The effect of paliperidone palmitate long-acting injectable (PP-LAI) on "non-core" symptoms of schizophrenia: a retrospective, collaborative, multicenter study in the "real world" everyday clinical practice

Effetto di paliperidone palmitato a rilascio prolungato (PP-LAI) sui sintomi "non-core" della schizofrenia: uno studio retrospettivo, collaborativo, multicentrico nella pratica clinica quotidiana nel "mondo reale"

DOMENICO DE BERARDIS[1,2,3*], FEDERICA VELLANTE[2], LUIGI OLIVIERI[1], GABRIELLA RAPINI[1], IDA DE LAURETIS[1], LAURA ORSOLINI[4,5], ALESSANDRO VALCHERA[4,6], ALESSANDRO CARANO[7], MASSIMILIANO BUSTINI[8], SIMONE DE PERSIS[8], SABATINO TROTTA[9], MICHELE FORNARO[10], ANTONIO VENTRIGLIO[11], VASSILIS MARTIADIS[12], LAURA SIMIONE[13], MAURIZIO POMPILI[14], GIANLUCA SERAFINI[15], MARCO DI NICOLA[16], MARCO ALESSANDRINI[2], GIOVANNI MARTINOTTI[2], SILVIA FRATICELLI[2], MASSIMO DI GIANNANTONIO[2]

*E-mail: domenico.deberardis@aslteramo.it

[1]NHS, Department of Mental Health, Psychiatric Service for Diagnosis and Treatment, Hospital "G. Mazzini", ASL 4, Teramo, Italy
[2]Department of Neurosciences and Imaging, Chair of Psychiatry, University "G. D'Annunzio" Chieti, Italy
[3]Contract Professor of Pharmacology, School of Nursing, University of L'Aquila, Italy
[4]Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK
[5]Department of Clinical Neurosciences/DIMSC, Section of Psychiatry, Polytechnic University of Ancona, Italy
[6]"Villa S. Giuseppe" Clinic, Hermanas Hospitalarias, Ascoli Piceno, Italy
[7]NHS, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "Madonna Del Soccorso", San Benedetto del Tronto (AP), Italy
[8]NHS, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "San Camillo de Lellis", Rieti, Italy
[9]NHS, Department of Mental Health, Pescara, Italy
[10]Department of Psychiatry, Federico II University, Naples, Italy
[11]Department of Psychiatry, University of Foggia, Italy
[12]NHS, Mental Health Service, DSB 45, Naples, Italy
[13]NHS, Department of Mental Health, Mental Health Service, Cassino (FR), Italy
[14]Department of Neuroscience, Mental Health, and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Sapienza University, Unit of Psychiatry, Sant'Andrea University Hospital, Rome, Italy
[15]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Italy
[16]Institute of Psychiatry and Psychology, Department of Geriatrics, Neuroscience and Orthopedics, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

SUMMARY. Background. Schizophrenia is frequently complicated by the occurrence of depressive symptoms, anhedonia, obsessions and compulsions, suicidal ideation, and substance abuse, that causes exacerbations and remissions and, in several cases, sustained morbidity and disability. **Aim.** The present study aimed to evaluate the effect of paliperidone palmitate once-monthly long-acting injection (PP-LAI) mainly on "non-core" symptoms in persons with recent diagnosis schizophrenia, during a follow-up period of almost 12 months (T1) in the context of the "real world" everyday clinical practice. **Results.** Concerning core symptoms of schizophrenia, PP-LAI was effective in reducing all symptoms at T1 as measured by Positive and Negative Syndrome Scale (PANSS), including depressive symptoms, and increased the functioning. Moreover, concerning the non-core symptoms of schizophrenia, PP-LAI treatment was effective in reducing scores of anhedonia, suicidal ideation and obsessive-compulsive symptoms at T1. However, the levels of alexithymia remained relatively stable, even if reduced. **Discussion.** The present retrospective, multicenter, non-sponsored, collaborative study showed that early PP-LAI treatment was effective in improving almost all the core dimensions and "non-core" symptoms of schizophrenia, and this may have positive repercussions on both functioning and quality of life. **Conclusions.** PP-LAI treatment should be offered earlier as possible and was effective on "non-core" symp-

toms of schizophrenia at follow-up, but had a little effect on alexithymia. However, study' limitations must be considered and future researches are needed to confirm these interesting findings.

