Actualities in immunological markers and electrochemical sensors for determination of dopamine and its metabolites in psychotic disorders (Review)

ADELA MAGDALENA CIOBANU[1,2], LUANA GEZA[1,2], IULIA GABRIELA DAVID[3], DANA ELENA POPA[3], MIHAELA BULEANDRA[3], ANTON ALEXANDRU CIUCU[3] and LIANA DEHELEAN[4]

[1]Department of Psychiatry, 'Prof. Dr. Alexandru Obregia' Clinical Psychiatric Hospital, 041914 Bucharest; [2]Discipline of Psychiatry, Neurosciences Department, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest; [3]Department of Analytical Chemistry, Faculty of Chemistry, University of Bucharest, 050663 Bucharest; [4]Department of Neurosciences-Psychiatry, Centre for Cognitive Research in Neuropsychiatric Pathology, 'Victor Babes' University of Medicine and Pharmacy of Timisoara, 300041 Timisoara, Romania

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Abstract. Psychotic disorders represent a serious health concern. At this moment, anamnestic data, international criteria for diagnosis/classification from the Diagnostic and Statistical Manual of Mental Disorders-5 and the International Classification of Diseases-10 and diagnostic scales are used to establish a diagnosis. The most commonly used biomarkers in psychotic illnesses are those regarding the neuroimmune system, metabolic abnormalities, neurotrophins and neurotransmitter systems and proteomics. A current issue faced by clinicians is the lack of biomarkers to help develop a more accurate diagnosis, with the possibility of initiating the most effective treatment. The detection of biological markers for psychosis has the potential to contribute to improvements in its diagnosis, prognosis and treatment effectiveness. The mixture of multiple biomarkers may improve the ability to differentiate and classify these patients. In this sense, the aim of this study was to analyze the literature concerning the potential biomarkers that could be used in medical practice and to review the newest developments in electrochemical sensors used for dopamine detection, one of the most important exploited biomarkers.

Contents

Correspondence to: Dr Luana Geza, Discipline of Psychiatry, Neurosciences Department, 'Carol Davila' University of Medicine and Pharmacy, 37 Dionisie Lupu, 020021 Bucharest, Romania
E-mail: geza.luana@gmail.com

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1. Introduction

Psychosis consists of a clinical disorder reflecting evident cognitive and perceptual function disturbances that are influenced, in most situations, by dysfunction of neurotransmission of dopamine and glutamate. Since the discovery of dopamine (3-hydroxytyramine) (DA), this catecholaminergic neurotransmitter has been of great interest to scientists due to its strong link to various diseases such as psychotic disorders, Parkinson's disease, Huntington's disease and addiction disorders. It was concluded that the symptoms of psychosis are caused by an increased activity of mesolimbic dopaminergic projections, leading to hyperstimulation of striatal dopaminergic D2 receptors (1).

Associated gene variants found in large-scale genetic analyses are reported to contribute to the risk of psychosis. Epidemiological research also suggests that there are numerous environmental causes of psychosis. Regardless of the etiology of the disorder, most patients may experience changes in function/structure of the brain, or alterations in neurophysiological parameters (2-4).

Biomarkers refer to a broad subgroup of biological signs, which are objective and can be measured accurately and reliably in a patient (5). Finding standardized biomarkers is an important concern of scientists in modern medicine. Their usefulness applies not only in establishing the diagnosis, but also in dividing patients into risk groups and establishing treatment and prognosis. For several years, the search for biomarkers for psychotic disorders has been continuous, but a non-invasive blood-based test that could be used for diagnostic or prognostic purposes remains uncertain (6). Many analytical techniques such as electrochemical techniques, especially

voltammetry [cyclic (CV), differential pulse (DPV) and square wave (SWV)] at different electrochemical sensors have been used to develop new methods for the determination of specific biomarkers in different psychiatric and neurological diseases, successful results being obtained (7,8).

Given the above information, in the attempt to discover biomarkers useful in clinical practice for the diagnosis of psychotic disorders, researchers have focused on developing methods for quantifying dopamine and its metabolites.

2. Scope of the review

The most frequently used methods to diagnose psychotic disorders on a regular basis are clinical tools that include psychiatric interviews, questionnaires and anamnestic data, as well as laboratory analysis of specific biomarkers. Therefore, the aim of this study was to present actualities in immunological markers and electrochemical sensors for the determination of dopamine and its metabolites levels in biological samples useful for holistic diagnosis of psychotic disorders.

