ORIGINAL PAPER

Impairment of the cardiac ejection fraction by blocking dopamine D2 receptors induced by long-acting injectable antipsychotic treatment

Liana Dehelean[1], Ileana Marinescu[2], Puiu Olivian Stovicek[3], Ana Maria Romoşan[4], Radu Ştefan Romoşan[1], Rita Bálint[4], Bianca Oana Bucatoş[4], Andra Vera Livia Ciobanu[4], Mariana Bondrescu[4], Dragoş Marinescu[5], Marinela Minodora Manea[6], Valentina Oana Buda[7], Minodora Andor[8], Adela Magdalena Ciobanu[9]

[1]Discipline of Psychiatry, Department of Neurosciences, Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania; Center for Cognitive Research in Neuropsychiatric Pathology, Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania

[2]Discipline of Psychiatry, 5th Department, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

[3]Department of Pharmacology, Faculty of Nursing, Târgu Jiu Subsidiary, Titu Maiorescu University, Bucharest, Romania

[4]PhD Student, Discipline of Psychiatry, Department of Neurosciences, Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania

[5]Doctoral School, University of Medicine and Pharmacy of Craiova, Romania

[6]Discipline of Psychology, Department of Medical Education, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

[7]Discipline of Pharmacology and Clinical Pharmacology, 2nd Department, Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania; Research Center for Pharmaco-Toxicological Evaluation, Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania

[8]Discipline of Medical Semiology II, Department of Internal Medicine I, Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania; Multidisciplinary Center for Heart Research, Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania

[9]Discipline of Psychiatry, Department of Neurosciences, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Abstract

Introduction: Atypical antipsychotics have numerous benefits compared to conventional ones in respect to the possible adverse effects. However, like the other ones, they may induce direct cardiovascular alterations, probably through the apoptotic effect of dopamine receptor D2 (DRD2) blockade. The main objective of the study was to assess the cardiac ejection fraction (EF) using transthoracic speckle tracking echocardiography (TSTE) in patients treated with long-acting injectable (LAI) atypical antipsychotics. *Patients, Materials and Methods*: This cross-sectional study was conducted on 123 patients with schizophrenia or schizoaffective disorder divided in four samples according to their treatment: Aripiprazole, Olanzapine, Paliperidone and Risperidone. We analyzed socio-demographic data, the intensity of psychiatric symptoms, the duration of psychosis and of LAI treatment, and the cardiac EF measured with TSTE. *Results*: We found no statistically significant differences between the four antipsychotics regarding the values of the EF. Nevertheless, we observed a trend indicating that patients treated with an antipsychotic associated with a lower affinity for the DRD2, such as Olanzapine, have higher EF values than patients treated with antipsychotics with a stronger binding to the DRD2, such as Paliperidone and Risperidone. Patients receiving Aripiprazole, which has the strongest affinity for the DRD2 from all four antipsychotics but is also a partial DRD2 agonist, display higher EF values than those on Paliperidone and Risperidone. *Conclusions*: Antipsychotics with a lower affinity for the DRD2 or a partial agonism for it may be associated with higher EF. Cardiac monitoring should be performed periodically in patients on LAI antipsychotic therapy.

Keywords: antipsychotics, ejection fraction, dopamine, metabolic syndrome.

⬄ Introduction

Patients with schizophrenia are at increased risk to develop cardiovascular complications, mainly coronary heart disease [1, 2] because of multiple factors. First, the disorder itself may increase the risk for developing metabolic disturbances or diabetes mellitus as it appears from retrospective studies analyzing patients with psychosis before the development of antipsychotic medication [3]. Several other factors may contribute, such as a genetic risk for the metabolic syndrome [4, 5], diet, level of education or poverty [5]. The excessive smoking and metabolic disturbances are considered the main risk factors for coronary heart disease in patients with schizophrenia [6].

Antipsychotic medication further increases the risk

of developing cardiovascular disorders. Its influence on the cardiovascular system is mainly indirect, through the development of the metabolic syndrome, but direct effects, such as QTc prolongation associated arrhythmias or myocarditis are also described.

Literature data shows that both conventional and atypical antipsychotics may induce the metabolic syndrome in patients with schizophrenia [7, 8]. Apart from the type of the antipsychotic, the formulation is also of great importance as there are differences between oral administration of antipsychotics and the long-acting injectable (LAI) formulations. Subjects on LAI antipsychotics have lower and less fluctuating concentrations [9] and a better and controllable adherence to treatment. Nevertheless, the metabolic syndrome has been also identified in patients with schizophrenia receiving LAI antipsychotics [10, 11]. The mechanism through which antipsychotics induce disturbances in the glucose and lipid metabolism is related to their pharmacodynamic profile. Molecules blocking the hypothalamic histamine H1 and serotonin 5-hydroxytryptamine 2C ($5HT_{2C}$) receptors increase the alimentary appetite, while those blocking the muscarinic M3 receptors in the pancreatic Langerhans islets influence the secretion of insulin [12, 13]. Among atypical antipsychotics, Clozapine and Olanzapine are reported to induce weight gain, diabetes, and lipid metabolism disturbances. Quetiapine and Risperidone induce weight gain but is unclear if they also predispose to diabetes and lipid metabolism disturbances. Aripiprazole, Ziprasidone and Amisulpride may induce weight gain but there are no reports of inducing diabetes or lipid metabolism disturbances [14].

A direct effect of antipsychotics on the cardiovascular system is the arrhythmogenic effect, probably due to the blockade of the potassium channels. It may range from sinus tachycardia to the prolongation of the QTc interval or, in rare cases, sudden death. The prolongation of the QTc interval is rarely clinically meaningful but, in the presence of other risk factors, such as bradycardia, hypokalemia, hypomagnesemia, polypharmacy, or genetic predisposition, it may lead to ventricular arrhythmias, such as torsade de pointes [15–17]. Conventional antipsychotics, such as Pimozide and Thioridazine and atypical antipsychotics like Sertindole, Ziprasidone and Quetiapine have a significant risk to prolong the QTc interval [17–19], while Aripiprazole has the lowest risk. The electrocardiographic (ECG) anomalies in patients with schizophrenia are associated predominantly with the antipsychotic medication [20].

Other direct effects of antipsychotics on the cardiovascular system are the structural (hypertrophy, inflammation, necrosis, and fibrosis) and functional changes (left ventricle dysfunctions) at the level of myocardium. The impairment increases when using combinations of antipsychotics [21]. Myocarditis is more frequently associated with Clozapine [22] in a causal manner [23]. The symptoms of myocarditis may include sinus tachycardia, hypotension, chest pain, heart failure and body temperature over 37ºC. The laboratory findings show high levels of troponin I or troponin T and of C-reactive protein [24–26]. Nevertheless, it is a very rare side effect [27], and there are no differences

in cardiac autopsy anomalies and cardiovascular mortality between Clozapine and other antipsychotics [28, 29].