KEY WORDS: schizophrenia, paliperidone palmitate, depression, functioning, anhedonia, obsessions, compulsions, suicidal ideation, craving, alexithymia, real world.

RIASSUNTO. Introduzione. La schizofrenia è spesso complicata dalla presenza di sintomi depressivi, anedonia, ossessioni e compulsioni, ideazione suicidaria e abuso di sostanze, che impattano in modo significativo sugli esiti e influenzano la morbilità e la disabilità. **Obiettivi.** Il presente studio è stato condotto per valutare l'effetto di paliperidone palmitato (PP-LAI) principalmente sui sintomi "non-core" della schizofrenia in persone con diagnosi recente valutate con un follow-up di 12 mesi (T1) nel contesto della pratica clinica quotidiana nel "mondo reale". **Risultati.** PP-LAI si è mostrato efficace nel ridurre i sintomi "core" della schizofrenia misurati con la PANSS al T1 Positive and Negative Syndrome Scale (PANSS), inclusi i sintomi depressivi, e ha migliorato il funzionamento globale. Per quanto riguarda i sintomi "non-core" della schizofrenia, il trattamento con PP-LAI ha mostrato una riduzione dell'anedonia, dell'ideazione suicidaria e dei sintomi ossessivo-compulsivi al T1, mentre i livelli di alessitimia sono rimasti relativamente stabili con una riduzione non statisticamente significativa. **Discussione.** Questo studio retrospettivo, multicentrico, non sponsorizzato, collaborativo e naturalistico ha mostrato che il trattamento precoce con PP-LAI è stato efficace sia sui sintomi "core" sia sui sintomi "non-core" della schizofrenia, e può esercitare un favorevole effetto sia sul funzionamento sia sulla qualità di vita. **Conclusioni**. Il trattamento con PP-LAI dovrebbe essere offerto il prima possibile e ha mostrato un significativo effetto anche sui sintomi "non core" della schizofrenia, esclusa l'alessitimia. Tuttavia devono essere considerati i limiti dello studio e sono necessarie ricerche future per confermare questi interessanti risultati.

PAROLE CHIAVE: schizofrenia, paliperidone palmitato, depressione, funzionamento, anedonia, ossessioni, compulsioni, ideazione suicidaria, craving, alessitimia, mondo reale.

INTRODUCTION

Schizophrenia is a chronic, severe, and disabling disorder that is characterized by positive, negative, cognitive, and affective symptoms[1,2]. Schizophrenia is frequently complicated by the occurrence of suicidal ideation and behaviors, violent and aggressive behaviors, substance abuse, and medical comorbidities that can arise over an illness course that causes exacerbations and remissions and, in several cases, sustained morbidity and disability[3-5]. The pharmacological treatment of schizophrenia is mandatory, as subjects with this disorder have a less life expectancy and higher mortality than the general population, especially if they are not treated[6,7].

The long-acting antipsychotic injections (LAIs) are considered as an adherence intervention for patients who are 'non-compliant' with the oral medication they have been prescribed[8]. However, the availability of the Long-acting injectable second-generation antipsychotics (SGAs-LAIs) has been an advance in the long-term management of schizophrenia, particularly regarding subjective and objective long-term tolerability[9].

Even if the SGAs-LAIs are usually used to maintain treatment adherence in patients with chronic schizophrenia, recent studies suggest that they may also provide an effective treatment strategy for persons with first-episode schizophrenia[10,11]. Moreover, these drugs may also have a potential "neuroprotective" effect, thus improving the neurodegenerative outcomes of psychosis. This effect may also be explained and is reinforced by the better quality of life that is often obtained in persons treated with the SGAs-LAIs[12,13]. However, even if the research on SGAs-LAIs effects on core symptoms of schizophrenia (i.e., positive and negative symptoms, disorganization, diminished emotional expression, and cognitive symptoms) is continuously growing, there are few data on the effects of such drugs on non-core symptoms of schizophrenia that often are present even when the core symptoms are improved. Frequently, it has been observed the emergence of depressive symptoms, suicidal ideation, anhedonia, obsessive-compulsive symptoms, alexithymia, and substance craving in schizophrenia, even if the core symptoms have been adequately treated[14-18].

