemical stability. Besides this, these electrodes present good analytical stability, sensitivity and reduce some adsorptive problems. Nonetheless, the use of silver amalgam electrodes has some advantages about the other

types of amalgams, such as the broad potential interval, and reproducibility of the amalgamatization [46,48,49].

J.J.B. Nevado et al. used hanging mercury drop electrode to the determination of fluvoxamine in pharmaceutical preparations. Initially, the CV was used to evaluate the reaction mechanism, supporting electrolyte that chosen was perchloric acid in pH 2.00 due to its sensibility. Posteriorly, SWV and SWAdSV were employed to the determination of the fluvoxamine pharmaceutical preparations samples, that enabled the minimize the sample preparation steps and preconcentration of the target compound, and obtain good analytical parameters [50].

4.2.2 Metal-based electrodes

The metal-based electrodes enable the determination of the antidepressants that have reactions in the wide anodic potentials. These electrodes are build using solid metals, such as gold, silver, platinum, palladium, nickel, and bismuth due to their good electric conductivity, so the platinum and gold are more employed in the antidepressants analyses. Moreover, metal-based electrodes normally have high reaction kinetic providing selectivity in the determination of the target compound [36].

Nonetheless, the disadvantage in their use is the adsorption of the production and/or reagents in the electrode surface making it necessary for the renovation of surface, which can be realized to electrochemical treatment or polishing. Besides this, the electrochemical treatment provokes the formation of oxides in the electrode surface, and consequently, the block and/or change the analytical signal. When the polishing of the electrode provides the substance remotion, but non-control can promote the alteration of the electroactive area minimizing the reproducibility of analyses [38].

New researches have shown the utilization of the metal microelectrodes, due to minimization of the signal-to-background, and decrease of the detection and quantification limits. Thus, P. Norouzi et al. used gold microelectrode together Fast Fourier Transform Continuous CV, that enables the determination of nortriptyline in the pharmaceutical formulations in flow-injection. The tables were initially diluted in distilled water and phosphoric acid, minimizing the sample preparation steps, and consequently, errors systematic. Furthermore, it obtains good analytical parameters, such as precision, accuracy, limit detection, and low relative standard deviation [51].

4.2.3 Carbon-based electrodes

Carbon-based electrodes had great popularity in the application of the analyses electrochemistry, in reason of the electrode surface has mechanical stability, chemical inertness, low cost, low background current, and wide anodic potential interval. Furthermore, these electrodes can

have different forms and origins of the carbon, such as boron-doped diamond, graphene, carbon films, screen-printed, carbon nanotubes, glassy carbon, carbon fibre, carbon paste, as presented in the Fig. 3. With this, the electrochemical activity is directly related to the carbon type and microstructure surface [52–54].

Nonetheless, the reaction of the electron-transfer can be influenced by the form of the carbon surface, thus being able to increase or decrease the sensitivity of the analytical methodology. Hence, some procedures of pretreatment and cleanliness can are used in the carbon surface to provokes the alteration in the electron-transfer providing an alteration in the analytical signal. Besides this, according to the bibliographic survey realized in this work the glassy carbon has the largest number of the article published using among the works that employed carbon-based electrode. Its broad wide use is due to wide potential window, good conductivity, high chemical resistance, gas impermeability and stability [36,53,55–59].

The graphite is the stable form of carbon, which have excellent electric conductivity, and electrochemical properties more similar to mercury. Furthermore, this material has a wide range of potential in the anodic region. Thus, graphite electrode was the first the be used as the carbon-based electrode, but in some types show high porous its surface, being one disadvantage due to the high charging currents. The quality of the graphite electrode is dependent on the oxidation degree of the graphite used in the fabrication of the electrode [44,60].

Besides this the fabrication of the mixture of graphite and organic binder in the adequate ration, that aid the good conductive and electroanalytical properties and minimize the surface porosity, which is known as carbon paste electrode. These electrodes were widely employed in the determination of antidepressants, which have a low cost. Moreover, these electrodes have high viscosity and hydrophobicity, that provided their high applicability. These electrodes have special properties, such as different pretreatment for cleaning and activation electrode surface, individual polarization, and ease of chemically modifying the surface [38,60].