Magnetic resonance imaging studies conducted in patients with schizophrenia taking antipsychotics revealed lower ventricular end-diastolic and stroke volumes compared with healthy subjects [30]. Echocardiographic studies found that patients treated with Clozapine display a more severe, yet subclinical, left ventricular dysfunction compared with those receiving other antipsychotics [31]. Patients with schizophrenia and schizoaffective disorder treated with LAI antipsychotics, such as Olanzapine and Risperidone showed echocardiographic changes related to regional contractility abnormalities and diastolic dysfunction [32]. It appears that the effect of antipsychotics on the cardiac myocyte is a consequence of the dopamine receptor D2 (DRD2) blockade. Agonism on DRD2 protects against apoptosis [33], while antagonism upregulates autophagy by Rab9 guanosine triphosphatase (GTPase) [34]. Acknowledging the risk for cardiovascular diseases and cardiovascular-related death in patients with schizophrenia [35, 36] and other severe mental illnesses [37] receiving psychotropic medication, is of critical importance in guiding the pharmacological management of these patients and deciding which molecules present the best benefit-side effects ratio.

Aim

The main objective of the study was to assess the cardiac ejection fraction (EF) using transthoracic speckle tracking echocardiography (TSTE) in patients treated with LAI atypical antipsychotics: Aripiprazole, Olanzapine, Paliperidone and Risperidone. The secondary objectives of the study were to identify possible correlations between EF values, duration of the psychosis and the intensity of negative symptoms of schizophrenia measured with Brief Psychiatric Rating Scale – Expanded (BPRS-E). The obtained results can be integrated in a neurobiological model, which facilitates the clinical and therapeutic approach of patients with schizophrenia and heart disease.

⌘ Patients, Materials and Methods

The present multicenter cross-sectional study was performed on outpatients with schizophrenia and schizoaffective disorder. The subjects were diagnosed according to the International Classification of Diseases 10 (ICD-10) criteria. Exclusion criteria were: (*i*) patients with acute psychotic symptoms, (*ii*) patients with the duration of LAI treatment less than two months, (*iii*) patients on oral treatment with the same antipsychotics, (*iv*) patients already diagnosed with hypertension, abnormalities of glucose or lipid metabolism, cardiac disease, or ECG and echocardiographic changes.

The study subjects were divided in four samples, in accordance with the type of the antipsychotic treatment: Aripiprazole LAI, Olanzapine LAI, Paliperidone LAI and Risperidone LAI. The LAI formulation was chosen to assure a better adherence to antipsychotic treatment. The patients diagnosed with schizoaffective disorder received in addition oral mood stabilizers, such as Sodium Valproate, Carbamazepine or Lamotrigine.

We analyzed the following parameters: socio-demographic (age at study entry, age at disorder onset, sex) and clinical data (total duration of psychosis, duration of LAI treatment, severity of psychiatric symptoms, cardiac EF). The total duration of the psychosis is the interval measured in months between the onset of the psychosis and the present assessment. The duration of LAI treatment is the interval measured in months from the LAI treatment initiation until the present assessment. The severity of the psychiatric symptoms was assessed with BPRS-E. We chose the expanded version (24 items) of BPRS because it appears to assess better affective and schizophrenic symptoms than the previous (18 items) version [38–40]. The cardiac EF was measured by a cardiologist using TSTE because the three-dimensional strain analysis better detects subclinical changes in the cardiac muscle [41].

The IBM Statistics for Windows program, version 20, was used to analyze data. As the Shapiro–Wilk test for normality of distribution showed a non-Gaussian distribution of data, differences between groups were checked using non-parametrical tests (the Kruskal–Wallis test). Potential associations between symptoms, the duration of the disease and the cardiac EF were assessed using Spearman's correlation coefficients. For all statistical tests, the level of significance was considered 0.05 and all the results were two-tailed.

The study was approved by the Scientific Research Ethics Committee of Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania, and was conducted in accordance with the Helsinki Declaration. The patients who accepted to participate to the study sign a written informed consent. The authors of the study received no funding from any source.

⊟ Results

A number of 123 patients with schizophrenia (77.2%) and schizoaffective disorder (22.8%) divided in four groups according to the LAI antipsychotic treatment were enrolled in the study. The socio-demographic data and clinical characteristics were analyzed for each of the four treatment groups, as well as for the entire study group (Table 1).

Table 1 – *Socio-demographic and clinical characteristics of the four treatment groups*

Sample characteristics	Olanzapine		Paliperidone		Risperidone		Aripiprazole		Entire sample		Kruskal–Wallis test / χ^2 test*
	N	%	N	%	N	%	N	%	N	%	
	39	31.7	25	20.3	31	25.2	28	22.8	123	100	
Age [years]: mean, SD	39.66 (SD: 10.35)		40.16 (SD: 13.31)		43.77 (SD: 11.08)		44.32 (SD: 11.83)		41.94 (SD: 11.53)		0.24
Age at disorder onset [years]: mean, SD	28.84 (SD: 9.40)		27.83 (SD: 8.26)		29.74 (SD: 11.53)		33.14 (SD: 10.96)		28.86 (SD: 10.16)		0.22
Disease duration [months]: mean, SD	128.52 (SD: 115.22)		150.29 (SD: 129.94)		169.67 (SD: 134.40)		150.64 (SD: 154.35)		149.08 (SD: 132.71)		0.53
Gender											
Males	19	48.7	19	76	19	61.3	12	42.9	69	56.1	0.07
Females	20	51.2	6	24	12	38.7	16	57.1	54	43.9	
Diagnosis											
Schizophrenia	27	69.2	17	68	25	80.6	26	92.9	95	77.2	0.08
Schizoaffective disorder	12	30.8	8	32	6	19.4	2	7.1	28	22.8	
Mood stabilizers											
Associated	27	69.2	16	64	20	64.5	12	42.9	75	61	0.15
Not associated	12	30.8	9	36	11	35.5	16	57.1	48	39	
BPRS-E score: mean, SD	39.79 (SD: 11.37)		44.20 (SD: 14.22)		37.90 (SD: 11.39)		36.32 (SD: 12.98)		39.39 (SD: 12.54)		0.05
EF: mean, SD	56.42 (SD: 5.96)		55.09 (SD: 6.83)		54.73 (SD: 8.62)		55.53 (SD: 6.09)		55.53 (SD: 7.04)		0.82

BPRS-E: Brief Psychiatric Rating Scale – Expanded; EF: Ejection fraction; N: No. of patients; SD: Standard deviation. *Level of significance (p) between the four samples.

Males were predominant for the whole group (56.1%), but also for the treatment groups with Paliperidone (76%) and Risperidone (61.3%). Women were the majority in the Olanzapine (51.2%) and Aripiprazole (57.1%) groups. The mean age of all patients was 41.94 years, with standard deviation (SD) 11.53, and the mean age of onset of psychiatric pathology was 28.86 years, with SD: 10.16. Patients received different doses for one or three months of treatment, depending on the clinical condition and the prescribed antipsychotic. Depending on the dose, the average duration of treatment was between 9.35 months and 30 months (Table 2). Statistical analysis found no significant differences between the four samples concerning the age at study entry, age at disorder onset, sex, and associated treatment with mood stabilizers.