Paliperidone palmitate once-monthly long-acting injection (PP-LAI) has been approved for the treatment of schizophrenia by the Food and Drug Administration in 2009 and by the European Medicines Agency in 2011[19]. PP-LAI is hydrolyzed to paliperidone, the primary active metabolite of risperidone. The PP-LAI mechanism of action is a combination of central dopamine D2 and serotonin 5HT2A receptor antagonism. As well, PP-LAI showed an antagonism for $\alpha 1$ and $\alpha 2$-adrenergic receptors and, to a lesser extent, for H1 histaminergic receptors, without affinities for cholinergic or muscarinic receptors.

Currently, there are not specific studies that have investigated the action of SGA-LAIs in all these "non-core" symptoms clusters. Therefore, the present study aimed to evaluate the effect of PP-LAI mainly on "non-core" symptoms in persons with recent diagnosis schizophrenia during a follow-up period of almost 12 months in the context of the "real world" everyday clinical practice.

METHODS

This multicentric, retrospective, and observational study, not funded or sponsored, was conducted in several mental health facilities in Central and South Italy among patients with recent diagnosis schizophrenia who were initiated with PP-LAI, based on an attending physician's clinical judgment and patient' agreement. Patients with five or fewer years of illness affected by schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[20], were evaluated and included in the analysis. Patients were allowed to continue on any prescribed anxiolytics or mood stabilizers (valproate), if any, during the trial. Patients who were taking other antipsychotics or

other psychotropic drugs were not considered for enrollment. The persons' charts were collected and reviewed, and data were obtained at baseline (T0) and prospectively followed up to 12 months (T1).

Persons were excluded based on the following criteria: 1) current or past comorbid diagnosis of autistic disorder or other pervasive developmental disorder; 2) history of severe head injury; 3) harsh medical conditions or significant neurological disorders, including mental retardation and dementia; and 4) any current other psychiatric diagnoses rather than schizophrenia. The use of cannabis wasn't considered an exclusion criterion because of the high prevalence of its use among schizophrenia patients.

Seventy subjects (41 males and 29 females with a mean age of 25.1±2.6 years) were evaluated, and data analyzed at T0 and T1. Data on sociodemographic and psychopathological variables were collected at the first clinical interview. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS)[21] and, as made by Corigliano et al.[22], we used the PANSS to extract the following five factors: a) positive (POS) (P1, delusions; P3, hallucinatory behavior; P5, grandiosity; and G9, unusual thought content); b) negative (NEG) (N1, blunted affect; N2, emotional withdrawal; N3, poor rapport; N4, passive withdrawal; N6, lack of spontaneity; and G7, motor retardation); c) disorganized/concrete (DIS) (N5, difficulty in abstract thinking; P2, conceptual disorganization; and G11, poor attention); d) excited (EXC) (P4, excitement; P7, hostility; G8, uncooperativeness; and G14, poor impulse control); depressed (DEP) (G2, anxiety; G3, guilt feelings; and G6, depression). Global functioning was assessed with the Global Assessment of Functioning (GAF) Scale[23]. All these measures were considered as an evaluation of the core symptoms of schizophrenia.

To assess the non-core symptoms of schizophrenia, the following scales were used. The suicide risk was assessed with the Scale for Suicide Ideation (SSI)[24]. The presence of obsessive-compulsive symptoms was assessed with the total score of the Yale-Brown Obsessive-Compulsive Scale (YBOCS)[25]. The anhedonia was measured with the Snaith-Hamilton Pleasure Scale (SHAPS)[26]. The presence of alexithymia was evaluated, considering the total score of the Italian version of the 20-items Toronto Alexithymia Scale (TAS-20)[27]. Finally, to assess the intensity of craving, we used VAScrav, a 10-cm ruler or straight line with one extreme (0) meaning no craving and the other (10) extremely intense craving, allowing a continuous, non-discrete rating of the extent of craving, differently from Likert-type scales[28].

Statistics

We first used the Kolgomorov-Smirnov normality test to test for the normality of distribution of our data. Since data distribution was found to be normal, we proceeded with parametric testing. Student's t-tests were conducted to assess changes in psychopathological variables from baseline (T0) to follow-up (T1). For all analyses, a conservative significance threshold of $p<0.001$ was used. All analyses were conducted with the statistical package SPSS (version 17.0.2).

RESULTS

The mean dosage of PP-LAI at the endpoint was 86.4±20.1 mg, and the majority of individuals received a dosage of 75 mg/once monthly at T1 (n=40, 57.1%). The mean duration of illness was 3.7±1.2 years, and the mean age at onset was 21.3±2.7 years.

