ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Clinical and biological outcomes of prolonged treatment with haloperidol in schizophrenia

MIHAI MUTICĂ[1,2)], ILEANA MARINESCU[3)], FELICIA MILITARU[3)], MIHAIL-CRISTIAN PÎRLOG[4)], ION UDRIŞTOIU[3)]

[1)]*PhD Student, Department of Psychiatry, University of Medicine and Pharmacy of Craiova, Romania*
[2)]*Department of Psychiatry, "Elisabeta Doamna" Psychiatric Hospital, Galati, Romania*
[3)]*Department of Psychiatry, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*
[4)]*Department of Medical Sociology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

Paranoid schizophrenia with long-term course is a challenge for the clinical and therapeutic research, particularly because chronic course is difficult to identify due to the high rate of mortality in this category of patients. The therapeutic stability on an antipsychotic molecule (haloperidol) is indeed an exception, since the current trend in the case of unfavorable course is based on therapeutic versatility and polypharmacy. Haloperidol is the first-generation antipsychotic that is referred in the therapeutic guidelines as the "golden standard" regarding its efficacy on positive symptoms. The research in fundamental and molecular psychopharmacology has shown the aggressivity of this molecule on the secondary and tertiary signaling chains, including mitochondrial alterations. On male patients with paranoid schizophrenia (positive symptoms) and a chronic course of more than 35 years who received exclusively haloperidol, our study demonstrated an negative outcome with the loss of social functioning, persistence of positive symptoms, chronic extrapyramidal symptoms and mild cognitive impairment. The neuroimaging evaluations have shown atrophy in the temporal poles, posterior ventriculomegaly, cerebellar atrophy and calcification on choroid plexus and pineal gland. The difference between the histological changes induced by haloperidol on animal model and the ones on the patients in our study is located in the frontal cortex, thus suggesting the presence of two neurobiological models of schizophrenia in men: fronto–striatal and temporal–limbic–striatal. The persistence of extrapyramidal symptoms during the treatment with haloperidol may be considered as a clinical marker of the risk for negative outcome and a potential indication for the therapeutic switch.

Keywords: neurotoxicity, paranoid schizophrenia, male gender, chronic course, haloperidol.

Introduction

The introduction of haloperidol was a huge step forward for the biological treatment of schizophrenia, raising hopes for a significant improvement of the outcome. The clinical efficacy was proved by observational and randomized trials and showed a significant improvement of the positive symptoms, psychomotor agitation and inner tension that was correlated with high doses. However, the positive results were associated with severe side effects, especially extrapyramidal symptoms that led to the akathisia–dysphoria syndrome and finally to aggressive behavior [1]. Recent studies suggest the fact that high-dose regimens do not have more therapeutic benefit compared with moderate or low doses [2], while akathisia was correlated with the chronic course of schizophrenia and the relatively high number of antipsychotics used during this course. The prevalence is estimated at 18–24% and predicts the risk for tardive dyskinesia when oral-facial dyskinesia is present [3]. The extrapyramidal effects, akathisia and violent behaviors were correlated with the potent blocking capacity of D2 receptors in basal ganglia, thus reducing the adherence to treatment, increasing progressively the cognitive dysfunction and ultimately, stigmatizing the patient. In the clinical evaluation, haloperidol has limited benefits in treating the negative symptoms and may also increase the depressive symptoms (the post-psychotic depression due to dopamine deficit). The biological perspective of schizophrenia, based on the models of Timothy Crow [4] and Nancy Andreasen [5] suggests the limited efficacy of the haloperidol in schizophrenia by employing the dopaminergic model of the disorder.

In the present study, we assess the cerebral changes in patients diagnosed with chronic paranoid schizophrenia treated for over 30 years with haloperidol, in order to correlate neuroimaging with clinical evolution and histopathology studies on animal model.

Patients, Materials and Methods

We studied between January 1, 2012 and December 31, 2015 a group of seven male patients, with ages between 65 an 71 years, diagnosed with paranoid schizophrenia according to ICD-10 criteria, based on initial admissions and existent medical documents. All patients had a chronic and dysfunctional course of schizophrenia for at least 30 years. The present evaluation was undertaken in the "Elisabeta Doamna" Psychiatric Hospital, Galati, Romania. The presence of cognitive and behavioral alteration, associated with extrapyramidal symptoms and social dysfunction determined an active follow-up and support in the community services.