Regarding the EF, we found no statistically significant differences between the four LAI antipsychotics (p=0.82). In our study, Olanzapine, which has the lowest affinity for the DRD2, when blocking it, is associated with the highest value of the EF. Paliperidone and Risperidone with higher affinities for the DRD2 when blocking it, are associated with lower values of EF. Aripiprazole has the highest affinity for the DRD2, but it is also a partial agonist of this receptor, which may explain why it is associated with a higher value of EF. The increase of the DRD2 blockade causes a decreasing trend of the EF values (Figure 1).

For the entire sample, the mean duration of the psychosis was 149.08 months. Moreover, patients with a history of multiple recurrences due to treatment non-adherence have the highest indication for the LAI formulations. For this reason, we analyzed possible correlations between EF values, duration of the psychosis and the intensity of negative symptoms of schizophrenia measured by BPRS-E: self-neglect, blunted affect, emotional withdrawal, and uncooperativeness. No statistically significant correlations were found between the EF values, the BPRS-E cluster of negative symptoms of schizophrenia and the duration of the psychosis.

On the other hand, the TSTE evaluation performed in the patients from the studied group revealed changes that suggest the alteration of the inotropic function, predominantly at the level of the left ventricle, with obvious differences from the normal appearance. Following the results obtained, a staging of left ventricular contractility changes can be established in patients treated with LAI antipsychotics: no contractility changes (Figure 2), with significant local changes (Figure 3), or with global contractility disorders (Figure 4). These changes were subclinical, and no symptoms were present. Functional contractility disorders may be associated with structural vascular disorders, such as coronary artery disease (Figure 5), or myocardial muscles, such as dilated cardiomyopathy (Figure 6).

These results demonstrate a reduction in the longitudinal myocardial contractile function of the left ventricle myocardium following antipsychotic LAI therapy, representing subclinical sign of cardiotoxicity. Early identification of functional changes, which anticipates the occurrence of structural disorders, show the usefulness of TSTE, such as longitudinal ventricular strain and strain parameters in identifying patients at risk of developing cardiotoxicity under antipsychotic LAI treatment. The predominant damage of the left ventricle suggests a decrease in inotropic mechanisms, which may be implicitly correlated with decreased EF.

Table 2 – *LAI antipsychotic dosages and duration of LAI treatment*

LAI antipsychotic	Dosage	N	%	LAI treatment duration [months]
Olanzapine	One injection: 210 mg/month	2	1.6	21.00 (SD: 12.72)
	One injection: 300 mg/month	8	6.5	27.28 (SD: 28.18)
	One injection: 405 mg/month	8	6.5	13.50 (SD: 11.50)
	Two injections: 300 mg/month	20	16.3	9.35 (SD: 7.22)
Paliperidone	One injection: 100 mg/month	5	4.1	4.20 (SD: 1.09)
	One injection: 150 mg/month	19	15.4	9.84 (SD: 10.61)
	One injection: 525 mg/three months	1	0.8	10
Risperidone	Two injections: 37.5 mg/month	14	11.4	19.85 (SD: 19.58)
	Two injections: 50 mg/month	18	14.6	30.00 (SD: 21.20)
Aripiprazole	One injection: 400 mg/month	28	22.8	13.10 (SD: 11.69)

