Professional paper
Stručni članak

ISSN 1848-817X
Coden: MEJAD6 48 (2018) 4

Clonazepam augmentation during treatment with antipsychotics in aggressive inpatients – pilot study

Clonazepam kao pojačavajuća terapija antipsihoticima tijekom bolničkog liječenja agresivnih psihijatrijskih bolesnika – pilot studija

Ninoslav Mimica, Suzana Uzun, Gordan Makarić, Oliver Kozumplik, Tajana Ljubin Golub, Petra Folnegović Grošić*

Summary

Introduction: The interest in studies related to aggressive behaviour in psychiatric patients has increased over time. Various factors are considered as determinants of aggression, such as social, environmental and situational determinants, hormones, drugs and other substances, neurotransmitters and genetic determinants.

Methods: Clonazepam was initially administered at a daily dose of 2 mg to all patients in the study. If satisfactory clinical improvement was not observed in 2 days, it was allowed to increase the dose up to a daily dose of 6 mg. Aggression was twice evaluated by the Social Dysfunction and Aggression Scale (SDAS): the first time at the moment of inclusion to the study, and second time 3 days after the administration of clonazepam.

Results: The results of our research show the efficiency of clonazepam as a serenic drug in combination with antipsychotic drug in the treatment of aggressive patients. It is particularly encouraging that no adverse effects of clonazepam were observed in this study.

Conclusion: Further relevant trials are needed to evaluate the use of clonazepam in treatment of long-term/persistent aggression in people living with psychosis.

Key words: aggression, antipsychotic, clonazepam, patient, psychosis

Sažetak

Uvod: Interes za istraživanja vezana uz agresivno ponašanje u psihijatrijskih bolesnika je u porastu. Pri tome se u obzir uzimaju različiti čimbenici, kao što su socijalni, okolinski i situacijski, te hormoni, lijekovi i druge tvari, neurotransmiteri i genetičke odrednice.

Metode: Svim bolesnicima u ovom istraživanju započeta je terapija klonazepamom u dozi od 2 mg. Ukoliko zadovoljavajući učinak nije postignut unutar dva dana dopušteno je povišenje doze do 6 mg dnevno. Agresivnost je dva puta procjenjivana sa Social Dysfunction and Aggression Scale (SDAS) – prvi puta kod uključenja u studiju i potom trećega dana nakon početka terapije klonazepamom.

Rezultati: Rezultati ovoga istraživanja pokazali su učinkovitost klonazepama kao serenika u kombinaciji s antipsihotikom za liječenje agresivnih bolesnika. Ohrabrujuće je što nisu zabilježene nuspojave tijekom liječenja.

Zaključak: Potrebna su daljnja istraživanja u cilju procjene učinkovitosti klonazepama u liječenju agresivnosti bolesnika koji se liječe zbog psihotičnih poremećaja.

Ključne riječi: agresija, antipsihotik, bolesnik, klonazepam, psihotični poremećaj

Med Jad 2018;48(4):217-223

* **University psychiatric hospital Vrapče, Zagreb, Croatia** (Associate professor Ninoslav Mimica, MD, MSc, DSc, Primarius, IFAPA; Assistant professor Suzana Uzun, MD, MSc, DSc, Primarius; Gordan Makarić, MD, Primarius; Assistant professor Oliver Kozumplik, MD, DSc, Primarius); **University of Zagreb, School of medicine** (Associate professor Ninoslav Mimica, MD, MSc, DSc, Primarius, IFAPA); **University of Osijek Josip Juraj Strossmayer, Faculty of medicine** (Assistant professor Suzana Uzun MD, MSc, DSc, Primarius, Assistant professor Oliver Kozumplik, MD, DSc, Primarius); **University of Zagreb, Faculty of teacher education** (Full Professor Tajana Ljubin Golub, PhD); **University hospital centre Zagreb, Department of psychiatry** (Petra Folnegović Grošić, MD, Primarius)

Adresa za dopisivanje / *Correspondence address*. Doc. prim. dr. sc. Suzana Uzun, dr. med., University psychiatric hospital Vrapče, Bolnička cesta 32, 10090 Zagreb, Croatia; E-mail address: suzana.uzun@bolnica-vrapce.hr

Primljeno/*Received* 2017-10-20; Ispravljeno/*Revised* 2018-04-03; Prihvaćeno/*Accepted* 2018-05-04

Introduction

The interest in studies related to aggressive behaviour in psychiatric patients has increased over time. The reasons for this are encompassing the fact that aggressive behaviour is an obstacle for the more effective rehabilitation of decompensated patients, greater concern about personnel and their reactions, recently developed pharmacological treatment strategies and the role of serotonin and other substances in aggressive and suicidal patients.