Concerning core symptoms of schizophrenia, PP-LAI was effective in reducing both positive and negative symptoms at T1 as measured by PANSS (respectively t=11.6 df 69 p<0.001 and t=8.7 df=69 p<0.001). As well, also DIS (t=11.4 df 69 p<0.001), EXC (t=5.2 df 69 p<0.001) and DEP (t=6.9 df 69 p<0.001) factors of PANSS improved with PP-LAI treatment at 12 months. Also functioning (as measured by GAF, t=-7.8 df 69 p<0.001) improved with the PP-LAI (Figure 1).

Concerning the non-core symptoms of schizophrenia, PP-LAI treatment was effective in reducing scores of anhedonia (as measured by SHAPS, t=6.5 df 69 p<0.001), suicidal ideation (as measured by SSI, t=5.9 df 69 p<0.001) and obsessive-compulsive symptoms (as measured by Y-BOCS total score, t=8.7 df 69 p<0.001) at T1. However, the overall rating on TAS-20 remained relatively stable and wasn't substantially influenced by the PP-LAI administration (Figure 2).

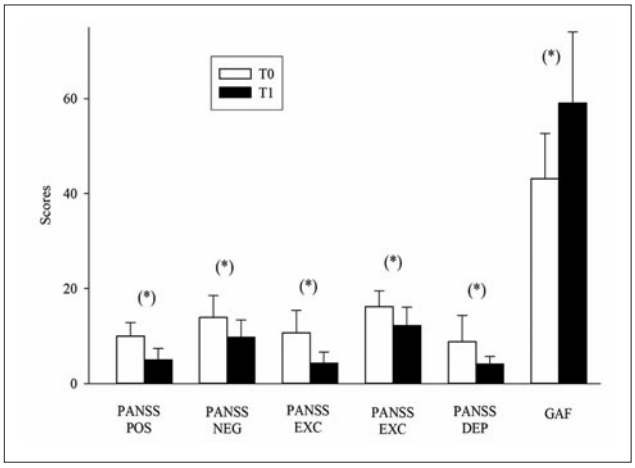

Figura 1. Effect of PP-LAI on "core" symptoms of schizophrenia (p<0.001).

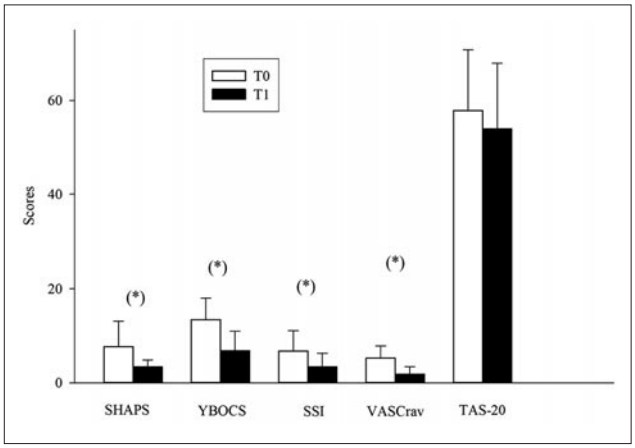

Figura 2. Effect of PP-LAI on "non-core" symptoms of schizophrenia (p<0.001).

During the entire study period, there were few side effects reported. PP-LAI was well tolerated, and eight subjects (11.4%) reported a slight increase in prolactin levels (all successfully managed with dosage reduction), seven subjects (10%) reported mild subjective sedation and 15 subjects (21.4) reported a slight pain on the site injection (in almost one administration). No other adverse effects were observed.

DISCUSSION

The present retrospective, multicenter, non-sponsored, collaborative study showed that PP-LAI was effective in improving the positive/negative dimensions, the disorganized and excited dimensions, and the depressive symptoms at 12 months of follow-up. Overall, these findings were is in accordance with most of the literature demonstrating the effectiveness of such drug in these dimensions of schizophrenia[19,29]. Moreover, offering an LAI antipsychotic is always an effective strategy, especially in early-episode patients, resulting in the administration of treatments when schizophrenia is most treatable[30,31]. Brown et al.[32] have demonstrated that PP-LAI showed symptomatic and functional improvement in patients with different durations of schizophrenia. Still, the magnitude of the effects was superior in subjects with early illness than in those with a chronic disease.