Thus the glassy carbon is the electrode more used in the antidepressants determination, that can be known also as vitreous carbon. Moreover, this electrode has high reproducibility, the wide interval of potential mainly in the way anodic, low resistance, impermeability to liquids and gases and low thermal and electrical conductivity. Thus, the quality of the signal is directly related to the type of treatment used for the remotion of the substances and noncarbon atom in the surface, that can be heat, polishing, exposition of organic solvent, laser, among other, and the choice of what to use is dependent of the conditions operational and analytical signals obtained [38].

Already, the electrodes made with carbon fibre can be considered as microelectrode, depending on their size. So, the use of small size has some advantages, such as smaller exposed area,

high resolution, quick analytical responses, and lower background current. Normally, the carbon fibre electrodes are produced from carbon precursor decomposition or different materials (rayon, lignin, pitch, and PAN). Therefore, it is necessary for the realization of the evaluated of microstructures and surface obtained, and they can be classified according to the temperature used in the production because can affect the carbon chemical structure. However, their area geometry of fibre can be modified by mechanical polished, hence, the activation and/or cleaning usually is realized using solvents, high-vacuum heat or laser treatments are employed [38].

The carbon nanotubes electrodes can be divided into single-walled and multi-walled according to the structure, that is graphene tubules. These electrodes are used in the determination of the antidepressants in different samples, due to chemical stability and electronic and mechanical properties. These properties and other electrochemistry properties can are directly related to the lattice helicity and diameter of the carbon nanotubes used, some researches have shown that the modification of this electrode with metals and glass can provide similar properties improvement. Nonetheless, heat treatment and mechanical polishing for the cleaning and activation of the surface can modify their chemical structure, so, the purification is considered a critical step in the analysis [38].

The boron-doped diamond electrode has a broad potential interval according to the quality of film realized in the electrode surface, due to potentials that occur the reactions for hydrogen and oxygen evolution, when compared with traditional materials, such as glassy carbon, platinum, and gold. Hence, this material enables the determination of the antidepressants in the anodic and cathodic potentials. Moreover, the boron-doped diamond electrode owns low double-layer capacitance, background current, and consequently, the low proportion of signal-to-background. This electrode type has low detection and quantification limit because the background voltammetric currents and double-layer capacitance are smaller than the glassy carbon electrode in the same geometric area [61].

Beyond of advantages that were shown above of the use of carbon-based electrodes, they still are easily chemically modified, due to the compatibility of the electrode surface with different modifiers, which can aid in the selectivity and sensibility in analyses, and decrease the adsorption in the surface during the experiments. Thus, new researches present also the possibility of accomplishing the screen-printed electrode using carbon materials. That allows the control of the electrode composition and surface area, replicate of the electrode with improvement quality, one catalytic compound can be added in the composition of the electrode easily [62,63].

Beyond this, Farjami et. at the used carbon-based electrode to the determination of the nortriptyline in tablets samples. Initially, glassy carbon, carbon paste, and carbon ionic liquid electrode were tested to evaluate the response electroanalytical, so, the best signal was obtained with the carbon ionic liquid electrode with 0.10 mol L^{-1} phosphate buffer in pH 7.4coupled CV and DPV,

that made it possible the evaluate of the mechanism of the electrode surface reaction and determination, respectively. The tablets were crushed and diluted in the methanol and water distilled, so, the solution obtained was employed in the analyses. This methodology was evaluated in quickly, sensitivity, and selectivity, according to the analytical parameters calculated [14,64,65].

4.2.4 Chemical modified electrode

The electrode properties can be improved using the modification of the electrode surface, which enables high of the catalysis, modification of the charge transference and minimize the adsorption of the compound in the surface. These modifications are realized using a specific material to modify the surface of the solid electrode with a polymeric film, multi-molecular, or ionic monomolecular. That can provide the alteration in the mechanical and chemical stability, potential interval and electric resistance, and consequently, the analytical parameters, such as sensitivity, selectivity, detection and quantification limit, and robustness [38].

Normally, the substrate used is can be classified as semiconductive and conductive, that have from traditional materials of electrodes. The materials more employed in the electrodes used in the antidepressants determination are the carbon-based, due to ease of the clean, reproducible, but some researches have shown the modification of the surface of the metal-based electrodes. Therefore, good reproducibility can be obtained using pre-treatment for verification of the substrate properties, these steps are traditional treatments or their modification when necessary because in specific cases need of this refined to enable the achieve the desired result [38,66].