LAI: Long-acting injectable; *N*: No. of patients; SD: Standard deviation.
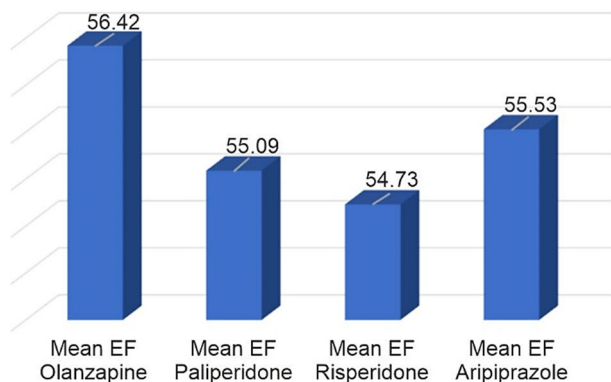
Figure 1 – *Mean EF for patients treated with Olanzapine, Paliperidone, Risperidone and Aripiprazole. EF: Ejection fraction.*
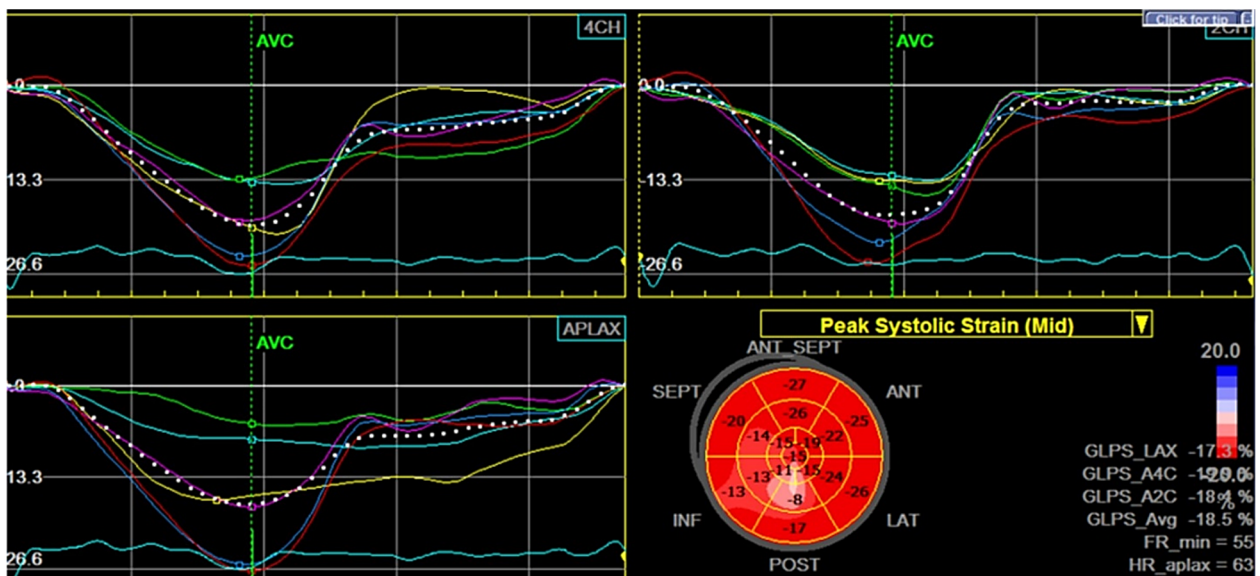
Figure 2 – *Speckle tracking imaging of the left ventricle longitudinal strain with no contractility changes. AVC: Aortic valve closure.*
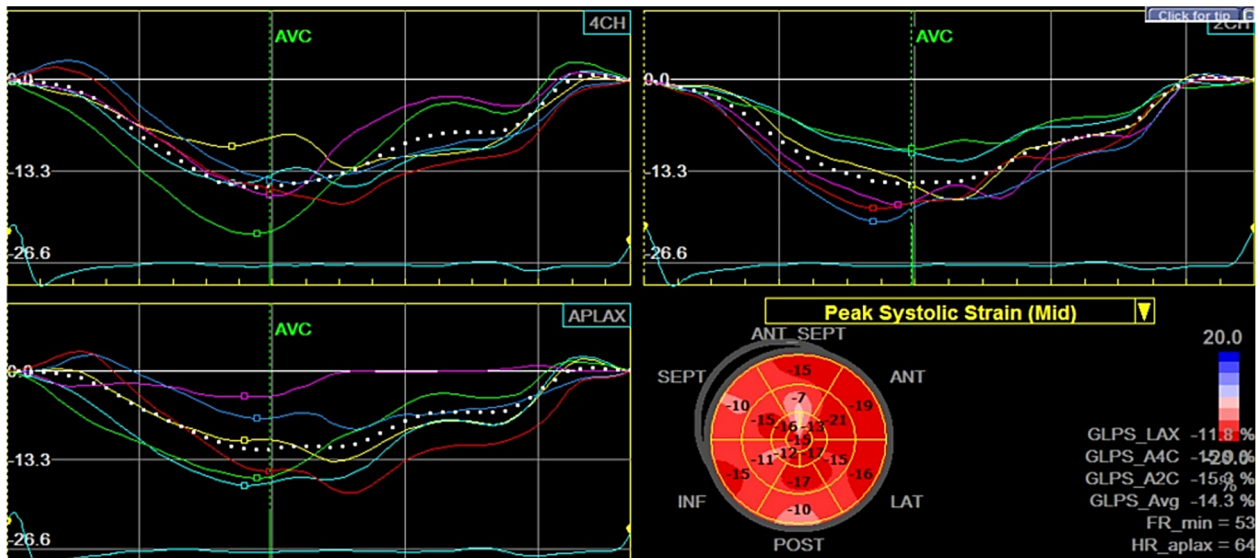
Figure 3 – *Speckle tracking imaging of the left ventricle longitudinal strain with local contractility changes. AVC: Aortic valve closure.*
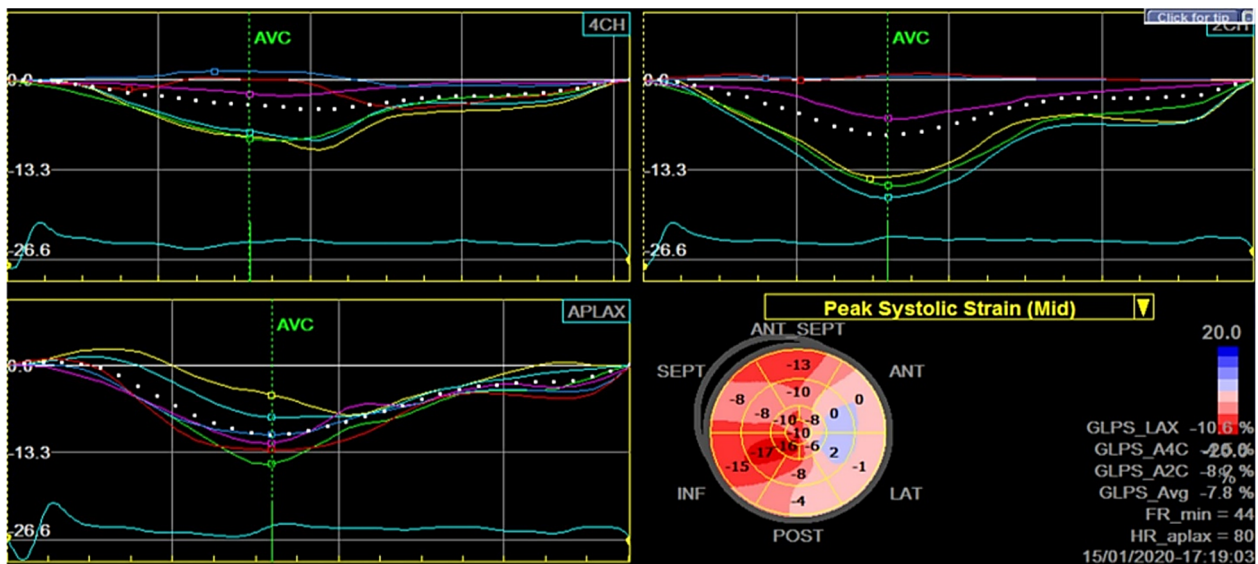

Figure 4 – *Speckle tracking imaging of the left ventricle longitudinal strain with global contractility changes. AVC: Aortic valve closure.*
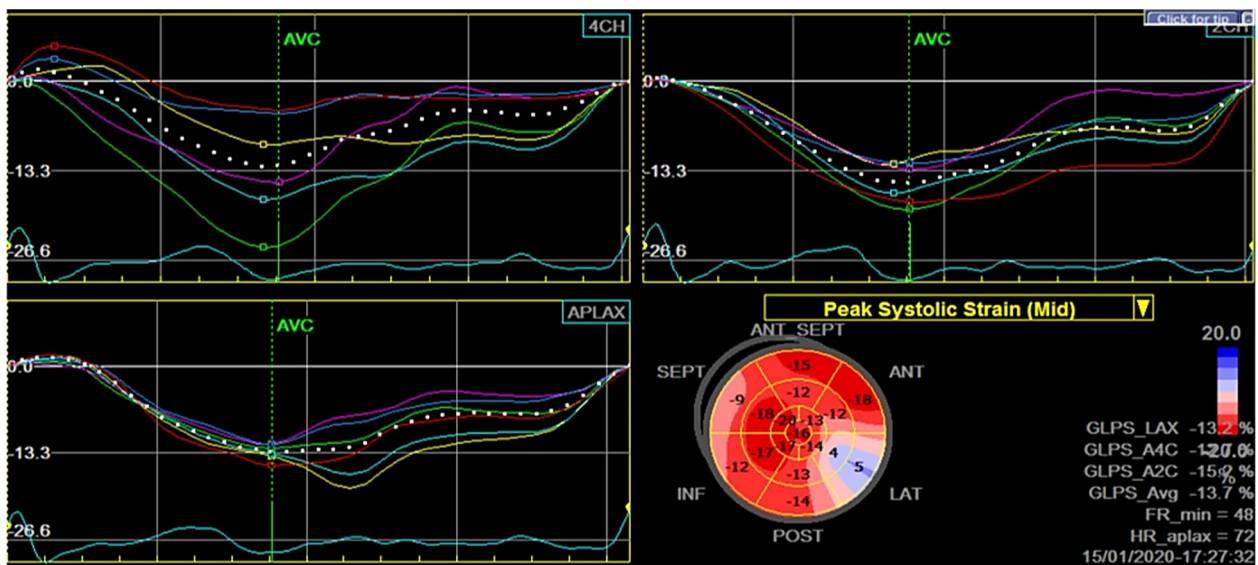