3. Research methods

We researched electronic databases such as Pubmed, Google Scholar, Science Direct, Wiley, Springer and Web of Science for publications referring to immunological markers and electrochemical sensors for dopamine determination. In order to obtain a broad perspective about the subject, we included cumulatively a total of 90 scientific publications, only written in English and published between 1990 to 2021. Due to the importance of the topic, the number of articles regarding the electrochemical sensors for dopamine analysis published in the literature is very high. Therefore, in this review we included reviews from the end of 2020 and the papers (9) published in the first three months of 2021. For a better understanding of the subject, we included scientific publications containing the terms 'immunology', 'psychosis', 'dopamine', 'electrochemical sensors', 'voltammetry'.

4. Results

Immunological biomarkers. For years, the role of the immune system in the pathophysiology of psychosis has been a controversial issue, with both supporting and opposing proof from a multitude of different disciplines and research approaches, including epidemiology, pharmacology, cell and animal modeling, neuroimaging and biochemical analysis (10).

Only 40% of patients with schizophrenia show evidence of inflammatory activity transposed through interleukins such as IL-6, IL-1B, IL-8 and α-1-antichymotrypsin transcript changes. These results are similar with the proportion of subjects with schizophrenia who exhibit brain abnormalities (11,12).

In studies where brain microglia were analyzed, a substantial growth in (^{11}C) PK-11195 binding was found, suggesting a relation between brain inflammation and psychotic symptoms (13,14).

An increase in the mean relative and absolute monocyte number in the peripheral circulation was described in individuals with non-affective psychosis (15). Patients with paranoid schizophrenia presented lower T cell numbers before treatment with normalized values over time after recovery (16).

IL-10, IL-6, tumor necrosis factor (TNF)-α, antagonist receptor of IL-1 and soluble tumor necrosis factor receptor-1 (sTNFR1) were found to be elevated during mania in affective psychosis, demonstrating reliable activation of the inflammatory immune system (17-19). Different studies have evaluated the peripheral cytokines as state [IL-1β, IL-6 and transforming growth factor (TGF)-β] trait (IL-12, IFN-γ, TNF-α and sIL-2R) markers, in correlation with their dynamic in the acute episode of psychosis (20).

Peripheral immunologic blood cells from patients suffering from psychosis show modification not only with respect to their number, but also regarding their function such as the abnormal response to mitogenic stimulation in association with smoking (21,22).

Proteomics. The term comprises the entire set of proteins that a biological system produces (23). It is a useful tool in the study of pathologies with complex etiology such as psychotic disorders (24). The most frequently studied biological product, from a proteomic point of view, is cerebrospinal fluid (CSF) (25).

Studies have shown the presence of the following biomarkers in CSF from the patients diagnosed with schizophrenia: Fibronectin 1 (FN1) (9), glutathione peroxidase 1 (GPX1) (26,27), chromogranin A (CHGA) (28,29), immunoglobulin superfamily member 8 (IGSF8) (30), microtubule-associated protein 2 (MAP2) (31,32), neurofascin (NFASC) (33), heat shock protein 12A (HSP12A) (34) and protein tyrosine phosphatase receptor type Z1 (PTPRZ1) (35). In addition, in these patients, the expression of proteins such as apolipoprotein E (APOE), apolipoprotein A1 (APOA1) and prostaglandin D2 (PGD2) was observed, which led to the confirmation of the hypothesis that patients with schizophrenia have metabolic alterations such as dyslipidemia (36-38). PGD2 is also an important component in the arachidonic acid pathway and has been previously correlated with psychotic pathology (39).

Studies analyzing the proteomic profile of peripheral markers of patients with bipolar affective disorder and psychotic symptoms, found a different expression of a number of 36 proteins, but after additional tests, only two proteins, LIM and SH3 domain protein1 have been shown to be altered in bipolar disorder with psychotic elements (40).

Due to the availability and greater ease of collection, peripheral blood is an important biological product for the detailed study of biomarkers in various pathologies (41).

Studies that have analyzed peripheral blood proteomics have established a correlation between IL-1ra and IL-10 and antipsychotic treatment, showing decreased levels during therapy while improving symptoms (42).