Various factors are considered as determinants of aggression, such as social, environmental and situational determinants, hormones, drugs and other substances, neurotransmitters and genetic determinants. According to the biological data, aggression seems to emerge when the drive of limbic-mediated affective prefrontal response to provocative producing stimuli is insufficiently constrained by inhibition.[1]

The influence of serotonin is best analysed within a broader framework that includes consideration of its role in the inhibition of impulses, the regulation of emotions and social functioning, domains that are closely linked to aggression. Impulsivity and strong emotional states often accompany violent acts. Aggressive individuals are likely to experience general difficulties with impulse control and emotional regulation, and they show impaired social cognition and affiliation. Serotonergic dysfunction will influence aggression differently, depending on the individual's impulse control, emotional regulation, and social abilities. Yet, aggressive acts occur in a broader social context. As such, serotonergic function has an effect not only on the individual but also on the group dynamics, and it is in turn influenced by these dynamics. Whether aggression will occur when serotonin dysfunction is present will depend on individual differences as well as the overall social context.[2]

Violent behaviour in adults with schizophrenia represents a risk for themselves and for those around them, so the opportune implementation of interventions aimed to calm the patient, in order to prevent potential negative outcomes is necessary. It is recommended to initiate these interventions with measures of verbal persuasion, and if these measures are not effective, appropriate use of parenteral drugs: haloperidol and benzodiazepines as first-line and olanzapine and ziprasidone as second choices.[3]

The aggression could be noticed in various clinical situations, some of them being mental retardation, cognitive disorders, psychotic and mood disorders and personality disorders.

The incidence of aggressive behaviour is higher among the patients with severe mental disorder such as schizophrenia than the general population.[4] The study of factors related to aggressive behaviour has great meaning in designing prevention and intervention methods with this population of patients.[5] The increased risk of violence in schizophrenia has been linked to several environmental, clinical and neuropsychological factors, including executive dysfunction. However, data about the nature of these effects are mixed and controversial.[6] Although most psychiatric patients are not violent, serious mental illness is associated with increased risk of violent behaviour. There were statistically significant increases of risk of violence in schizophrenia and in bipolar disorder in comparison with the general population. The evidence suggests that the risk of violence is greater in bipolar disorder than in schizophrenia. Most of the violence in bipolar disorder occurs during the manic phase. The risk of violence in schizophrenia and bipolar disorder is increased by comorbid substance use disorder. Violence among adults with schizophrenia may follow at least two distinct pathways-one associated with antisocial conduct, and another associated with the acute psychopathology of schizophrenia.[7,8] Research in Chinese inpatients with schizophrenia also showed that they had a high risk of aggression, and it is urgent to establish the scientific, standardized, operational systems for assessing and treating the aggression of these patients.[9]

In addition, elevations of impulsive behaviour have been observed in a number of serious mental illnesses. These phenomena can lead to harmful behaviours, including violence, and thus represent a serious public health concern. Such violence is often a reason for psychiatric hospitalization, and it often leads to prolonged hospital stays, suffering by patients and their victims, and increased stigmatization. On a psychological level, aggression in schizophrenia has been primarily attributed to psychotic symptoms, desires for instrumental gain, or impulsive responses to perceived personal slights. Often, multiple attributions can coexist during a single aggressive incident. Hoptman's numerous studies conducted in inpatient settings have highlighted how mental disorders are associated with an increased risk of violence, particularly during acute phases. Violent behaviour is relatively common among outpatients.[10] Neurocognitive dysfunction, a core feature of schizophrenia, is thought to contribute to the impulsive violent aggression manifested by some individuals with schizophrenia,[11] while according

to Knezevic et al., socio-demographic variables and clinical characteristics seem to be not such good predictors of aggressive behaviour in hospitalized schizophrenic patients.[12]

Acute agitation and aggression are common symptoms not only in patients with schizophrenia, but also in patients with bipolar disorder.[13,14]