Figure 5 – *Speckle tracking imaging of the left ventricle longitudinal strain with local contractility changes and coronary artery disease. AVC: Aortic valve closure.*
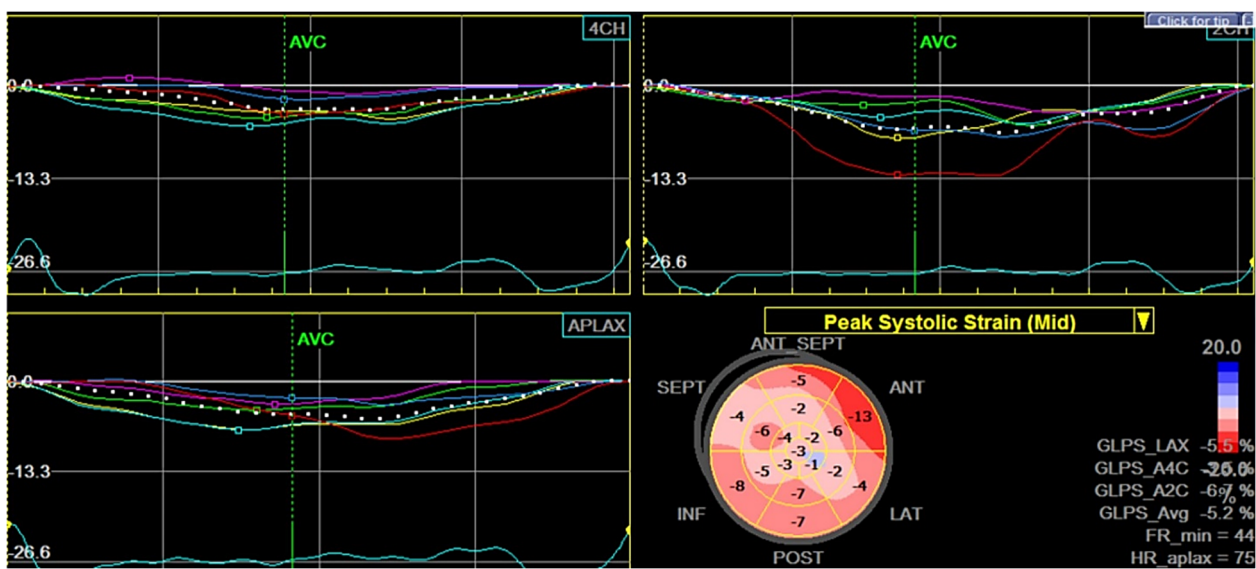
Figure 6 – *Speckle tracking imaging of the left ventricle longitudinal strain with global contractility changes and dilated cardiomyopathy. AVC: Aortic valve closure.*

⊡ Discussions

The four antipsychotics differ among themselves according to their pharmacodynamic properties. The affinity of a drug for a receptor is measured by the equilibrium dissociation constant, Ki, representing the concentration of the antipsychotic that blocks 50% of the receptors *in vitro*. The lower the Ki, the higher the affinity of the drug is for its receptors. Among the four studied antipsychotics, in respect to the DRD2 affinity, Olanzapine has the lowest affinity, followed by Paliperidone and Risperidone, while Aripiprazole has highest affinity [42, 43]. Patients having negative symptoms (deficit symptoms) of schizophrenia are prone to a sedentary lifestyle which may affect the cardiac performance. The longer the duration of psychosis, the higher is the risk of treatment resistance and the persistence of negative symptoms. Treatment resistance often is indicated by persistent positive symptoms (hallucinations, delusions), and cognitive deficits despite adequate treatment, or a lower increase of prolactin levels under antipsychotic medication [44].

Although counterintuitive because of its high potential of inducing the rapid appearance of the metabolic syndrome, Olanzapine seems to be more protective on the cardiac function than Paliperidone or Risperidone. Olanzapine induces the metabolic syndrome by blocking three classes of receptors with an important role in energy metabolism: the hypothalamic histamine H1 and the serotonin 5HT$_{2C}$ receptors that regulate the appetite for food, and the muscarinic M3 receptor on the pancreatic *β*-cells involved in the secretion of insulin and glucagon. Aripiprazole, although has a significantly higher affinity for the DRD2, is also a partial agonist for it. Moreover, his distinct receptor blocking profile makes him a lower candidate in inducing the iatrogenic metabolic syndrome in comparison with other new generation antipsychotics. In clinical settings, Aripiprazole showed a lower risk to induce metabolic syndrome compared with Olanzapine [45].

The development of biological psychiatry and psycho-pharmacology of schizophrenia is associated with the dopamine hypothesis involved in the pathogenesis of this disease. Most drugs with an antipsychotic effect act on dopamine receptors by reducing the excess dopamine involved in triggering positive symptoms. The main receptors that are blocked by this type of antipsychotics are dopamine D2-like receptor family (type D2, D3 and D4). In contrast, negative symptoms and cognitive impairment are ameliorated by the pharmacological action exerted on dopamine D1-like receptor family (type D1 and D5) [46]. Clinical psychopharmacology has benefited from the class of atypical antipsychotics to reduce the side effects induced by first generation antipsychotics (neuroleptics). In schizophrenia, therapeutic guidelines support the need to administer antipsychotics over a long period of time, even years. For the safety of administration and to facilitate compliance with treatment, LAI antipsychotics are administered, which can consistently improve the patient's quality of life and functional recovery [47]. From a pharmacological point of view, there are no significant differences between oral antipsychotics and LAI, regarding the receptor binding profile and the mechanism of action [48].

It has been considered that in the brain there is a majority population of dopamine receptors, which is why it was thought that the action of antipsychotics takes place mostly at cerebral level. Subsequently, the presence of dopamine receptors in the cardiac [49], pancreatic [50], renal or mesenteric levels was highlighted [51]. In this context, antipsychotics cause both psychotropic effects and somatotropic or metabolic symptoms. The dopamine transmission constant ensures the dispersion of dopamine in the cerebral or somatic territory, while maintaining functional, metabolic, and vascular homeostasis. Based on these premises, the interpretation of the results of this study can support differentiated pathogenic patterns in the clinical course of patients with schizophrenia.

Dopamine normally acts in the brain by maintaining a balance between D1 and D2 receptors. Thus, both the cerebral and the functional morphological aspect are preserved. The large number of dopamine receptors in the cerebral vessels influences the cerebral vascularization and the preservation of a normal cerebral blood flow (CBF). Stimulation of DRD2 at the heart level causes an

inotropic effect [52], which ensures efficient contraction of the myocardium, especially in the left ventricle. In this way, a normal EF is maintained which ensures a normal CBF, while maintaining the proper functioning of all brain structures (Figure 7).