Neurotransmitter biomarkers. Catecholamines play an important role in the organism and the general adaptation syndrome as neurotransmitters. Their concentration in various biological fluids is used as an indicator to determine a wide range of diseases. Due to their neurotransmitter functions in the brain, the concentration of catecholamines in body fluids can serve as a biochemical indicator for various mental

disorders and for their pharmacological treatment. In this direction, great progress has been made in establishing the etiopathology of different neurotransmitters (43-45).

In the serum from patients with psychosis, multiple dopaminergic function biomarkers have been evaluated (43). Studies have demonstrated a correlation between dopamine uptake by platelets and the delusional state of patients with psychosis (22,46,47).

The enzyme required for the synthesis of dopamine, tyrosine hydroxylase (TH), may be an important marker in psychotic disorders. One study concluded that the TH levels were abnormal in schizophrenia, whereas the levels of mRNA expression were not impacted, indicating that TH pathology may take place post-transcriptionally in this area (44). In addition, elevated levels of TH in lymphocytes of schizophrenia patients have been reported (45).

Homovanillic acid (HVA) is the main metabolite of dopamine; therefore, it may be a valuable biomarker for the diagnosis and prognosis of psychotic disorders. Elevated levels of HVA in plasma or CFS samples of patients with schizophrenia have been observed (48-50). Increased HVA levels in prodromal-phase patients may help the early diagnosis of schizophrenia (51).

In post-mortem human brains, as well as in the peripheral blood cells of schizophrenia patients, hypomethylation of the catechol-O-methyltransferase (COMT) gene promoter, leading to overexpression of COMT, was found (52,53).

The absorption of ^{18}F-DOPA in the striatum of both drug-naive and drug-free schizophrenia patients was found to be increased compared to healthy participants, as shown by most research (54). Regarding the D2 dopaminergic receptors in striatum, a study conducted by Abi-Dargham *et al* did not find any difference between healthy subjects and a schizophrenia group (55).

While functional magnetic resonance imaging (fMRI) studies have found alterations in prefrontal and striatal dopaminergic projection fields, neurochemical research has shown subcortical striatal dysregulation of dopaminergic neurotransmission in psychotic patients (56).

Levels of norepinephrine (NEP) were found to be lower in psychotic patients, while epinephrine levels were similar in schizophrenic patients and a control group (57). Elevated levels of norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) have been noted in the plasma of psychotic patients, but not in CSF (58).

The most commonly reported scientific proof of serotoninergic system implication in psychosis was a reduction in the density of the 5-HT transporter (5-HTT), an improvement in the 5-HTR1A number and a decrease in 5-HTR2 levels in the brain (59). Elevated platelet 5-HT concentrations were ascertained in psychotic manic patients, while the manic patients without psychotic features group had platelet 5-HT levels similar to the values in a healthy control group (60).

Neuroendocrine biomarkers. For determination of the implication of the HPA (hypothalamic/pituitary/adrenal) axis in psychosis, the most investigated paraclinical test that supports this theory is the dexamethasone suppression test. In one study, significant elevated plasma cortisol levels in psychotic patients were determined (61). Some studies suggest that prolonged dexamethasone non-suppression is correlated with a poor outcome of the disorder (62).

Regarding cortisol levels in psychotic patients, a meta-analysis of patients at first episode of psychosis covering 23 studies emphasized increased plasma cortisol concentrations in patients with psychotic symptoms, compared to healthy control groups (63).

One study concerning the testosterone levels from saliva in teenager patients with prodromal symptoms of psychosis found that the concentrations of testosterone are higher in healthy controls (64,65).

Electrochemical sensors for dopamine analysis. Electrochemical sensors are devices that transduce rapidly the information associated with the analyte/biomarker redox reaction that takes place at the electrode-solution interface into a measureable electrical signal, which can be easily exploited for the qualitative and quantitative analysis of the target compound (66). Due to their additional advantages such as the possibilities of miniaturization and of operating in both static and flow conditions, they are valuable candidates for the point-of-care (PoC) detection of various biologically important analytes. Due to the high importance of neurotransmitters and of the even increasing necessity of simple, sensitive and selective methods for their accurate and rapid quantification in biological samples and/or pharmaceuticals, the literature contains a tremendous number of reports (hundreds of articles only in 2020) related to the electrochemical detection of dopamine (DA) using various bare or modified sensors. There are also recent reviews that have focused on molecularly imprinted polymers (67) and metal-organic framework (68) modified electrodes for catecholamine neurotransmitters detection, sensors and biosensors for DA determination (69), whereas the most recent one presents a critical discussion on the state-of-the-art advanced analytical techniques applied for *in vivo* tonic DA assessment in humans, special attention being paid to electrochemical techniques (70). Therefore, we will briefly discuss only the electrodes and the corresponding methods developed for DA analysis reported in the first months of 2021.