Persistent violence not due to acute psychosis or mania can be managed only after appropriate characterization of the aggressive episodes (psychotic, impulsive, or predatory/planned/ instrumental). The type of violence combined with the psychiatric diagnosis dictates the evidence-based pharmacologic approaches for psychotically motivated and impulsive aggression, whereas instrumental violence mandates forensic/behavioural strategies. For non-acute inpatients, schizophrenia spectrum disorders, traumatic brain injury, and dementia comprise the majority of individuals who are persistently aggressive, with impulsive actions the most common form of violence across all diagnoses.[15]

A combination of adverse and traumatic life events such as a history of violence, vulnerabilities in one's personality (e.g. impulsive or antisocial tendencies) and psychopathology of current illness (e.g. significant anxiety and depressive symptoms) contribute to aggressive behaviour in male inpatients with schizophrenia.[5]

Personality factors and substance abuse may be more important than psychotic symptoms in the development of aggressive behaviour in patients with first-episode psychosis.[16]

Epidemiological studies suggest a positive but controversial correlation between the major mental disorders, particularly schizophrenia and delinquent or criminal acting out.[17] The majority of schizophrenic patients do not commit any crime, and the risk of the general population to be a target of a violent act by a person with schizophrenia is low. The causes of delinquency in schizophrenia are complex, but certain risk characteristics (e.g. an accompanying substance abuse) have been identified.[18]

Violent behaviour associated with mental disorders is a common reason for admission to a psychiatric inpatient unit. Once hospitalized, patients may continue to be intermittently agitated and have persistent aggressive behaviours, preventing their discharge back into the community. Managing agitation quickly with effective pharmacological agents can avoid further escalation to aggression and violence. In the acute setting, this usually involves the parenteral use of antipsychotics, with or without benzodiazepines. In contrast to agitation associated with schizophrenia or bipolar mania, no agents have yet been approved by regulatory agencies for the treatment of persistent aggressive behaviour. The strongest evidence supports the use of clozapine as an anti-hostility agent, followed by olanzapine. Adjunctive strategies with anticonvulsants and beta-adrenergic agents may also be worthwhile to consider.[19.]

Acute psychotic illness, especially when associated with agitated or violent behaviour, can require urgent pharmacological tranquillisation or sedation. In several countries, clinicians often use benzodiazepines (either alone or in combination with antipsychotics) for this outcome.[20]

Lithium, anticonvulsants, antipsychotic medication and antidepressants are usually considered as drugs of major promise for violent patients.[21,22] In addition to this, it is also considered that antiandrogen agents, beta-blockers and stimulants may be effective in some aggressive patients. However, it is considered that antianxiety agents have just a limited role in reducing aggression. Clonazepam is considered as the high-potency benzodiazepine with a rapid rate of absorption. It is regarded as a long-acting drug, with an average half-life of metabolites of 34 hours. Usual adult dosage range is between 0.5 and 10 mg per day. Among other indications, clonazepam is usually suggested as a medication of choice at the initiation of therapy for bipolar I disorder as an adjuvant to lithium, as long as the initial phase of the manic episode is lasting. Recent reports have supported the innovative use of clonazepam in the treatment of various psychiatric conditions.[23]

Subjects

The inclusion criteria relevant for this study were as follows:

- clinical manifestation of an aggressive behaviour of a larger scale in continuous duration over 3 days;
- antipsychotic medication was applied as a principal therapy for at least 10 days before the inclusion in a study;
- just one antipsychotic drug is used in treatment, without combination with any other psychoactive agent;
- clinically significant improvement of psychotic symptoms was observed during the period when antipsychotic medication was used, while aggressive symptoms remained the same, or have even increased during the course of antipsychotic therapy.

The exclusion criteria relevant for this study were as follows:

- clinical manifestation of an aggressive behaviour of a larger scale in continuous duration less than 3 days;
- antipsychotic medication was applied as a principal therapy for 1-9 days before the inclusion in a study;
- combination of two or more antipsychotics;
- clinically significant improvement of psychotic and aggressive symptom.

Patients in a study were chosen on a random basis among the inpatients who fulfilled the above mentioned criteria.

Methods

Clonazepam was initially administered in a daily dose of 2 mg to all patients in a study. If satisfactory clinical improvement was not observed in 2 days, it was allowed to increase dose up to a daily dose of 6 mg.

During the period when clonazepam was administered, all patients continued to use the antipsychotic medication of the same type and in the same daily dose as at the moment of inclusion. Just one antipsychotic drug was required to be used in the treatment in order to avoid possible interactions with some other psychoactive agent.