Though it should be noted that we observed a remarkable action on affective symptoms such as depression, and this finding may explain the improvement seen in terms of functioning[33]. Moreover, PP-LAI significantly improved the anhedonia. This finding may be related to the reduction in negative/depressive symptoms or the improvement in global functioning (or both)[13]. Still, it can be hypothesized a peculiar action on PP-LAI on anhedonia itself[34], but further studies are needed. The subjects affected by schizophrenia may have functional impairment in anticipatory, but not consummatory reward, anticipating lower pleasure from future activities than healthy controls, and resulting in a decrease in goal-directed behaviors[14]. PP-LAI, through the effects on serotonin 5HT2a and 2-adrenergic receptors, may restore the dysfunction of dopamine neurotransmission in reward circuitry, thus improving anhedonia[35,36].

Moreover, PP-LAI treatment was effective in reducing scores of obsessive-compulsive symptoms (even if Y-BOCS total scores were relatively low at the baseline). Obsessive-compulsive disorder (OCD) is often associated with schizophrenia and may represent a significant challenge in the treatment[17,37]. The percentage of comorbidity between OCD and schizophrenia varies from 7 and 26%, and it has been suggested the existence of a new clinical entity called 'schizo-obsessive disorder' subtype of psychosis that may often be treatment-resistant[38,39]. In fact, to date, few studies have examined the effect of oral paliperidone in OCD, suggesting that oral paliperidone augmentation is well tolerated and has potential efficacy in the short-term treatment of some patients with SRI-resistant OCD[40,41]. In the present study, PP-LAI treatment demonstrated a beneficial action on both obsessions and compulsions, and this was the first study that evaluated this long-acting formulation in 70 subjects[42].

Another remarkable finding of our study was the observed reduction in suicide ideation with PP-LAI treatment. Suicide is a significant cause of death amid subjects affected by schizophrenia[43]. The deaths by suicide have been reported in approximately 5% of subjects affected by schizophrenia though this rate appears to underestimate the phenomenon[44]. One of the suicide risk factors is represented by poor treatment adherence, and the introduction of a long-acting medication may be a good option in this case[45,46]. Moreover, rehospitalizations during antipsychotic treatment may be correlated with higher suicide risk[47,48]. Tiihonen et al.[49] found that available LAI-APs treatments led to a reduction in hospitalizations with PP-LAI superior to other treatments. As well, ensuring a continuous treatment may protect the brain contrasting the gray matter loss that is related to schizophrenia and its relapses, and this may also explain the better functioning, the overall good quality of life and the lower suicide risk associated with second generation LAI-APs[50].

The craving for substances was significantly reduced by PP-LAI as measured with VASCrav. Substance use disorders (SUDs) are relatively common in subjects affected by schizophrenia. A recent meta-analysis showed that the occurrence of any SUD amid subjects affected by schizophrenia or first-episode psychosis was 42%, with the most common SUDs being those related to illegal drugs (28%), cannabis (26%), alcohol (24%) and psychostimulants (7%)[51]. The use of LAIs has been demonstrated to be effective in reducing SUDs especially when administered at the first episode[52]. Substance use is always associated with poor outcomes in schizophrenia, in part because of its negative impact on adherence[53] and in part because the neurotoxicity of the substances[54]. To date, this was the first report that analyzed the effect of PP-LAI on substance craving and the results were similar to those reported for aripiprazole long-acting[55]. The adherence and the potential neuroprotective effects of PP-LAI and other second generation LAIs may explain this effect. Moreoever, the observed positive effects of PP-LAI on core features, depressive symptoms, anhedonia, global functioning and rumination may have also contributed to the craving attenuation and relief.

On the other hand, the total score on TAS-20, even reduced by PP-LAI administration, remained relatively stable and was not significantly influenced by the treatment, suggesting that alexithymia may be considered an independent variable not related to negative symptoms[56]. This is in accordance with previous studied that pointed out the alexithymia is a relatively stable personality trait that isn't addressed by medications[57]. However, as a reduction is TAS-20 total score was observed, we argue that alexithymia would be also a state-dependent phenomenon that increases with higher perceived stress and more prominent symptoms[56,58]. The state-dependent alexithymia may be relieved by PP-LAI treatment and this may further explain the positive effects on non-core symptoms of schizophrenia, as alexithymia is often associated with more severe depressive symptoms and anhedonia, rumination, and higher suicide risk and SUDs[59-61].