Due to its high electrical conductivity and electrocatalytic properties, graphene, a two-dimensional carbon allotropic form, and its derivatives attracted even more interest and applicability as a sensing electrode material. Butler *et al* (71) demonstrated that commercially available graphene ink can be used for sensitive and selective DA detection after a thermal annealing process. Without the need of microfabrication processes, they developed a patterned three-electrode (with graphite ink electrode as the sensing part) all-solution processable platform on a flexible polyimide substrate which could be used in PoC testing.

One of the most sensitive DA electrochemical sensor is a carbon nanotube (CNT)-implanted polymer micropillar arrays electrode with the sensing part of CNTs exposed to the sample and the rest of it embedded in the sensor base, assuring the electrical conduction. DA quantification at this sensor presented two linear ranges $1x10^{-9}$-$6x10^{-8}$ mol x liter^{-1} and $6x10^{-8}$-$1x10^{-6}$ mol x liter^{-1} and a limit of detection of $7.7x10^{-10}$ mol x liter^{-1} DA (72).

Table I. Electrochemical sensors for DA quantification reported recently (in 2021) in the literature and their performance characteristics.

Sensor	Biomarker/ analyte	Linear range (mol x liter^{-1})	LoD (mol x liter^{-1})	Sample	(Refs.)
BDDE	DA	$5.0x10^{-7}$-$2.0x10^{-6}$	$6.0x10^{-8}$	*In vitro* measurements	(73)
Nb_2C/ZnS/CGE	DA	$9.0x10^{-5}$-$8.2x10^{-4}$	$1.4x10^{-6}$		(74)
ZIF/GCE	DA	$2.5x10^{-7}$-$5.9x10^{-4}$	$1.2x10^{-8}$	Injections, urine	(75)
NiO/$NiCo_2O_4$/GCE	DA	$1.0x10^{-7}$-$1.0x10^{-4}$	$4.0x10^{-8}$	Injections, urine, serum	(76)
$LaMnO_3$ NPs/GCE		$1.0x10^{-6}$-$6.0x10^{-4}$	$3.2x10^{-8}$	Urine, saliva	(77)
SiTi/AuNPs/CPE	DA	$2.0x10^{-5}$-$1.8x10^{-4}$	$3.2x10^{-7}$	Synthetic urine, saliva	(78)
	NEP		$1.9x10^{-7}$		
CPC/α-ZrP/GCE	DA	$1.3x10^{-5}$-$5.2x10^{-4}$	$3.3x10^{-6}$	Urine	(79)
	AA	$4.0x10^{-5}$-$1.5x10^{-3}$	$1.0x10^{-5}$		
GA/YVO/SPCE	DA	$9.0x10^{-9}$-$8.3x10^{-6}$	$1.5x10^{-9}$	Serum	(80)
G/GQDs/GCE	DA	$1.0x10^{-7}$-$1.0x10^{-4}$	$3.0x10^{-8}$		(81)
GO/WO_3/GCE	DA	$3x10^{-7}$-$1.245x10^{-3}$	$3.06x10^{-7}$	Urine, tap water	(82)
Ag@CQDs-rGO/GCE	DA	$1.0x10^{-7}$-$3.0x10^{-4}$	$1.59x10^{-9}$	Injections, bovine serum	(83)
G/SWCNT/Ce-Cu-Tween-20	DA	$1.0x10^{-7}$-$1.0x10^{-4}$	$7.2x10^{-9}$	Blood serum	(84)
	UA	$8.0x10^{-8}$-$1.0x10^{-4}$	$6.3x10^{-9}$		
	Glu	$1.0x10^{-6}$-$1.0x10^{-3}$	$9.5x10^{-8}$		
MWCNT-NH_2/AuNPs/GCE	DA	$7.0x10^{-7}$-$1.1x10^{-4}$	$2.1x10^{-7}$	Urine	(85)
	UA	$9.7x10^{-7}$-$2.0x10^{-4}$	$2.9x10^{-7}$		
PPy/TA/CTAB/SPCE	DA	$5.0x10^{-7}$-$1.0x10^{-4}$	$2.9x10^{-7}$		(86)
PANI/H/rGO	DA	$5.0x10^{-5}$-$3.5x10^{-4}$	$2.0x10^{-8}$		(87)
	UA	$1.0x10^{-4}$-$7.0x10^{-4}$	$7.0x10^{-8}$		
	AA	$1.0x10^{-4}$-$7.0x10^{-4}$	$5.0x10^{-8}$		
MWCNT/oxCAP/GCE	DA	$5x10^{-6}$-$1.15x10^{-4}$	$1.8x10^{-6}$	Injections	(88)
	UA	$5.0x10^{-6}$-$7.0x10^{-6}$	$1.56x10^{-6}$	Synthetic blood plasma	
	AA	$5.0x10^{-6}$-$7.5x10^{-5}$	$1.95x10^{-6}$	Synthetic urine	
	XA	$1.0x10^{-5}$-$9.5x10^{-5}$	$8.76x10^{-6}$		
	EP	$5x10^{-5}$-$1.15x10^{-3}$	$7.2x10^{-6}$	Injections	
POA@Ag/GCE	DA	$5.0x10^{-6}$-$4.5x10^{-5}$	$8.3x10^{-7}$		(89)
PET/GCE	DA	$1.0x10^{-7}$-$6.0x10^{-5}$	$7x10^{-9}$	Pharmaceuticals	(90)
	PA	$1.0x10^{-7}$-$1.8x10^{-4}$	$1.8x10^{-8}$		