Aggression was twice evaluated by Social Dysfunction and Aggression Scale (SDAS): the first time at the moment of inclusion to the study, and second time 3 days after the administration of clonazepam. Social Dysfunction and Aggression Scale (SDAS) contains 11 items with anchoring-definitions of five grades and was particularly developed as a mean to enable the observers' evaluation of aggression. Nine of the SDAS items cover outward aggression and two items reflect inward aggression. Eleven items evaluated in SDAS include non-directed verbal aggressiveness, directed verbal aggressiveness, irritability, negativism, dysphoric mood, socially disturbed behaviour, physical violence to personnel, physical violence to others, apart from personnel, self-mutilation, physical violence to things and suicidal thoughts and impulses. Each item was evaluated with four grades (0 = not present, 1 = doubtful or very mild, 2 = mild to moderate, 3 = severe and 4 = extremely severe).[24,25]

Evaluation by SDAS was done by trained psychiatrists. All clinical procedures were done in line with the rules of Good Clinical Practice. Patients were treated with standard medication, without placebo group, and groups were compared among themselves. All subjects gave their consent for hospital treatment, which included the pharmacotherapy provided.

Investigation was performed as analysis of treatment with standard medications according to the rules of Good Clinical Practice. The examinees gave their consent to hospital treatment which included the application of the mentioned medications.

Results

39 inpatients were included in the study. The age of the patients involved in the study was between 18 and 50 years (mean age = 36.3 ± 5.2 years). There were 31 males and 8 female patients included.

The following diagnostic categories (Schizophrenia, Alcoholism, Mental retardation, Posttraumatic stress disorder and Personality disorder) were diagnosed in persons included in the study. The number of each diagnostic category is shown in Table 1.

Table 1 Number of patients included in a study due to diagnosis
Tablica1. Broj bolesnika uključenih u studiju uslijed dijagnoze

Diagnosis *Dijagnoza*	No. of patients *Broj pacijenata*
Schizophrenia *Šizofrenija*	24
Alcoholism *Alkoholizam*	7
Mental retardation *Mentalna retardacija*	2
Posttraumatic stress disorder *Postraumatski stresni poremećaj*	4
Personality disorder *Poremećaj osobnosti*	2
Total *Sveukupno*	39

Patients included in the study were on one of the following antipsychotics as basic therapy, before adding clonazepam. Table 2 presents the number of patients on basic antipsychotic drug therapy.

Based on the overall clinical impression, the increase in daily dose two days after clonazepam administration was needed in 12 patients. Out of this number, in 9 patient's clonazepam daily dose was increased to 4 mg and in 3 patients to 6 mg.

The average SDAS score at the time of inclusion to a study, i.e. prior to clonazepam administration and 3 days after the clonazepam administration is shown in Table 3.

No adverse events were observed while using clonazepam in aggressive patients.

Table 2 Number of patients on each basic antipsychotic before clonazepam augmentation
Tablica 2. Broj bolesnika na svakom temeljnom antipsihotičnom lijeku prije povećanja klonazepama

Antipsychotic drug *Antipsihotički lijek*	No. of patients *Broj pacijenata*
Chlorpromazine	7
Promazine	6
Fluphenazine	5
Thioridazine	3
Haloperidol	14
Droperidol	2
Chlorprothixene	2
Total / *Sveukupno*	39

Table 3 Average total SDAS score prior and after clonazepam administration
Tablica 3. Prosjek sveukupnog SDAS bodova prije i poslije primjene klonazepama

SDAS total score at Day 0 *Sveukupan broj SDAS bodova na dan 0*	SDAS total score at Day 3 *Sveukupan broj SDAS bodova na dan 3*
29 ± 4.4	18 ± 6.1
N = 39	N = 39

Discussion

Psychotic disorders can lead some people to become agitated. Characterised by restlessness, excitability and irritability, this can result in verbal and physically aggressive behaviour - and both can be prolonged. Aggression within the psychiatric setting imposes a significant challenge to clinicians and risk to service users; it is a frequent cause for admission to inpatient facilities. If people continue to be aggressive it can lengthen hospitalisation.[26]

It is generally considered that benzodiazepines have just a limited role in the treatment of aggression. However, the decrease in total SDAS score in this study is considerable: while the average being 29 ± 4.4 prior to adjuvant administration of clonazepam, after 3 days it decreased to 18 ± 6.1. As antipsychotic in treatment was used for at least 10 days prior to the introduction of clonazepam, we believe that the vast majority of decrease in aggressiveness could be attributed to clonazepam. Nevertheless, the possible synergistic effect between clonazepam and antipsychotic drugs should not be completely disregarded.