Even if the findings of the present study were interesting, the limitations must be considered. The most significant limitation of this study is the possibility of treatment selection biases as the treatment groups were not randomized or consecutive and were carefully selected, which are often the intrinsic flaws of any naturalistic, "real world" studies. Moreover, in the absence of randomization and in presence of a selection bias, one cannot completely exclude the influence of unknown con-

founders. A possible confounder lies in psychosocial interventions; although the same services were equally offered to every participant, they were not specifically quantified or analysed in this study. Furthermore, the present study did not assess the total number of relapse or hospitalization events over the entire observation period. Finally, other limitations of the present study include the small sample size and the retrospective design using secondary data.

CONCLUSIONS

The present retrospective, multicenter, non-sponsored, collaborative study showed that the early administration of PP-LAI was effective in improving the positive/negative dimensions, the disorganized and excited dimensions, depressive symptoms and the global functioning at 12 months of follow-up.

Moreover, the action of PP-LAI treatment was remarkable also on "non-core" symptoms of schizophrenia at follow-up. PP-LAI treatment was effective in reducing levels of anhedonia, obsessive-compulsive symptoms, suicide ideation and substance craving, but had a little effect on alexithymia. Even if the study' limitations must be considered, the results are encouraging and strengthen the hypothesis that second generation LAIs should be offered and introduced as early as possible to obtain a better effect on all schizophrenia dimensions and associated symptoms.

Funding source statement and conflicts of interest: all authors underscore that this paper was not funded by any research grants, and no pharmaceutical companies were informed of or involved in. The Authors have no conflicts of interest to declare.

REFERENCES

1. Galderisi S, Rucci P, Kirkpatrick B, et al. Interplay among psychopathologic variables, personal resources, context-related factors, and real-life functioning in individuals with schizophrenia: a network analysis. JAMA Psychiatry 2018; 75: 396-404.
2. Mazza M, Tripaldi S, Pino MC, et al. Assessment of attention network efficiency in schizophrenic patients with positive and negative symptoms. Riv Psichiatr 2013; 48: 252-60.
3. Fornaro M, Solmi M, Stubbs B, et al. Prevalence and correlates of major depressive disorder, bipolar disorder and schizophrenia among nursing home residents without dementia: systematic review and meta-analysis. Br J Psychiatry 2020; 216: 6-15.
4. Martinotti G, Di Iorio G, Sepede G, De Berardis D, De Risio L, Di Giannantonio M. Cannabis use and psychosis: theme introduction. Current Pharmaceutical Design 2012; 18: 4991-8.
5. Kahn RS. On the origins of schizophrenia. Am J Psychiatry 2020; 177: 291-7.
6. Correll CU. [Pharmacotherapy of schizophrenia]. Der Nervenarzt 2020; 91: 34-42.
7. Orsolini L, Tomasetti C, Valchera A, et al. An update of safety of clinically used atypical antipsychotics. Expert Opin Drug Saf 2016; 15: 1329-47.
8. De Berardis D, Marini S, Carano A, et al. Efficacy and safety of long acting injectable atypical antipsychotics: a review. Curr Clin Pharmacol 2013; 8: 256-64.
9. Fang SC, Liao DL, Huang CY, Hsu CC, Cheng SL, Shao YJ. The effectiveness of long-acting injectable antipsychotics versus oral antipsychotics in the maintenance treatment of outpatients with chronic schizophrenia. Hum Psychopharmacol 2020; 35: e2729.
10. Jeong HG, Lee MS. Long-acting injectable antipsychotics in first-episode schizophrenia. Clin Psychopharmacol Neurosci 2013; 11: 1-6.
11. Petric D, Racki V, Gaco N, Kastelan A, Graovac M. Retrospective analysis of the effectiveness and tolerability of long-acting paliperidone palmitate antipsychotic in adolescent first-episode schizophrenia patients. J Child Adolesc Psychopharmacol 2019; 29: 197-204.
12. Niolu C, Bianciardi E, Di Lorenzo G, et al. Enhancing adherence, subjective well-being and quality of life in patients with schizophrenia: which role for long-acting risperidone? Ther Adv Psychopharmacol 2015; 5: 278-88.
13. Saglam Aykut D. Comparison of paliperidone palmitate and second-generation oral antipsychotics in terms of medication adherence, side effects, and quality of life. J Clin Psychopharmacol 2019; 39: 57-62.
14. Sagud M, Simunovic Filipcic I, Jaksic N, et al. Anhedonia in schizophrenia: mini-review. Psychiatria Danubina 2019; 31 (Suppl 2): 143-7.
15. Conley RR. The burden of depressive symptoms in people with schizophrenia. Psychiatr Clin North Am 2009; 32: 853-61.
16. Yan F, Xiang YT, Hou YZ, et al. Suicide attempt and suicidal ideation and their associations with demographic and clinical correlates and quality of life in Chinese schizophrenia patients. Soc Psychiatry Psychiatr Epidemiol 2013; 48: 447-54.
17. De Berardis D, Vellante F, Fornaro M, et al. Rapid improvement of obsessive-compulsive disorder associated with schizophrenia with cariprazine add-on in a subject under paliperidone long-acting injection: a case report. Int Clin Psychopharmacol 2020; 35: 113-8.
18. Marasco V, De Berardis D, Serroni N, et al. [Alexithymia and suicide risk among patients with schizophrenia: preliminary findings of a cross-sectional study]. Riv Psichiatr 2011; 46: 31-7.
19. Valsecchi P, Barlati S, Garozzo A, et al. Paliperidone palmitate in short- and long-term treatment of schizophrenia. Riv Psichiatr 2019; 54: 235-48.
20. American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Association, 2000.
21. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13: 261-76.
22. Corigliano V, Comparelli A, Mancinelli I, et al. Long-acting injectable second-generation antipsychotics improve negative symptoms and suicidal ideation in recent diagnosed schizophrenia patients: a 1-year follow-up pilot study. Schizophr Res Treat 2018; 2018: 4834135.
23. Aas IH. Guidelines for rating Global Assessment of Functioning (GAF). Ann Gen Psychiatry 2011; 10: 2.
24. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol 1979; 47: 343-52.
25. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989; 46: 1006-11.
26. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry 1995; 167: 99-103.
27. Bressi C, Taylor G, Parker J, et al. Cross validation of the factor structure of the 20-item Toronto Alexithymia Scale: an Italian multicenter study. J Psychosom Res 1996; 41: 551-9.