GCE, glassy carbon electrode; BDDE, boron doped diamond electrode; Nb_2C/ZnS/CGE, niobium carbide-zinc sulfide nanocomposite modified GCE; ZIF/GCE, zeolite imidazolate framework modified GCE; NiO/$NiCo_2O_4$/GCE, nickel oxide-mixt nickel cobalt oxide nanocomposite modified GCE; $LaMnO_3$, perovskite nanoparticles modified GCE; SiTi/AuNPs/CPE, silica/titania material incorporating gold nanoparticles modified GCE; CPC/α-ZrP/GCE, cetylpyridinium chloride/α-zirconium phosphate nanocomposite modified GCE; GA/YVO/SPCE, graphene aerogel-yttrium vanadate nanocomposite modified screen printed carbon electrode; G/GQDs/GCE, graphene-graphene quantum dots modified GCE; GO/WO_3/GCE, graphene oxide-tungsten trioxide modified GCE; Ag@CQDs-rGO/GCE, polysaccharide-based carbon quantum dots-silver nanoparticles-graphene oxide modified GCE; G/SWCNT/Ce-Cu-Tween-20, graphene-single-walled carbon nanotubes-copper and cerium bimetallic nanoparticles modified GCE in the presence of the nonionic surfactant Tween-20; MWCNT-NH_2/AuNPs/GCE, aminofunctionalized multiwalled carbon nanotubes-gold nanoparticles modified GCE; PPy/TA/CTAB/SPCE, polypyrrole/tannin/cetyltrimethylammonium bromide/screen printed carbon electrode; PANI/H/rGO, polyaniline/hemin/reduced graphite oxide modified GCE; MWCNT/oxCAP/GCE, multiwalled carbon nanotubes-oxidized capsaicin modified GCE; POA@Ag/GCE, poly(o-aniside)-silver nanoparticles nanocomposite modified GCE; PET/GCE, polyethionine modified GCE; DA, dopamine; NEP, norepinephrine; AA, ascorbic acid; UA, uric acid; Glu, glucose; XA, xanthurenic acid; EP, epinephrine; PA, paracetamol; LoD, limit of detection.

The performance characteristics of other recently reported electrochemical sensors for DA detection are summarized in Table I (73-90).

Using a sensor array consisting of gold electrodes unmodified and modified with cross-reactive films, i.e., the biopolymer chitosan and chitosan-CNTs, and two chemometric approaches (artificial neural network and a partial least squares regression), Shukla *et al* (91) predicted DA levels in undiluted and untreated urine samples, eliminating the effects of the main interfering redox species, norepinephrine (NEP) and uric acid (UA). The disadvantage of the systems is related to the electrode surface contamination during the analysis.

Therefore, this system is designed for single use applications but recent studies emphasized the CNTs antifouling properties. This electrode's array could be miniaturized and integrated into a portable device, in order to be used for the *in situ* analysis of clinical samples, obtaining physiological information that may help to diagnose and monitor various diseases.