Normal EF ensures the correct vascularization of the *locus coeruleus* (LC), dorsal raphe nucleus and the *nucleus basalis* of Meynert (NBM), but also of other cerebral areas, maintaining a normal functionality at the level of the autonomic nervous system. The dopamine system has very close links with the pancreas because dopamine receptors regulate the release of insulin from the pancreatic β-cells. Normal insulin levels help preserve the functionality of cardiac inotropism [53].

In the acute psychotic episode of schizophrenia, there is a massive release of dopamine in *substantia nigra* (SN) and ventral tegmental area (VTA), which causes a significant increase in CBF (Figure 8). By overstimulating DRD2, hyperdopaminergia appears in the frontal cortex, the temporoparietal cortex and the *nucleus accumbens*, which triggers the clinical picture of positive symptoms, characterized by hallucinations, delusional ideas, psychomotor agitation. The *nucleus accumbens* together with the thalamus thus become a gateway for the dopamine signal that maintains an excessive cortical level of dopamine, and by stimulating DRD1 increases the secretion of dopamine in the brain's lower-level structures, including the basal ganglia [54]. In the acute psychotic episodes, it was demonstrated by transcranial sonography, the increase of CBF and the velocity of blood flow from the posterior pole to the anterior pole, at the level of the Willis polygon, but also in other cerebral areas [55].

Hyperdopaminergia in VTA and SN connects LC, stimulating excessive noradrenaline (NA) release and acetylcholine (Ach) decrease. This mechanism triggers the dysautonomia state, defined as a disorder of the contractility of small cerebral, myocardial, and renal vessels, manifested by arterial spasm. In the absence of rebalancing the homeostasis of this system, the dysautonomia syndrome will be installed, with specific clinical manifestations. At the cardiac level, hyperdopaminergia is manifested by excessive increase in inotropic effect and EF, which implicitly increase CBF and LC vascularization. The consequence of long-term dopamine stimulation (long period of untreated psychotic episode) leads to left myocardial hypertrophy. Due to the dysautonomia state and the increased activity of NA, acute myocardial ischemia can be installed. At the pancreatic level, excess dopamine overstimulates pancreatic β-cells with increased insulin release that cause hypoglycemia. Hypoglycemia acts on the myocardium producing myocardial lesions, with ischemic changes on the ECG. In severe hypoglycemia, there is an acute metabolic imbalance, which can be favored by the appearance of stress by involuntary hospitalization of the patient with acute psychotic episode and psychomotor agitation. In this case appears serious risk of acute myocardial infarction. At the brain level, hypoglycemia causes neuronal apoptosis, oxidative stress, small vessel disease (SVD) and demyelinating axonopathy [56]. At the peripheral level, hypoglycemic axonopathy is manifested by painful neuropathy [57]. Hypoglycemia is another factor that destabilizes the autonomic nervous system, ensuring the transition to dysautonomia syndrome.