When the adlayers are the material that is used to modify the electrode and they can have different source and properties, which can interact chemically or physically and adsorb in the electrode surface. Beyond this, the use of the characterization techniques is employed for the compression of the electrode surface composition and also to improve the analytical signal obtained. The adlayers can be DNA, metallic nanoparticles, polymers, sol-gel, enzyme, zeolites and clays, and their choice is directly dependent on the end-application in the electroanalytical [38,67].

Thus, Jat et. al employed the glassy carbon modified with multiwalled carbon nanotube electrode with Britton-Robison buffer for the determination of clomipramine in analyses of urine and bulk. The CV is used to evaluate the sweep rate and renovation of the electroactive electrode surface. Moreover, the DPV is utilized to the determination of clomipramine and enable the calculus of analytical parameters that allowed the verification of a methodology good sensitivity, selectivity, low limit of detection [68].

In Table 2 is shown works from 1996 to 2020 of electrochemical to the determination of antidepressants in the water, biologic, pharmaceutical formulation samples. Thus, it was possible to

perceive that the carbon-based electrodes and chemical modified electrodes had a predominance due to easily and minimization and/or avoid residue generation during the analyses. Furthermore, the electrochemical techniques most employed were CV, SWV and DPV, because CV and SWV enable the study of the reaction mechanism, and SWV and DPV have more sensitivity compared with CV and other techniques.

TABLE 2

6. Perspectives

In this review was presented the 22 antidepressants used in Brazil, which are used in the pharmaceutical formulations. These substances were classified in norepinephrine and dopamine reuptake inhibitors, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, atypical antidepressants, monoamine oxidase inhibitors, and melatonergic agonist and serotonin (5-hydroxytryptamine, 5-HT) 2C receptors (5-HT2CRs) antagonist. Moreover, it was presented the type of actuation of these compounds in the human body according to each antidepressants class.

The electrochemical techniques can be used in the antidepressants control in the different samples type, that can have some advantages, such as low cost, good analytical parameters, minimization of the sample preparation steps, operational ease, and reduced analysis time. This way, it was realized n the specific literature from 1996 to 2020 were used and developed diverse analytical procedures employing electroanalytical techniques to quantification and identification of the antidepressants.

Nonetheless, the material used in the making of the working electrode can influence the analytical signal and analytical parameters of the methodology developed. New researches have wanted materials that presented toxicity and excellent sensibility, selectivity, robustness, precision, and accuracy. Besides this, the use of mercury-based electrodes has been less employed than other materials electrodes as shown in Fig. 3, such as the carbon-based electrodes and chemically modified electrodes, which follow the guidelines of the Green Analytical Chemistry.

Furthermore, carbon-based, metals-based and chemically modified electrodes enable the build screen printed and adhesives electrodes, that can facilitate the analyses in the complex sample and high the analytical frequency. The use of the carbon-based, metals-based electrodes made possible the analyses of the antidepressants that reduce or oxide in the anodic potential, and still the minimization of the toxic waste. While the chemically modified electrodes aid in the high of the sensibility and selectivity in the analyses of these compounds.