28. Cuomo I, Kotzalidis GD, de Persis S, et al. Head-to-head comparison of 1-year aripiprazole long-acting injectable (LAI) versus paliperidone LAI in comorbid psychosis and substance use disorder: impact on clinical status, substance craving, and quality of life. Neuropsychiatr Dis Treat 2018; 14: 1645-56.
29. Graffino M, Montemagni C, Mingrone C, Rocca P. [Long acting injectable antipsychotics in the treatment of schizophrenia: a review of literature]. Riv Psichiatr 2014; 49: 115-23.
30. Abdel-Baki A, Medrano S, Maranda C, et al. Impact of early use of long-acting injectable antipsychotics on psychotic relapses and hospitalizations in first-episode psychosis. Int Clin Psychopharmacol 2020; 35: 221-8.
31. Montemagni C, Birindelli N, Castagna F, et al. [Functional outcome in schizophrenia: a comparative cross-sectional study on first versus second generation antipsychotics]. Riv Psichiatr 2009; 44: 110-6.
32. Brown B, Turkoz I, Mancevski B, Mathews M. Evaluation of paliperidone palmitate long-acting injectable antipsychotic therapy as an early treatment option in patients with schizophrenia. Early Interv Psychiatry 2020; 14: 428-38.
33. Ohnishi T, Kobayashi H, Yamaoka T, et al. The effects of paliperidone palmitate 1 month on the employment status and social functioning of patients with schizophrenia. Innov Clin Neurosci 2020; 17: 36-44.
34. Lee JS, Jung S, Park IH, Kim JJ. Neural basis of anhedonia and amotivation in patients with schizophrenia: the role of reward system. Curr Neuropharmacol 2015; 13: 750-9.
35. Strauss GP, Cohen AS. The schizophrenia spectrum anhedonia paradox. World Psychiatry 2018; 17: 221-2.
36. Choi SH, Lee H, Ku J, Yoon KJ, Kim JJ. Neural basis of anhedonia as a failure to predict pleasantness in schizophrenia. World J Biol Psychiatry 2014; 15: 525-33.
37. Singh A, Beniwal RP, Bhatia T, Deshpande SN. Prevalence and clinical correlations of obsessive-compulsive symptoms in schizophrenia. Asian J Psychiatr 2019; 39: 48-52.
38. Attademo L, De Giorgio G, Quartesan R, Moretti P. Schizophrenia and obsessive-compulsive disorder: from comorbidity to schizo-obsessive disorder. Riv Psichiatr 2012; 47: 106-15.
39. Nolfe G, Milano W, Zontini G, et al. Obsessive-compulsive symptoms in schizophrenia: their relationship with clinical features and pharmacological treatment. J Psychiatr Pract 2010; 16: 235-42.
40. Storch EA, Goddard AW, Grant JE, et al. Double-blind, placebo-controlled, pilot trial of paliperidone augmentation in serotonin reuptake inhibitor-resistant obsessive-compulsive disorder. J Clin Psychiatry 2013; 74: e527-32.
41. Angelucci F, Ricci V, Martinotti G, Caltagirone C, Bria P. Paliperidone for treatment of obsessive compulsive resistant symptoms in schizophrenia: a case report. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33: 1277-8.
42. Vazquez-Bourgon J, Rodriguez-Rodriguez P, Gomez-Ruiz E, Artal J, Crespo-Facorro B. Obsessive-compulsive symptoms induced by long-acting injectable paliperidone in a patient with schizophrenia: a case report. Ann Clin Psychiatry 2014; 26: 301-2.