The assessment of therapeutic history showed that, for at least half of the course of disorder, the patient were treated with haloperidol and have had extrapyramidal symptoms treated with antiparkinsonian medication. No

evidence for the use of other antipsychotic substances during the course of illness was found. The severity of illness was assessed with the Clinical Global Impression – Severity of Illness Scale (CGI-S). The psychotic symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS). The cognitive evaluation employed the Mini Mental State Examination (MMSE); the severity of extrapyramidal symptoms was assessed with the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson–Angus Extrapyramidal Side Effects Scale (SAS). We considered useful to employ several assessment scales for the extrapyramidal syndrome based on the hypothesis of dopamine deficiency in basal ganglia, secondary to excessive and prolonged blockade of D2 receptors induced by haloperidol. This may increase the dysfunction and/or alteration of cortical–striatal circuits and could explain the persistence of psychotic features associated with extrapyramidal symptoms. The social functioning was evaluated with the Global Assessment of Functioning Scale (GAF) and Personal and Social Performances (PSP) respectively, in order to correlate the negative outcome with the social dysfunction, characterized by a significant decrease of communication and self-care abilities. For the correlation of clinical data with the cerebral biological changes, we performed computed tomography (CT) scans in all patients. The present study was approved by the Ethical Committee of the "Elisabeta Doamna" Psychiatric Hospital, Galati.

In the animal model were studied a group of five male adults Wistar rats each (200–250 g), held through the study in temperature, humidity, food and ambient stressless conditions, and haloperidol was administered intraperitoneal (equivalent of 3 mg), and a similar control group. After 14 days, the rats were sacrificed and sections of their frontal cortex and hippocampus were histopathologically processed: formalin (10%) and ethanol (96%) fixation, and paraffin embedding. Microtome slices were stained in Hematoxylin–Eosin (HE), Goldner–Szekely (GS) trichrome, Periodic acid–Schiff (PAS)–Hematoxylin, Toluidine blue, Methylene blue for Nissle corpuscles and argentic impregnation for neurofibrils. The obtained slices were studied with optical microscopy. The animal model study was approved by Ethical Committee of the University of Medicine and Pharmacy of Craiova, Romania.

Results

The demographic data of the study group showed that the age interval of the patients at the moment of inclusion was between 65 and 71 years, with an almost equal residential dispersion (four patients from rural areas and three from urban areas). Several difficulties were encountered in evaluating the level of education, when three of the patients did not provide valid proof of their educational degree. The marital status has shown the absence of a nuclear family, five out of seven patients being institutionalized at the time of evaluation (Table 1).

At the time of current assessment, we were surprised by the high intensity of positive symptoms, as shown on PANSS scores, correlated with extrapyramidal symptoms of different levels of intensity. These results may confirm the hypothesis of cortical–striatal dysconnectivity secondary to haloperidol treatment, which sustains the psychotic symptoms, but also the cognitive dysfunction, as shown on the MMSE scores that varied between 22 and 28 points.

Table 1 – ***Current demographic data of the patients in the study group***

Age [years]	Residence*	Education	Marital status	Current social status**
65	Rural	Vocational school	Widowed	Community
67	Urban	Not specified	Never married	Institutionalized
71	Rural	Undergraduate	Never married	Institutionalized
66	Urban	High school	Divorced	Institutionalized
65	Rural	Not specified	Never married	Institutionalized
66	Urban	Vocational school	Divorced	Community
72	Rural	Not specified	Never married	Institutionalized

*Residence at the onset of the disease. **Community: Family and community psychiatric care; Institutionalized: Chronic hospitalization or centre for permanent care.

We found a significant correlation between the PANSS, CGI-S and GAFS scores. The results obtained on the PSP scale that assesses the last 30 days before the evaluation on four domains (self-care, social activities, social and personal relations, disturbed and aggressive behavior) showed that the patients in our group had the insight of illness and its potential for disability. They have also recognized the incapacity for optimal social functioning, as well as the illness-related limits on the level of social integration. The scores of PSP scale varied between 21 and 40 points indicating the category of severe social and personal inabilities (Table 2).