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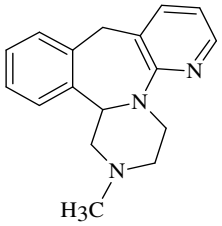
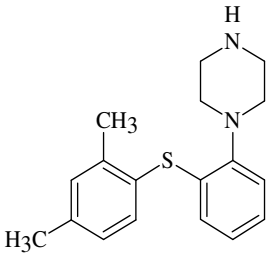
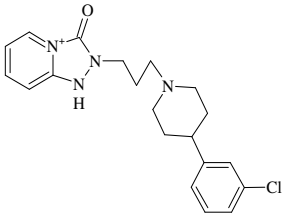
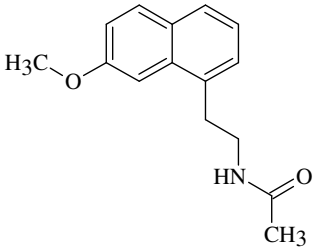
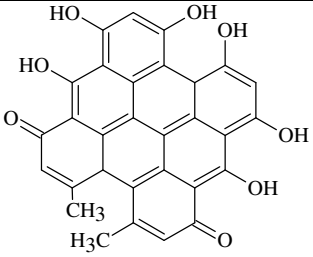
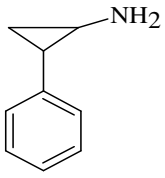
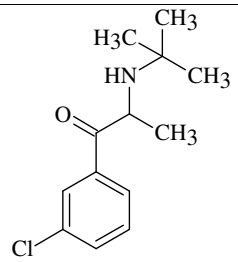
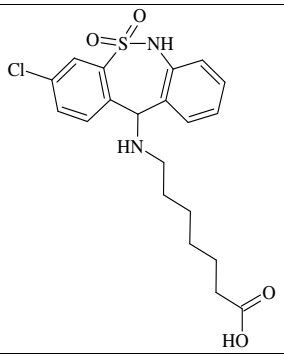
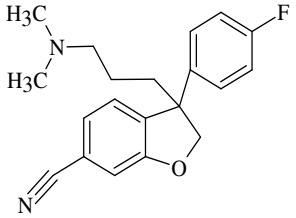
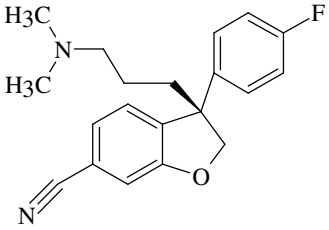
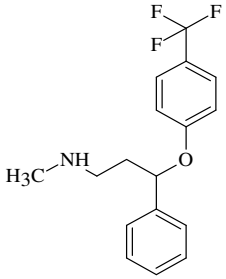
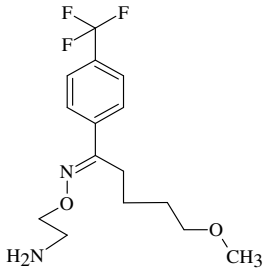
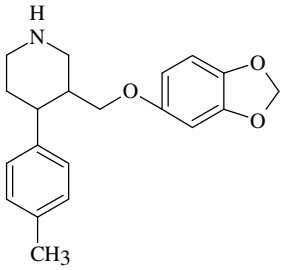
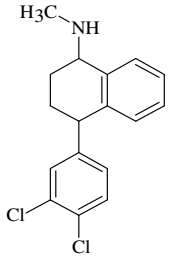
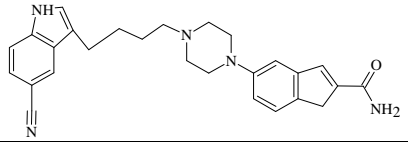
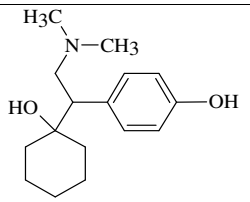
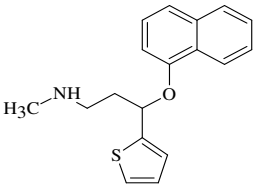
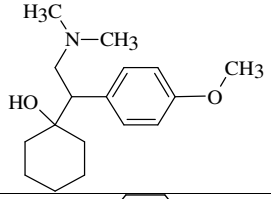
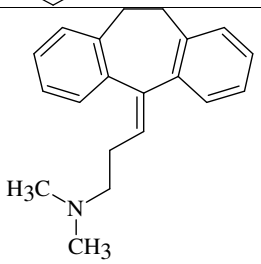
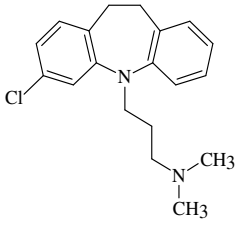
Tables

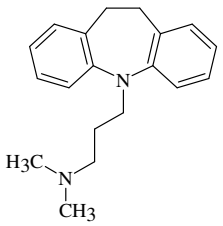
Table 1: Classes, compounds and chemical structures of pharmaceutical compounds allowed in Brazil for use as antidepressants.