Dysautonomia syndrome is manifested mainly by orthostatic intolerance and a tendency to severe hypotension, accentuated by psychomotor agitation. Under these conditions, patients may suffer mild traumatic brain injury (mTBI) or severe trauma, following lipothymic conditions. mTBI favors disconnected axonal disorganization, with rapid and irreversible progression of cognitive impairment. This may explain the pseudo-dementia character of schizophrenia. When axonal dysconnectivity is associated with the apolipoprotein E4 (*APOE4*) genetic spectrum, β-amyloid (Aβ) proliferation may occur, predominantly in the hippocampus and frontal cortex. This biological model may support the neurodegenerative theory of schizophrenia with secondary cognitive dysfunction, favored by mTBI [58].
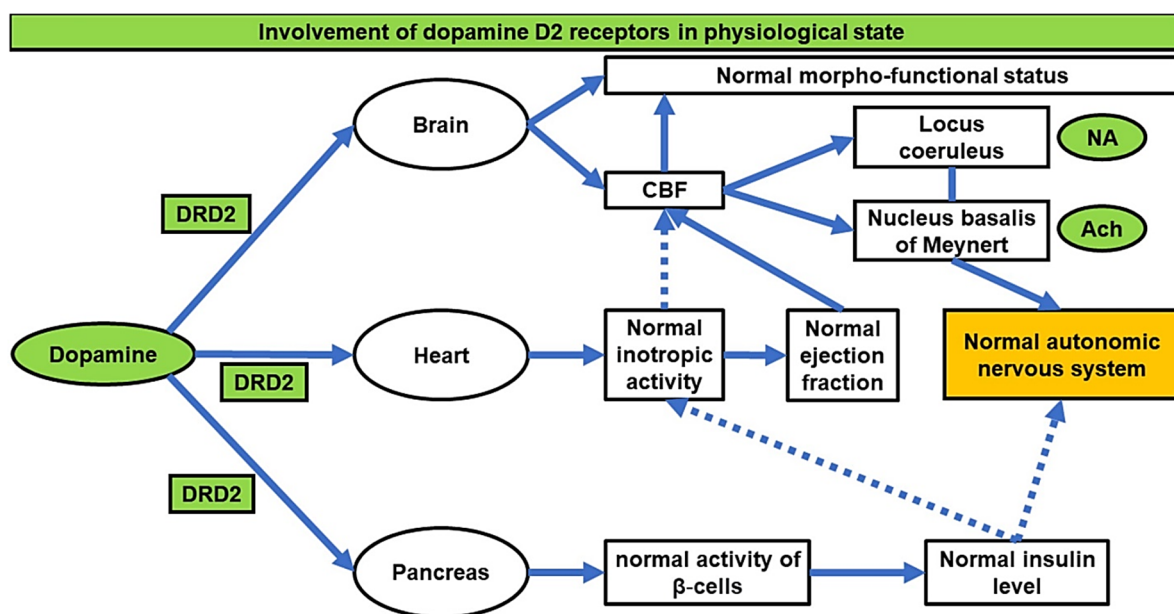
Figure 7 – Mechanisms of dopamine D2 receptor involvement in physiological state. Ach: Acetylcholine; CBF: Cerebral blood flow; DRD2: Dopamine receptor D2; NA: Noradrenaline.
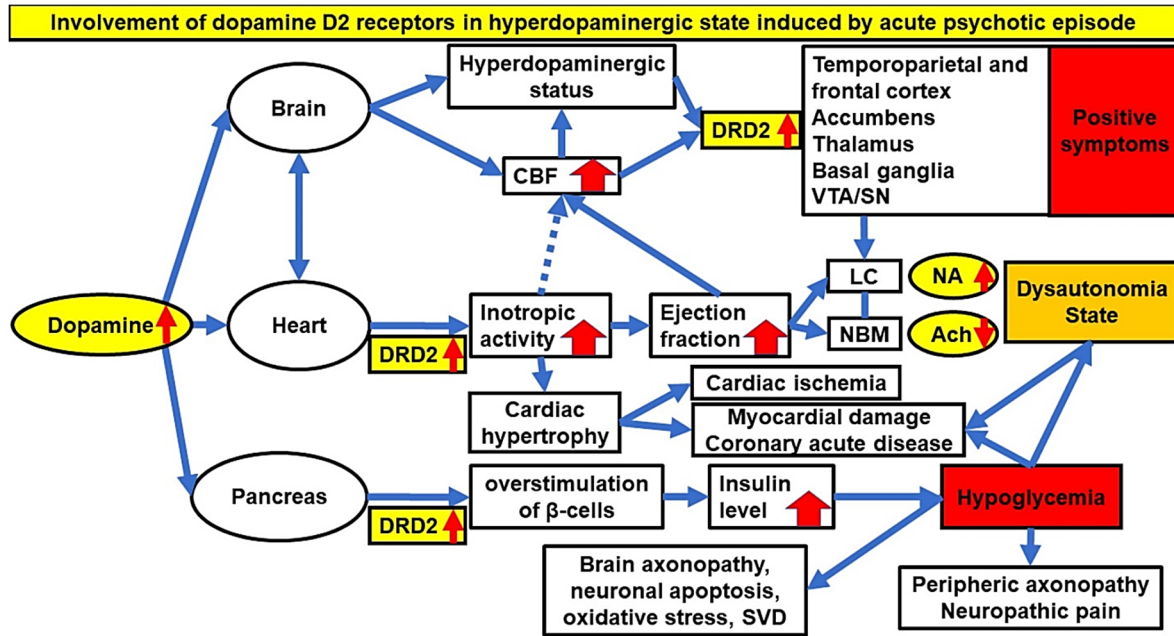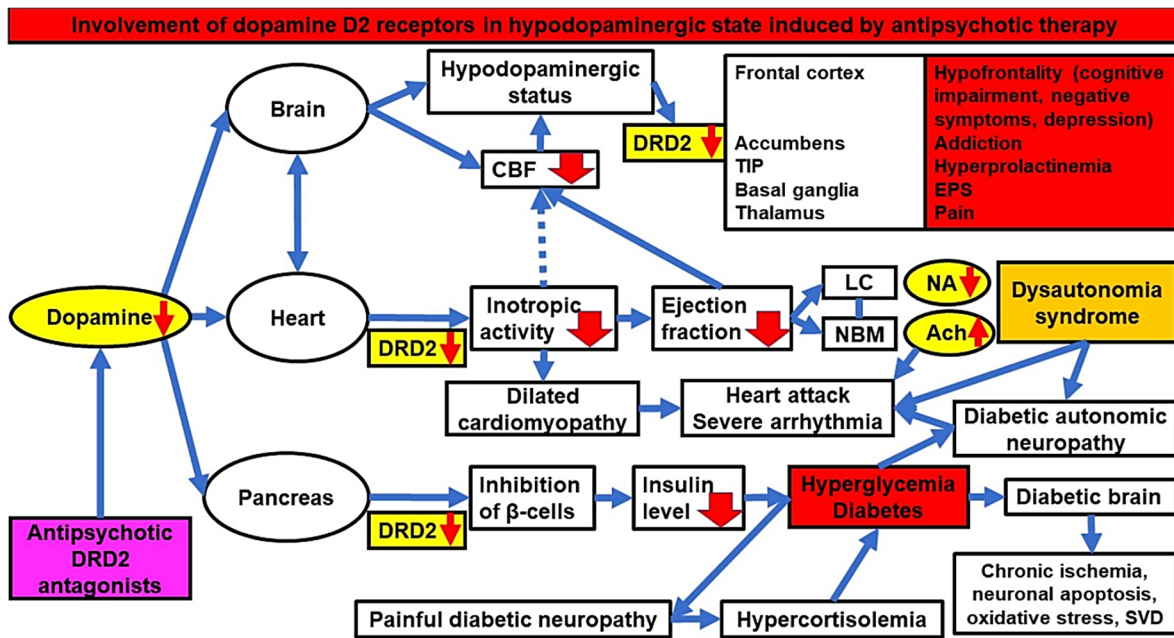
Figure 8 – *Mechanisms of dopamine D2 receptor involvement in hyperdopaminergic state induced by acute psychotic episode. Ach: Acetylcholine; CBF: Cerebral blood flow; DRD2: Dopamine receptor D2; LC: Locus coeruleus; NA: Noradrenaline; NBM: Nucleus basalis of Meynert; SN: Substantia nigra; SVD: Small vessel disease; VTA: Ventral tegmental area.*

In the conditions of the onset of the acute hyper-dopaminergic psychotic episode with positive symptoms, pharmacological treatment with antipsychotics is administered. Psychomotor agitation is common and is a real test of effort for cardiac activity. The cardiovascular risks associated with the symptoms of schizophrenia, but also the cardiotoxicity of some antipsychotics, require careful monitoring of these patients to avoid a negative prognosis and even the risk of mortality [59, 60]. In clinical psycho-pharmacology, the effectiveness of antipsychotics on delirium and hallucinations is associated with the ability to bind rapidly and effectively to DRD2. Thus, blocking cerebral DRD2 by antipsychotics therapy, determines the hypodopaminergic status with the obvious decrease of CBF (Figure 9).

Figure 9 – *Mechanisms of dopamine D2 receptor involvement in hypodopaminergic state induced by antipsychotic therapy. Ach: Acetylcholine; CBF: Cerebral blood flow; DRD2: Dopamine receptor D2; EPS: Extrapyramidal symptoms; LC: Locus coeruleus; NA: Noradrenaline; NBM: Nucleus basalis of Meynert; SVD: Small vessel disease; TIP: Tubero-infundibular pathway.*

Reduction of the efficiency of dopaminergic transmission in the frontal cortex is clinically manifested by hypofrontality syndrome [61], characterized by cognitive deficit, exacer-bation of negative symptoms and depressive symptoms. Hypodopaminergia in the *nucleus accumbens* causes a marked decrease in reward capacity that promotes addiction

and dual pathology. Decreased dopamine levels in the thalamus promote hyperalgesia syndrome.

Hypodopaminergia in the hypothalamic tuberoinfundibular pathway (TIP) causes an increase in prolactin and that in the basal ganglia triggers extrapyramidal symptoms (EPS). Hyperprolactinemia is an important marker that announces potential medium-term and long-term side effects of treatment with dopamine-blocking antipsychotics [62]. The main dysfunctions appear at the cardiovascular level, following endothelial dysfunction and increased oxidative stress, predominantly in the territory of the coronary blood vessels, with the risk of an acute coronary event. Hyperprolactinemia causes an alteration of cardiomyocytes that favor the development of dilated cardiomyopathy [63]. Excessive DRD2 blocking action in the infundibular area appears to be symmetrical with the ability to block DRD2 in pancreatic β-cell islands.