Table 2 – ***Scores of the rating scales for the patients in the study group***

PANSS	AIMS	BARS	SAS	MMSE	CGI-S	GAF	PSP
84	5	1	6	24	4	59	34
107	1	2	3	28	5	21	22
103	3	0	2	28	4	23	23
105	2	1	4	26	4	25	24
110	2	0	3	24	4	27	29
117	3	1	3	22	5	24	23
109	3	0	2	25	6	16	21

PANSS: Positive and Negative Syndrome Scale; AIMS: Abnormal Involuntary Movement Scale; BARS: Barnes Akathisia Rating Scale; SAS: Simpson–Angus Extrapyramidal Side Effects Scale; MMSE: Mini Mental State Examination; CGI-S: Clinical Global Impression – Severity of Illness Scale; GAF: Global Assessment of Functioning Scale; PSP: Personal and Social Performances.

The results obtained in the assessment scales related to the cognitive dysfunction and extrapyramidal symptoms were confirms by the CT examination that revealed several alterations including atrophy in the temporal poles (correlated with secondary firing of dopamine and glutamate mechanisms that trigger positive symptoms), predominant posterior ventriculomegaly with cerebellar atrophy of different intensities (supporting the involvement of this structures in the cognitive alteration and persistent extrapyramidal symptoms) and calcification of choroid plexus and pineal gland (Figure 1).

On the animal model, the rats treated with haloperidol have shown significant alterations in frontal cortex (neuronal

loss, pinocytosis and neuronal depopulation in III, IV and VI layers) and hippocampal areas (neuronal loss), changes induced by acute administration of haloperidol in high doses (Figure 2).

Discussion

In the theoretical neurobiological and psychopharmacological model of chronic evolution of paranoid schizophrenia are distinguished at least two patterns, which can be correlated with clinical patterns proposed by Crow [4]:

- Type I is associated with presynaptic dopamine hyperactivity and increase of postsynaptic D2 receptors;
- Type II is characterized by presynaptic dopamine hypoactivity and reduced number of postsynaptic D2 receptors (Figure 3).

The bimodal dopamine model in schizophrenia may explain the limited efficacy of haloperidol in treating the negative, depressive and cognitive symptoms and could also explain the persistence of extrapyramidal symptoms, the increased risk for cognitive dysfunction, the violent behavior, the social dysfunction and the therapeutic resistance (Figure 4).

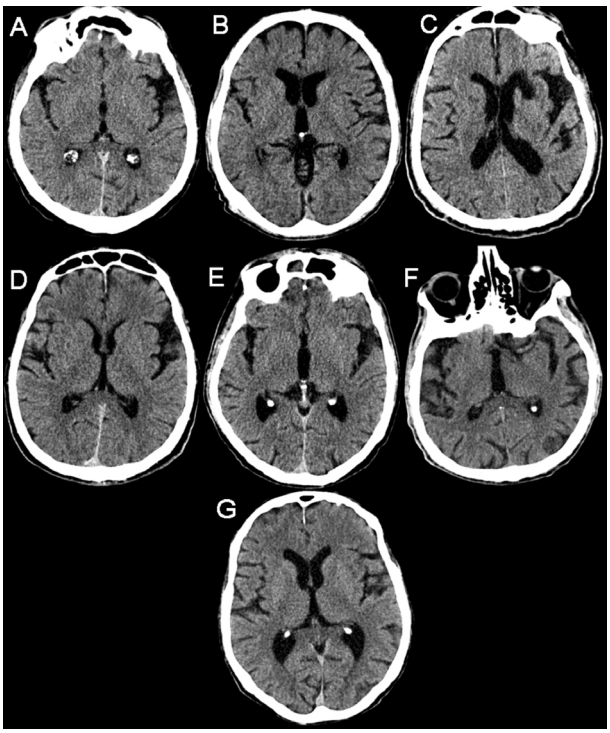

Figure 1 – *CT scans showing structural alterations in several areas in the brain of haloperidol-treated patients: (A) Left temporal lobe atrophy, posterior ventriculomegaly, pineal gland and choroid plexus calcifications; (B) Posterior ventriculomegaly, bilateral temporal lobes and cerebellum atrophy; (C) Severe ventriculomegaly and left temporal lobe atrophy; (D) Left temporal lobe atrophy, ventriculomegaly, cerebellum atrophy; (E) Left temporal lobe atrophy, posterior ventriculomegaly, cerebellum atrophy, pineal gland and choroid plexus calcifications; (F) Massive right temporal lobe atrophy, cerebellum and left posterior lobe atrophy, choroid plexus calcifications; (G) Bilateral temporal lobes atrophy, posterior ventriculomegaly, cerebellum atrophy, choroid plexus calcifications, minimal frontal atrophy.*