Classes	Compounds	Structure chemical
Atypical antidepressants (AA)	Mirtazapine	
	Vortioxetine	
	Trazodone	
Melatonergic agonist of Serotonin and antagonist receptors (MASRA)	Agomelatine	
Monoamine oxidase inhibitors (MOI)	Hypericum Perforatum	
	Tranylcypromine	

Norepinephrine and Dopamine reuptake inhibitors (NDRI)	Bupropion	
Selective Serotonin reuptake enhancer (SSRI)	Tianeptine	
Selective Serotonin reuptake inhibitors <u>(SSRE)</u>	Citalopram	
	Escitalopram	
	Fluoxetine	
	Fluvoxamine	

	Paroxetine	
	Sertraline	
	Vilazodone	
Serotonin and Norepinephrine reuptake inhibitors	Desvenfalaxine	
	Duloxetine	
	Venlafaxine	
Tricyclic antidepressants (TCA)	Amitriptyline	
	Clomipramine	

Imipramine



Nortriptyline

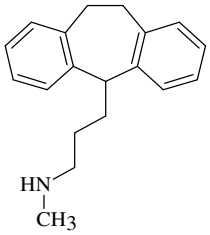


Table 1: Electroanalytical methods for antidepressants determination, indicating the class, pharmaceutical compound, electroanalytical technique, working electrode, limit detection and the type of the sample in which the method was applied.

Class	Pharmaceutical Compound	Technique	Working Electrode	LD ($\mu g\ L^{-1}$)	Sample	Ref
TCA	Amitriptyline	CV	Carbon-based	6.65	Human blood samples and human urine samples	[69]
TCA	Amitriptyline	CV, DPV and SWV	Chemically modified	33.29	Pharmaceutical preparation	[70]
TCA	Amitriptyline	CV and DPV	Carbon-based	446.62	Pharmaceutical preparation	[23]
TCA	Amitriptyline and imipramine	CV	Chemically modified	NR	Pharmaceutical preparation	[71]
SSRI	Citalopram	FFTCV	Metal-based	$2.3x10^{-6}$	Pharmaceutical preparation	[72]
SSRI	Citalopram	CV, SWV and SWAdSV	Chemically modified	2.027	Human blood samples, human urine samples and pharmaceutical preparation	[73]
SSRI	Citalopram	CV and DPV	Chemically modified	21.56	Human blood samples and pharmaceutical preparation	[74]
SSRI	Citalopram	CV and DPV	Carbon-based	14.59	Pharmaceutical preparation and water samples	[75]

SSRI	Citalopram	CV and EIS	Chemically modified	17.83	Human blood samples and pharmaceutical preparation	[76]
SSRI	Citalopram	SWV and SWAdSV	Mercury-based	20.26	Pharmaceutical preparation	[77]
TCA	Clomipramine	CV and DPV	Carbon-based	0.01315	Pharmaceutical preparation	[68]
TCA	Clomipramine	CV and DPV	Carbon-based	98.36	Pharmaceutical preparation	[78]
TCA	Clomipramine	CV	Chemically modified	2.108	Pharmaceutical preparation	[79]
TCA	Clomipramine	CV and DPV	Chemically modified	0.3153	Pharmaceutical preparation	[80]
SNRI	Desvenfalaxine	CV and DPV	Chemically modified	173.0	Human urine samples and pharmaceutical preparation	[81]
SNRI	Duloxetine	CV and SWV	Chemically modified	118.96	Human urine samples and pharmaceutical preparation	[82]
SNRI	Duloxetine	CV and SWV	Carbon-based	NR	Human blood samples and pharmaceutical preparation	[83]
SSRI	Escitalopram	CV, DPV and SWV	Chemically modified	81.10	Urine and cerebrospinal fluid samples	[84]
SSRI	Escitalopram	CV	Chemically modified	53670	Pharmaceutical preparation	[85]

SSRI	Escitalopram	CV and EIS	Chemically modified	64.88	Pharmaceutical preparation	[86]
SSRI	Fluoxetine	DPV	Chemically modified	NR	Human blood samples and pharmaceutical preparation	[87]
SSRI	Fluoxetine	CA and CV	Chemically modified	24.44	Pharmaceutical preparation	[88]
SSRI	Fluoxetine	CA, CV, DPV and SWV	Carbon-based	NR	Water sample and pharmaceutical preparation	[89]
SSRI	Fluoxetine	CV and DPV	Chemically modified	123.73	Pharmaceutical preparation	[24]
SSRI	Fluoxetine	CV, DPV and SWV	Carbon-based	NR	Pharmaceutical preparation	[90]
SSRI	Fluoxetine	SWAdSV and FIA-SWAdSV	Mercury-based	24.44	Pharmaceutical preparation and human blood samples	[91]
SSRI	Fluoxetine	CV, DPV, LS, SWCAdSV and SWV	Mercury-based	12.06	Water sample and pharmaceutical preparation	[92]
SSRI	Fluoxetine,citalopram and sertraline	ITSV	Chemically modified	10.13 - 13.78	Water sample	[93]
SSRI	Fluvoxamine	CV and DPV	Chemically modified	3183,3	Human urine samples and pharmaceutical preparation	[94]
SSRI	Fluvoxamine	CA, CC and CV	Chemically modified	254.66	Human blood samples and pharmaceutical preparation	[95]