By involvement in the activity of pancreatic β-cells, elevated prolactin levels are associated with the risk of diabetes [62], pancreatic fibrosis and progression of pancreatic ductal adenocarcinoma [64, 65]. Pancreatic adenocarcinoma, in which DRD2 blockade may bring therapeutic benefits [66], may progress to its transformation into a neuroendocrine cancer [67]. In this case, dopaminergic agonists may play an important pharmacological role by lowering prolactin levels and reducing liver metastases [68]. Long-term hyperprolactinemia may be a risk factor for the onset of breast or prostate cancer [69], and for an unfavorable evolution of oncological disease [70]. The involvement of dopamine in cancer remains intensely debated, which on the one hand can promote the development of cancer and on the other hand can induce apoptosis of cancer cells, depending on the mechanisms involved in oncogenesis [71, 72].

The involvement of dopamine in the kidneys is complex and the dysfunction of the relative balance between DRD1 and DRD2, following the blocking action of DRD2 accompanied by hyperprolactinemia, announces an unfavorable progression of chronic kidney disease and increased mortality due to cardiovascular events [73].

At the cardiac level, DRD2 blockade decreases the inotropic effect and favors the installation of dilated cardiomyopathy with risk of myocardial infarction or severe rhythm disorders, and even sudden death. The significant decrease in EF decreases CBF and exacerbates cerebral hypodopaminergia. The data presented in this study show that Olanzapine has the best preservation of EF, the lowest value is in Paliperidone and Risperidone, and an intermediate value was observed in Aripiprazole therapy. The theoretical models presented by us claim that the active potential of EF decrease is based on two differentiated mechanisms of receptor binding: DRD2 antagonist capacity at the cardiac level associated with the potential to modulate adrenergic and cholinergic function and DRD2 partial agonist capacity. In the case of Olanzapine, EF was better preserved due to its simultaneous action on adrenergic (α1, α2) and muscarinic (M1, M5) receptors, which protect the heart from dysautonomia effects. Paliperidone and Risperidone block α1 and α2 receptors, but have no antimuscarinic effects, this receptor profile being associated with exacerbation of the predominantly parasympathetic dysautonomia syndrome and the risk of cardiac arrhythmias. Aripiprazole, through its partial agonist effect, greatly

increases the inotropic effect, but compensates other mechanisms that decrease EF.

The decrease of dopamine in LC by the decrease of CBF determines the onset of dysautonomia syndrome and orthostatic intolerance. DRD2 blockade and dopamine deprivation of the pancreas inhibit β-cell activity with dramatic decrease in insulin release [74]. This mechanism is a contributing factor to diabetes, dyslipidemia, and metabolic syndrome. Decreased insulin in the context of dysautonomia syndrome causes autonomic diabetic neuropathy with heart and gastrointestinal disorders. The consequence of diabetes is hyperglycemia which, in the long-term, causes the "diabetic brain" characterized by increased oxidative stress, SVD, chronic cerebral ischemia with altered neurovascular unit, neuronal apoptosis and glial destruction [75]. Vascular and metabolic changes induced by diabetes trigger cognitive disorders [76]. At the peripheral level, diabetes causes painful diabetic neuropathy, a real secondary stressor that causes activation of the hypothalamic–pituitary–adrenal (HPA) axis, with high levels of endogenous cortisol [77]. Thus, a vicious pathogenic circle is closed because hypercortisolemia causes, in turn, diabetes, dyslipidemia, metabolic syndrome, hypertension, coronary and cerebral atherosclerosis.

Pathogenic patterns based on elements of clinical psychopharmacology suggest the importance of personalizing antipsychotic treatment, depending on cerebral and cardiac vascular vulnerabilities, but also pancreatic ones, which may be influenced by DRD2. These receptors have genetic variability and an individual dispersion at the cerebral or somatic level, that can influence the binding capacity of each antipsychotic. Depending on the receptor affinity, side effects may occur, EPS and hyperprolactinemia being the main indicators of neurobiological and somatic vulnerabilities to treatment with a particular antipsychotic. One must consider the difference between the genetic map of the distribution of dopamine receptors and receptor profile of the antipsychotic. Without of this pharmacological personalization, the following may occur: side effects, significant cardiac, metabolic and dysautonomia risks, as well as negative evolutions of patients with schizophrenia.

The main limitation of our study is the relatively low number of subjects in the four samples. The strength of the study is that there are few studies that performed echocardiographic measurements in patients receiving antipsychotic medication, except for Clozapine. Our hypothesis can be confirmed or refuted by subsequent clinical and paraclinical studies, especially as dynamic cardiological investigations have made obvious progress, one of the roles of TSTE being presented in this study. This investigation can measure myocardial changes in the three dimensions, both in a specific area and globally [78], can become a marker for monitoring the evolution of schizophrenia, along with recognized biological and neuroimaging markers. The use of LAI therapies, by decreasing the recurrences of psychiatric disease, could reduce the cardiac, oncological, metabolic, and cognitive risks associated with the evolution of schizophrenia.

⊟ Conclusions

Antipsychotic therapy is frequently used in severe psychiatric disorders and schizophrenia. Patients treated

with antipsychotics with a lower affinity for the DRD2, such as Olanzapine or a partial agonist effect on the same receptor, such as Aripiprazole may present higher EF. The action of antipsychotics is correlated with the ability to block DRD2, and antipsychotic effects are accompanied by side effects triggered predominantly in the brain (EPS, hyperprolactinemia, SVD) or cardiovascular (deficiency of inotropic action predominantly in the left ventricle, EF reduction, decreased CBF). Atypical antipsychotics, through the multi-receptor pharmacological profile, can compensate for the EF decrease caused by DRD2 blockade.

Less known are the consequences of DRD2 blockade at the pancreatic level, which initially causes the onset of axonopathies due to cerebral and peripheral hypoglycemia, following a high level of insulin. Prolonged dopamine blockade promotes pancreatic fibrosis and the destruction of β-cells with the onset of diabetes. Hyperglycemia associated with endothelial dysfunction and oxidative stress may trigger acute coronary pathology. A major importance has dysautonomia and the installation of orthostatic intolerance, with a major risk of accidents. In the long-term, increased prolactin may be a risk marker for cardiovascular disorders and neoplastic pathology of the breast, prostate, pancreas. Medium and long-term cardiovascular risks, correlated with EF and impaired cognitive circuits, can be anticipated by monitoring with functional explorations, such as TSTE and by biological indicators, such as prolactin, proinflammatory factors, endothelial dysfunction, and oxidative stress. In our opinion, cardiac monitoring should be performed periodically in patients with antipsychotic LAI treatment.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding authors

Ileana Marinescu, Associate Professor, MD, PhD, Discipline of Psychiatry, 5th Department, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40251–522 458, e-mail: marinescu_psy@yahoo.com

Puiu Olivian Stovicek, Lecturer, MD, PhD, Department of Pharmacology, Faculty of Nursing, Târgu Jiu Subsidiary, Titu Maiorescu University, Bucharest, 100 Ecaterina Teodoroiu Avenue, Gorj County, Romania; Phone +40253–221 116, e-mail: puiuolivian@yahoo.com