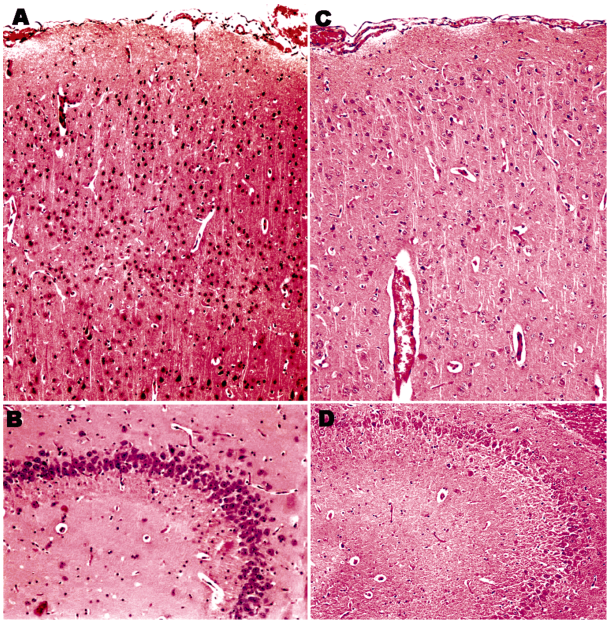

Figure 2 – *Structural alterations in rats receiving haloperidol compared to controls: (A) Control frontal cortex; (B) Control hippocampus; (C) Frontal cortex after 14 days of intraperitoneal administration of haloperidol (equivalent of 3 mg) neuronal loss, pinocytosis and neuronal depopulation in III, IV and VI layers; (D) Hippocampus after 14 days of intraperitoneal administration of haloperidol (equivalent of 3 mg) neuronal loss and necrosis, vacuolization. HE staining: (A and B) ×100; (C and D) ×200.*

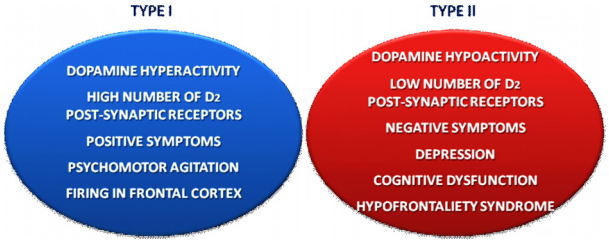

Figure 3 – *Proposal for a dopaminic biological model of schizophrenia.*

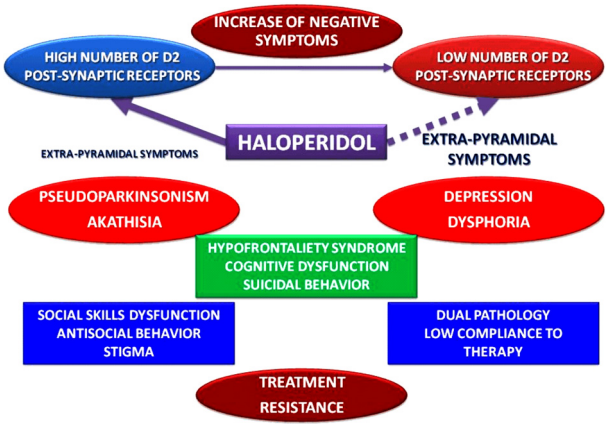

Figure 4 – *Negative outcome of the treatment with haloperidol in the frames of bimodal dopamine dysfunction.*

Our study shows that male patients with a chronic course of paranoid schizophrenia and long-term treatment with haloperidol, experience extrapyramidal symptoms of various intensity, which underlines the dysconnectivity

of cortical–striatal circuits that may predominantly reduce the cognitive abilities. The neuroprotection of the frontal cortex seems to be superior to our previous study on rats and literature reports, but we cannot support this hypothesis due to a limited number of patients in our study. The lesional alterations induced by the treatment with haloperidol in the patients of our study suggest the dysconnectivity of the striatal–limbic circuits with the alterations of the temporal lobe. This fact may explain the prominent positive symptomatology and psychotic behavior, according to the PANSS scores correlated with the CGI-S results.