SSRI	Fluvoxamine	CV	Chemically modified	24.83	Human blood samples, pharmaceutical preparation and human urine samples.	[96]
SSRI	Fluvoxamine	SWV and SWAdSV	Mercury-based	NR	Pharmaceutical preparation	[50]
TCA	Imipramine and Amitriptyline	CV	Chemically modified	5.328 and 6.658	Human blood samples and pharmaceutical preparation	[97]
TCA	Imipramine	CA, CC, CV and DPV	Carbon-based	NR	Pharmaceutical preparation	[98]
TCA	Imipramine	CV, DPV and SWV	Carbon-based	NR	Human blood samples and pharmaceutical preparation	[99]
TCA	Amitriptyline, clomipramine, imipramine and nortriptyline	CV and FIA	Carbon-based	0.1574 - 284.45	Human blood samples	[100]
TCA	Imipramine	CV and SWV	Chemically modified	1.29	Pharmaceutical preparation	[101]
TCA	Imipramine	CV and DPV	Carbon-based	8.412	Pharmaceutical preparation and human urine samples	[102]
TCA	Imipramine	CV and SWV	Carbon-based	12.20	Pharmaceutical preparation	[103]
AA	Mirtazapine	CV, DPV and SWV	Carbon-based	NR	Pharmaceutical preparation	[104]

TCA	Nortriptyline	CV, DPCAdSV and SWCAdSV	Mercury-based	15.01 – 13.17	Pharmaceutical preparation	[105]
TCA	Nortriptyline	CV	Metal-based	0.004728	Pharmaceutical preparation	[51]
TCA	Nortriptyline	CV, DPCAdSV and SWCAdSV	Mercury-based	242.31	Pharmaceutical preparation	[106]
TCA	Nortriptyline	CV and DPV	Chemically modified and carbon-based	79.01	Pharmaceutical preparation	[65]
TCA	Nortriptyline	CV	Chemically modified	NR	Human blood samples, human urine samples and pharmaceutical preparation	[107]
SSRI	Paroxetine	AdsDPV, CV and SWV	Carbon-based	0.3392	pharmaceutical preparation	[108]
SSRI	Paroxetine	FIA-SWAdSV, SWAdSV and SWV	Mercury-based	NR	pharmaceutical preparation	[109]
SSRI	Sertraline	CV and DPV	Chemically modified	29.09	Human blood samples	[110]
SSRI	Sertraline	CV, DPV, LS and SWV	Mercury-based	60.63	pharmaceutical preparation	[111]
AA	Trazodone	CV	Carbon-based	NR	pharmaceutical preparation	[112]
AA	Trazodone	CV and SWV	Mercury-based and Carbon-based	1.606	pharmaceutical preparation and human blood human samples	[113]

AA	Trazodone	CV and DPV	Chemically modified	8.925	Human urine samples and pharmaceutical preparation	[114]
AA	Trazodone	CV and DPV	Metal-based	632.16	Pharmaceutical preparation	[115]
SSRI	Viladozone	CA, CV and DPV	Chemically modified	0.3881	Human urine samples and pharmaceutical preparation	[116]
SNRI	Venlafaxine	AdSV, CV and SWV	Mercury-based	192.24	Human urine samples	[117]
SNRI	Venlafaxine and Desvenlafaxine	AdSDPV , CV, CC and EIS	Chemically modified	3.44 - 8.42	Pharmaceutical preparations, human urine samples and human blood samples	[118]
SNRI	Venlafaxine	AdSDPV, CV, DPV and EIS	Chemically modified	1.664	Human urine samples and human blood samples	[20]
SNRI	Venlafaxine	CHA, CV and DPV	Chemically modified	138.7	Human urine samples and pharmaceutical preparation	[119]
SNRI	Venlafaxine	CHA, CV and DPV	Chemically modified	58.25	Pharmaceutical preparation, human urine samples, and water samples	[120]
SNRI	Venlafaxine	SWV	Mercury-based	124	Pharmaceutical preparation	[121]
SNRI	Venlafaxine	CV and SWV	Chemically modified	468.81	Pharmaceutical preparation	[122]