It should be mentioned that patients included in the study had strongly expressed aggressiveness prior to treatment with clonazepam, and it is likely that, by administrating clonazepam as an adjuvant to antipsychotic, more effective rehabilitation of severely decompensated patients could be reached.

In this study clonazepam was applied in daily doses of a medium range (initially 2 mg, with possible increase up to 6 mg). The sample size and dose increment just in 12 patients did not allow any conclusions about the relation between the dose increase and a desired clinical effect. As larger daily doses were not applied, at this moment it is not possible to discuss about the ultimate responder's rate.

As patients with several diagnostic categories were included in the study, it could be assumed that clonazepam is, at least to some degree, efficient in decreasing aggressiveness in patients regardless of the diagnostic category. Still, it is certain that separate studies which will analyse the efficiency of clonazepam in each particular diagnostic category will enable more precise clonazepam positioning in the treatment of aggressive patients. Double-blind studies involving the use of clonazepam with or without antipsychotic in comparison with placebo effect will be especially useful in determining the more precise clonazepam position.

According to Citrome et al., the strongest evidence supports the use of clozapine as an anti-hostility agent, followed by olanzapine. Adjunctive strategies with anticonvulsants and beta-adrenergic agents may also be worthwhile to consider.[27]

Violent behaviour in adults with schizophrenia represents a risk for themselves and for those around them, so the opportune implementation of interventions aimed to calm the patient, in order to prevent potential negative outcomes is necessary. It is recommended to initiate these interventions with measures of verbal persuasion, and if these measures are not effective, appropriate use of parenteral drugs: haloperidol and benzodiazepines as first-line and olanzapine and ziprasidone as second choices.[3]

Gillies et al. conclude that adding a benzodiazepine to other drugs does not seem to confer clear advantage and has potential for adding unnecessary adverse effects. Sole use of older antipsychotics unaccompanied by anticholinergic drugs seems difficult to justify. Much more high-quality research is needed in this area.[20]

Violent behaviour of patients with schizophrenia and bipolar disorder is a public health problem. Pharmacological and non-pharmacological approaches should be used to treat not only violent behaviour, but also contributing comorbidities such as substance

abuse and personality disorders. Treatment adherence is very important for successful management of violent behaviour.[7]

It is particularly encouraging that no adverse events of clonazepam were observed in this study. However, for drawing a precise conclusion concerning this issue, the studies involving a larger number of patients with a more prolonged clonazepam medication are certainly needed.

Study limitations

There are several limitations of the study. First, the study does not include double blind control group of patients in which aggressive behaviour is treated with some alternative medication than clonazepam or with clonazepam alone. However, the observed decrease in aggressive behaviour following clonazepam treatment is not likely due to antipsychotic medication alone, since all patients have continued to use the antipsychotic medication of the same type and in the same daily dose as at the moment of inclusion in the study, and all were had to have clinically significant improvement of psychotic symptoms while aggressive symptoms being the same, or had even increased before inclusion in the study. Second, the small number of patients did not allow us to control for specific diagnostic category and the type of antipsychotic therapy. Thus, the study did not allow us to disentangle the combined effect of clonazepam and antipsychotic therapy and clonazepam effect alone.

Conclusion

The results of our research show the efficiency of clonazepam as a serenic drug in combination with antipsychotic drug in treatment of aggressive patients. It is particularly encouraging that no adverse effects of clonazepam were observed in this study.

Additional studies are needed for more precise clonazepam positioning in treatment of aggressive patients. It particularly refers to researches that will be oriented to some specific diagnostic category and to the use of clonazepam as a monotherapy in aggressive patients.

Further relevant trials are needed to evaluate the use of clonazepam in treatment of long-term/persistent aggression in people living with psychosis.