The excessive striatal blockade induced by haloperidol could trigger excitotoxic activations of glutamate in the connections with the limbic system and temporal lobe, generating glutamate hyperactivity with apoptotic mechanisms and significant atrophy in the temporal areas. The lesions of the white matter, particularly the periventricular ones may explain the posterior ventriculomegaly and are associated with cerebellar atrophy. These alterations may partially explain the motor alterations and the cognitive dysfunction, as cerebellum is demonstrated to have a significant role in both motor activity and integration of cognitive functioning.

Behavioral disruption and social disabilities are characteristic for the patients with schizophrenia, thus the direct correlation of low scores on scales assessing the social functioning with the high levels of cerebral structural abnormalities reflects both the defects induced by the chronic course of disorder and the negative effects of psychopharmacological therapy with vulnerability potential. Moreover, the influence of the marital status on the course of disorder and particularly on the social functioning of the patient with schizophrenia is unanimously recognized. Many studies identified solitude related to marital status (celibacy, divorce, widowhood) as an aggravating risk factor. This status was frequent in our study group and has been related with multiple hospitalizations [6], suicidal behavior [7], comorbid depressive episodes [8], aggressive behavior [9] and social disabilities [10].

The small number of patients in our study group may be explained by the low survival rate of the patients with chronic and severe psychiatric disorder (paranoid schizophrenia) and the low number of cases maintained on haloperidol nowadays in order to meet the inclusion criteria.

The limited efficacy of haloperidol in the treatment of schizophrenia is also sustained by epidemiological arguments (high rate of relapses, high number of incomplete remissions with cognitive, behavioral and functional alterations), as well by fundamental research that has shown that the molecular mechanisms of neurotoxicity for haloperidol are apoptosis, necrosis, decreased cell viability, inhibition of cell growth, increased caspase activity (the "death spiral"), impaired glutamate transport and mitochondrial damage [11, 12]. The information related to these molecular mechanisms of haloperidol neurotoxicity is clinically associated with cognitive dysfunction, supported by imaging data (frontal and cerebellar atrophy and ventriculomegaly). The excessive blockade of D2 receptors induced by haloperidol may also influence the cerebral small vessels, inducing the small vessel disease that favors the cognitive decline with aging [13]. This may be a surrogate marker for the negative outcome in schizophrenia that was chronically treated with haloperidol and shows signs of extrapyramidal symptoms correlated with the cognition, mood and daily functioning [14].

The studies on animal model (rats) [15] have shown significant structural alterations in frontal cortex and hippocampus of the rats that were administered haloperidol compared to controls.

In contrast with neuroimaging results in our sample of schizophrenic patients, in which cerebral atrophies were dominant in temporal cortex, phenomena explained through persistence of haloperidol in human brain tissues especially in temporal cortex [16], emphasized by long-term administration (over 30 years).

Conclusions

Male patients with chronic paranoid schizophrenia and exclusive, long-term treatment with haloperidol, show after at least 35 years of chronic course of illness, persistent positive symptoms and severe behavior disruption, both affecting their capacity of social integration. Haloperidol is a potent antipsychotic on positive symptoms, but demonstrates the lack of specific efficacy due to the alteration of cortical–striatal and striatal–limbic circuits. We may discuss a difference between the histological alterations induced by haloperidol in rats and the neurostructural changes shown on CT scans of the frontal cortex of the patients in our study. Male patients with paranoid schizophrenia that had long-term treatment with haloperidol have structural alterations, particularly in the temporal lobes. Based on these results, we suggest the possibility of two distinct neurobiological models in the case of chronic, long-term course, paranoid schizophrenia in men. The first is the frontal–striatal model, where negative symptoms are prominent and may or may not associate anhedonia. The second is the temporal–limbic–striatal model with the dominance of positive, psychotic symptomatology. The extrapyramidal symptoms may be a common point for both models, while the cerebellar atrophy remains unclear and further studies are needed in that matter. The persistence of extrapyramidal symptoms throughout the treatment with haloperidol may be considered a clinical marker for the negative outcome and a potential indication for the therapeutic switch.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Schulte JR. Homicide and suicide associated with akathisia and haloperidol. Am J Forensic Psychiatry, 1985, 6(2):3–7.
[2] Oosthuizen P, Emsley R, Jadri Turner H, Keyter N. A randomized, controlled comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. Int J Neuropsychopharmacol, 2004, 7(2): 125–131.
[3] Halstead SM, Barnes TR, Speller JC. Akathisia: prevalence and associated dysphoria in an in-patient population with chronic schizophrenia. Br J Psychiatry, 1994, 164(2):177–183.
[4] Crow TJ. The two-syndrome concept: origins and current status. Schizophr Bull, 1985, 11(3):471–486.
[5] Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in