SNRI	Venlafaxine	CHA and CV	Chemically modified	11.10	Human urine samples and pharmaceutical preparations	[123]
SNRI	Venlafaxine	CV	Chemically modified	NR	Human blood samples and human urine samples	[124]
AA	Vortioxetine	AdsDPV and CV	Chemically modified	18.97	Pharmaceutical preparation	[125]

TCA = Triciclic antidepressives; SSRI = Selective Serotonin reuptake inhibitor; SNRI = Serotonin and Norepinephrine reuptake inhibitor; AA = Atypical antidepressive; CV = Cyclic voltammetry; DPV = Differential pulse voltammetric ; SWV = Square wave voltammetry; FFTCV = Fast fourier transform continuous cyclic voltammetric technique; SWAdSV = Square-wave adsorptive-stripping voltammetric; EIS = Electrochemical impedance spectroscopy; CA = Chronoamperometry; FIA = Flow-injection; LS = Linear sweep; ITSV = Ion transfer stripping voltammetry; DPCAdSV = Differential pulse cathodic adsorptive stripping voltammetric; CC = Chronocoulometry; LD = Limit detection and Ref. = Reference.

LEGEND OF FIGURES

Figure 1: Classes of antidepressants commercially allowed in Brazil.

Figure 2: Electroanalytical techniques applied in the antidepressants analysis in different samples and using various working electrodes materials.

Figure 3: Commons materials employed in the working electrodes preparations for electroanalysis of antidepressants.

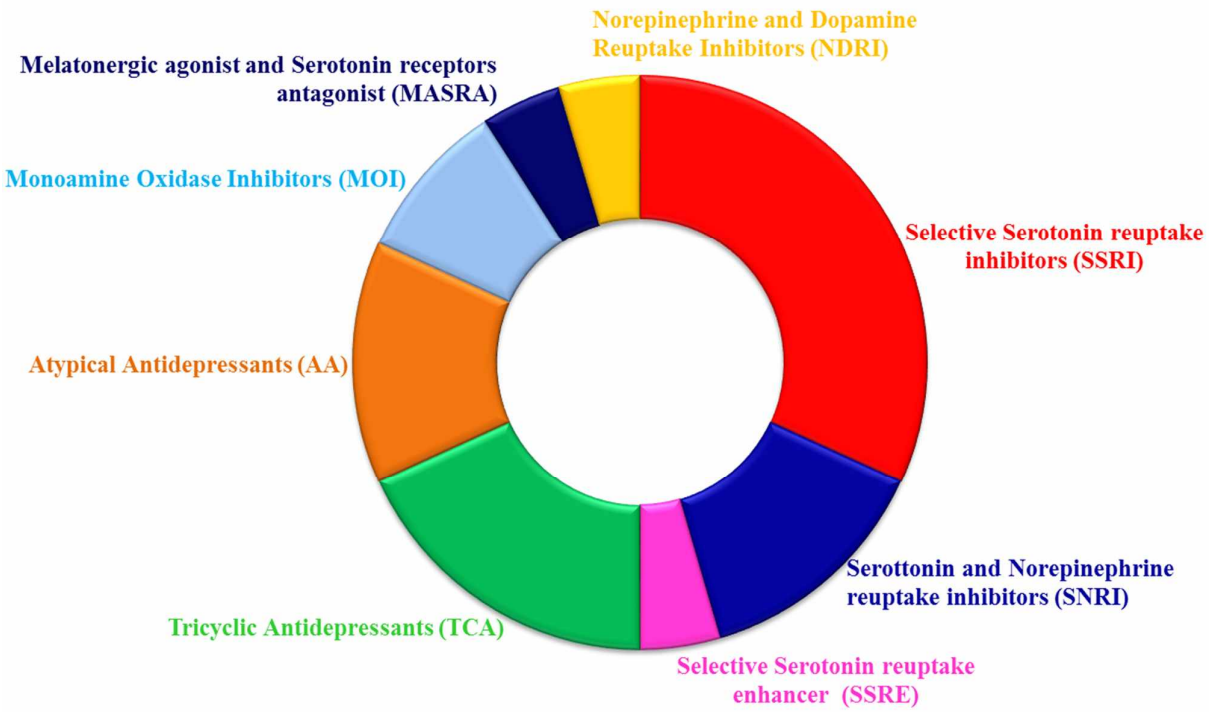


Figure 1: Laura C. Pimenta et. al.