References

1. Giotakos O. Aggressive behavior: theoretical and biological aspects. Psychiatriki. 2013;24:117-31.
2. Krakowski M. Violence and serotonin: Influence of impulse control, affect regulation and social functioning. J Neuropsychiatry Clin Neurosci. 2003;15:294-305.
3. Gómez-Restrepo C, Bohórquez Peñaranda AP, Ávila MJ et al. Pharmacological treatment for adult diagnosed with schizophrenia with agitation or violent behavior. Rev Colomb Psiquiatr. 2014;44 Suppl 1:59-65.
4. Mimica N, Folnegović-Šmalc V, Folnegović Z, Makarić G, Kozarić-Kovačić D. Aggressivity in schizophrenics. 16. Donausymposion für Psychiatrie. Prague, Czech Republic, 10.-13. August 1994. Abstracts, pp. 37.
5. Zhu X, Li W, Wang X. Characteristics of aggressive behaviour among male inpatients with schizophrenia. Shanghai Arch Psychiatry. 2016;28:280-88.
6. Bulgari V, Iozzino L, Ferrari C et al. Clinical and neuropsychological features of violence in schizophrenia: a prospective cohort study. Schizophr Res. 2017;181:124-30.
7. Volavka J. Violence in schizophrenia and bipolar disorder. Psychiatr Danub. 2013;25:24-33.
8. Witt K, van Dorn R, Fazel S. Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies. PloSOne. 2013;8:e55942.
9. Chen Q, Zhou J. Aggression of Chinese inpatients with schizophrenia: a systematic literature review. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2012;37:752-6.
10. Pinna F, Tusconi M, Dessì C, Pittaluga G, Fiorillo A, Carpiniello B. Violence and mental disorders. A retrospective study of people in charge of a community mental health center. Int J Law Psychiatry. 2016;47:122-8.
11. Stratton J, Brook M, Hanlon RE. Murder and psychosis: neuropsychological profiles of homicide offenders with schizophrenia. Crim Behav Ment Health. 2017; 27:146-61.
12. Knezevic V, Mitrovic D, Drezgic-Vukic S et al. Prevalence and correlates of aggression and hostility in hospitalized schizophrenic patients. J Interpers Violence. 2015;32:151-63.
13. Yu X, Correll CU, Xiang YT et al. Efficacy of atypical antipsychotics in the management of acute agitation and aggression in hospitalized patients with schizophrenia or bipolar disorder: results from a systematic review. Shanghai Arch Psychiatry. 2016;28:241-52.
14. Manchia M, Fanos V. Targeting aggression in severe mental illness: The predictive role of genetic, epigenetic, and metabolomic markers.

Prog Neuropsychopharmacol Biol Psychiatry. 2017;77:32-41.
15. Meyer JM, Cummings MA, Proctor G, Stahl SM. Psychopharmacology of persistent violence and aggression. Psychiatr Clin North Am. 2016;39: 541-56.
16. Látalová K. Violence and duration of untreated psychosis in first-episode patients. Int J Clin Pract. 2014;68:330-5.
17. Rafrafi R, Bahrini L, Robbana L, Bergaoui H, Melki W, El Hechmi Z. Violence in schizophrenia: a study of 60 cases. Tunis Med. 2013;91:729-34.
18. Boudriot F, Guldimann A, Habermeyer E. Schizophrenia and violence. Praxis (Bern 1994) 2013;103:27-32.
19. Citrome L, Du Y, Risinger R et al. Effect of aripiprazole lauroxil on agitation and hostility in patients with schizophrenia. Int Clin Psychopharmacol. 2016;31:69-75.
20. Gillies D, Sampson S, Beck A, Rathbone J. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database Syst Rev. 2013; 18:9:CD003079.
21. Makarić G, Folnegović-Šmalc V, Folnegović Z, Mimica N. Agitation in acute episode of schizophrenia; carbamazepine treatment in combination with haloperidol vs. combined neuroleptics. Schizophrenia Research. 2000;41(1 – special issue): 210.
22. Uzun S, Kozumplik O, Mimica N, Folnegovic-Smalc V. Patients with schizophrenia and aggressive behavior: treatment with combination of risperidone and topiramat. Česká a Slovenská Psychiatrie. 2008;104 Suppl 2:1257.
23. Binder RL. Three case reports of behavioral disinhibition with clonazepam. Gen Hosp Psychiatry. 1987;9:151-3.
24. European Rating Aggression Group (ERAG) (1992) Social dysfunction and aggression scale in generalized aggression and in aggressive attacks. A validity and reliability study. Int J Methods Psychiatr Res. 1992;2:15-29.
25. Wistedt B, Rasmussen A, Pedersen L et al. The development of an observer scale for measuring social dysfunction and aggression. Pharmacopsychiatry. 1990; 23:249-52.
26. Khushu A, Powney MJ. Haloperidol for long-term aggression in psychosis. Cochrane Database Syst Rev. 2016;11:CD009830.
27. Citrome L, Volavka J. The psychopharmacology of violence: making sensible decisions. CNS Spectr. 2014;19:411-8.