An enhanced enzyme-free CV detection of DA performed at a bare GCE, based on the intrinsic peroxidase-like activity of the Fe_3O_4@Au nanoparticles, exhibited a linear range from $1x10^{-5}$ to $1x10^{-3}$ mol x $liter^{-1}$ DA, with a LoD of 0.0109 mg x $liter^{-1}$. The feasibility of the developed method was successfully tested by DA assessment in pork samples (92).

Based on the above mentioned examples, electrochemical sensors proved to be useful tools for the rapid and selective monitoring of neurotransmitter levels in various biological samples, generating actual values that could support a better diagnose and even the treatment of certain psychotic disorders improving the quality of life of these patients.

5. General discussion

Dopamine is the most investigated system of neurotransmitters in psychotic disorders. There is heterogeneity of dopaminergic dysfunction that can be limited to only a subset of patients with schizophrenia. Dopamine works closely with 5-HT, glutamate and other systems; therefore, changes in one of the systems closely affect the balance of the other systems (93).

Among the dopaminergic hypotheses that are listed in the etiology of schizophrenia, studies have shown that an increase in activity in the mesolimbic dopaminergic pathway leads to positive psychotic symptoms while a decrease in dopaminergic transmission in the mesocortical pathway causes negative symptoms (94). The dopaminergic hypothesis is also strengthened by the mechanism of action of antipsychotics. Typical antipsychotics have a mechanism of action based on the antagonism of dopaminergic receptors and increased affinity for D2 receptors, while atypical antipsychotics are inhibitors of postsynaptic serotoninergic 5-HT2A receptors, most having a mild ability to antagonize dopamine D2 receptors (95).

Dopamine is involved in the stress response, leading to relapses in patients with schizophrenia (96). In addition, changes in 5-HT activity are involved in suicide and impulsive behavior of psychotic patients (97,98).

Biomarkers represent an important tool in medical practice. Their usefulness applies not only to the diagnosis, but also for dividing patients into risk groups and establishing treatment and prognosis. In the case of inflammatory biomarkers (IL-1B, IL-6, IL8 and α-1-antychymotripsin), studies have shown a marked inflammatory response in patients with schizophrenia (11,12). There is also a strong correlation between the values of TNF-α and the triggering of psychosis (17-19). Proteomics represents the study of proteins on a broad scale, including immunological proteins. The most frequently studied biological product, form a proteomic point of view, is CSF (22-24). Studies have shown that the most frequent biomarkers in CSF include FN1, GPX1, CHGA, IGSF8, MAP2, NFASC, HSP12A and PTPRZ1 (9,26-38).

6. Conclusions

Changes in the concentrations of the neurotransmitters involved in psychotic pathology may be present as alterations in the metabolites of major neurotransmitters implicated in their pathogenesis, such as the dopamine, serotonin and norepinephrine system. As a result, elevated HVA values have been observed in the prodromal phase of patients with schizophrenia, elevated serum MHPG levels in psychotic patients and decreased 5-HTT. Because of the significance of neurotransmitters in psychotic disorders and the growing need for quick, responsive, and selective methods for rapid quantification and higher accuracy in biological samples, the electrochemical identification of dopamine (DA) using various bare or modified sensors has been investigated.

Many findings in sensor design have been made in research laboratories, resulting in a wealth of knowledge on the development of sensitive electrochemical sensors, for selective (no interference from commonly co-existing redox species such as AA and UA) and precise DA quantification, but simple to operate and reusable or single-use yet cost-effective. Proper sensor characterization, which includes determining the analytical performances, and then correlating these with electrode material properties, is as critical as the constant use of new materials in sensor construction. Sensitive electrochemical sensors have been shown to be effective instruments for the rapid monitoring of dopamine and its metabolite levels in various biological samples, advantages that could help improving the diagnosis, prognosis and even the treatment of psychotic disorders.

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Authors' contributions

AMC contributed in all the stages of the article and gave the final approval of the version to be published. LG was involved in the writing, reviewing and editing of the manuscript. IGD, DEP and MB were responsible for analysis and interpretation of the literature data and contributed to drafting of the manuscript and revising it critically for important scientific content. AAC and LD were involved in revising the review critically for important intellectual content. All authors read and approved the final manuscript for publication.

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Competing interests

The authors declare that they have no competing interests.

Authors' information

Adela Magdalena Ciobanu: ORCID: ID 0000-0003-2520-5486.

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