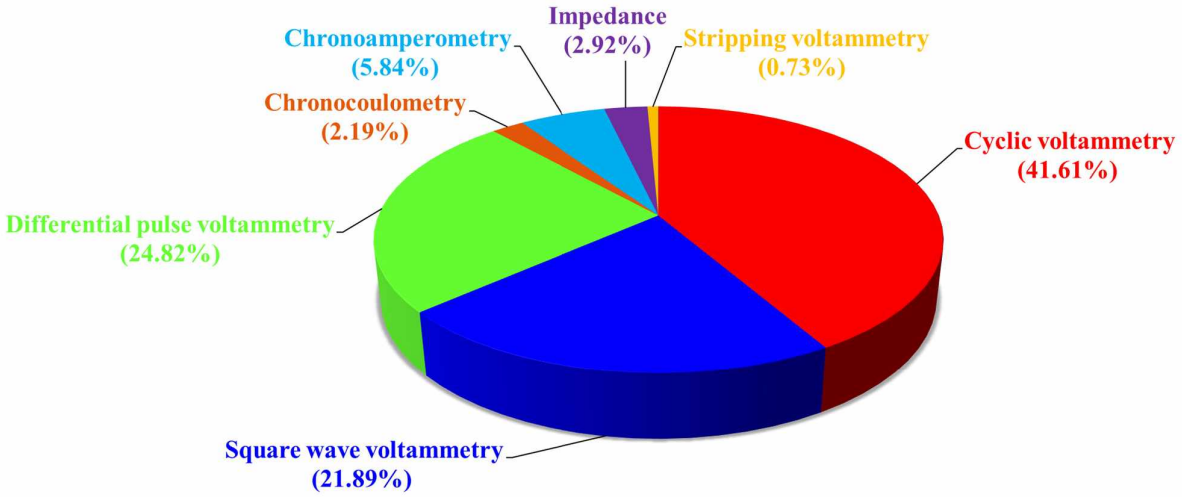


Figure 2: Laura C. Pimenta et. al.

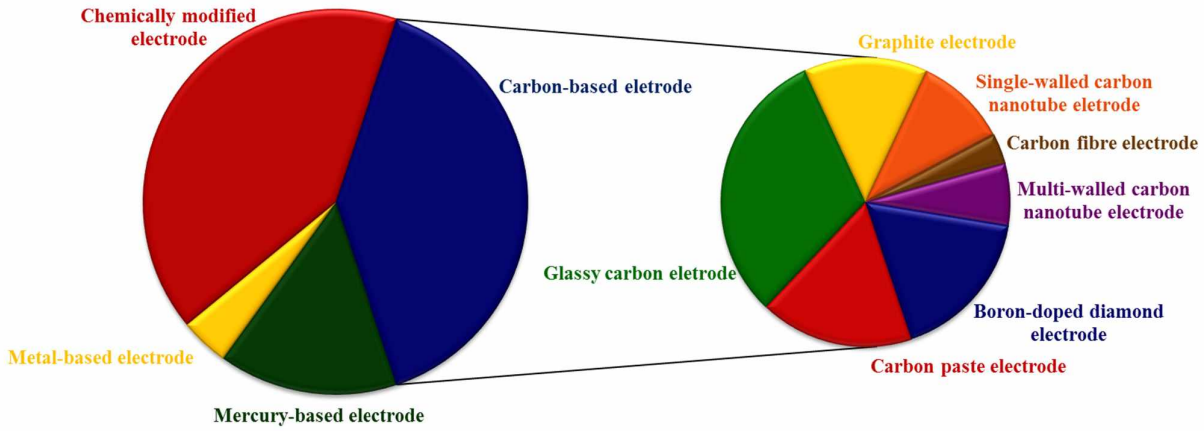


Figure 3: Laura C. Pimenta et. al.