cortical–subcortical–cerebellar circuitry? Schizophr Bull, 1998, 24(2):203–218.
[6] Sanguineti VR, Samuel SE, Schwartz SL, Robeson MR. Retrospective study of 2,200 involuntary psychiatric admissions and readmissions. Am J Psychiatry, 1996, 153(3):392–396.
[7] Harkavy-Friedman JM, Restifo K, Malaspina D, Kaufmann CA, Amador XF, Yale SA, Gorman JM. Suicidal behavior in schizophrenia: characteristics of individuals who had and had not attempted suicide. Am J Psychiatry, 1999, 156(8):1276–1278.
[8] Thara R, Srinivasan TN. Outcome of marriage in schizophrenia. Soc Psychiatry Psychiatr Epidemiol, 1997, 32(7):416–420.
[9] Fresán A, de la Fuente-Sandoval C, Juárez F, Loyzaga C, Meyenberg N, García-Anaya M, Nicolini H, Apiquian R. Características sociodemográficas asociadas a la conducta violenta en la esquizofrenia. Actas Esp Psiquiatr, 2005, 33(3): 188–193.
[10] Ganev K. Long-term trends of symptoms and disability in schizophrenia and related disorders. Soc Psychiatry Psychiatr Epidemiol, 2000, 35(9):389–395.
[11] Nasrallah HA. Haloperidol clearly is neurotoxic. Should it be banned? Why use an old and harmful antipsychotic when safer alternatives are available? Curr Psychiatry, 2013, 12(7):7–8.
[12] Nasrallah HA, Rush SJ. A189: First generation antipsychotics are neurotoxic and impair neuroplasticity *via* multiple mechanisms. Society of Biological Psychiatry, 68th Annual Scientific Convention and Meeting, May 16–18, 2013, San Francisco, USA, Biol Psychiatry, 2013, 73(9 Suppl):61S.
[13] van Norden AG, de Laat KF, Gons RA, van Uden IW, van Dijk EJ, van Oudheusden LJ, Esselink RA, Bloem BR, van Engelen BG, Zwarts MJ, Tendolkar I, Olde-Rikkert MG, van der Vlugt MJ, Zwiers MP, Norris DG, de Leeuw FE. Causes and consequences of cerebral small vessel disease. The RUN DMC study: a prospective cohort study. Study rationale and protocol. BMC Neurol, 2011, 11:29.
[14] Baker JG, Williams AJ, Ionita CC, Lee-Kwen P, Ching M, Miletich RS. Cerebral small vessel disease: cognition, mood, daily functioning, and imaging findings from a small pilot sample. Dement Geriatr Cogn Dis Extra, 2012, 2:169–179.
[15] Marinescu D, Mogoanta L, Udristoiu T. P03–353: Neuroprotective effect of haloperidol *vs.* aripiprazole at hippocampal and frontal cortex at rats. 18th European Congress of Psychiatry, February 27–March 2, 2010, Munich, Germany, Eur Psychiatry, 2010, 25(Suppl 1):968.
[16] Kornhuber J, Schultz A, Wiltfang J, Meineke I, Gleiter CH, Zöchling R, Boissl KW, Leblhuber F, Riederer P. Persistence of haloperidol in human brain tissue. Am J Psychiatry, 1999, 156(6):885–890.

Corresponding author
Felicia Militaru, Teaching Assistant, MD, Department of Psychiatry, 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: feliciobanu@yahoo.com

Received: November 27, 2015

Accepted: July 28, 2016