43. Pompili M, Amador XF, Girardi P, et al. Suicide risk in schizophrenia: learning from the past to change the future. Ann Gen Psychiatry 2007; 6: 10.
44. Pompili M, Lester D, Grispini A, et al. Completed suicide in schizophrenia: evidence from a case-control study. Psychiatry Res 2009; 167: 251-7.
45. Pompili M, Orsolini L, Lamis DA, et al. Suicide prevention in schizophrenia: do long-acting injectable antipsychotics (LAIs) have a role? CNS Neurol Disord Drug Targets 2017; 16: 454-62.
46. Pompili M. [Suicide prevention and the role of the psychiatrist]. Riv Psichiatr 2014; 49: 197-8.
47. Qin P, Nordentoft M. Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. Arch Gen Psychiatry 2005; 62: 427-32.
48. Bellantuono C, Santone G. [Efficacy, tolerability and safety of paliperidone extended-release in the treatment of schizophrenia and schizoaffective disorder]. Riv Psichiatr 2012; 47: 5-20.
49. Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia. JAMA Psychiatry 2017; 74: 686-93.
50. Pompili M. Adding suicide prevention to the triple advantages of injectable long-acting second-generation antipsychotics. Front Psychiatry 2019; 10: 931.
51. Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990-2017: systematic review and meta-analysis. Drug Alcohol Depend 2018; 191: 234-58.
52. Abdel-Baki A, Thibault D, Medrano S, et al. Long-acting antipsychotic medication as first-line treatment of first-episode psychosis with comorbid substance use disorder. Early Interv Psychiatry 2020; 14: 69-79.
53. Lynn Starr H, Bermak J, Mao L, Rodriguez S, Alphs L. Comparison of long-acting and oral antipsychotic treatment effects in patients with schizophrenia, comorbid substance abuse, and a history of recent incarceration: an exploratory analysis of the PRIDE study. Schizophr Res 2018; 194: 39-46.
54. DeLisi LE, Fleischhacker WW. Schizophrenia and substance abuse: is schizophrenia forgotten? Curr Opin Psychiatry 2017; 30: 169-70.
55. Szerman N, Basurte-Villamor I, Vega P, et al. Once-monthly long-acting injectable aripiprazole for the treatment of patients with schizophrenia and co-occurring substance use disorders: a multicentre, observational study. Drugs Real World Outcomes 2020; 7: 75-83.
56. De Berardis D, Fornaro M, Valchera A, et al. Alexithymia, resilience, somatic sensations and their relationships with suicide ideation in drug naive patients with first-episode major depression: an exploratory study in the "real world" everyday clinical practice. Early Interv Psychiatry 2020; 14: 336-42.
57. Salminen JK, Saarijarvi S, Aairela E, Tamminen T. Alexithymia: state or trait? One-year follow-up study of general hospital psychiatric consultation out-patients. J Psychosom Res 1994; 38: 681-5.
58. De Berardis D, Olivieri L, Rapini G, et al. Alexithymia, suicide ideation and homocysteine levels in drug naive patients with major depression: a study in the "real world" clinical practice. Clin Psychopharmacol Neurosci 2019; 17: 318-22.
59. De Berardis D, Fornaro M, Orsolini L, et al. Alexithymia and suicide risk in psychiatric disorders: a mini-review. Front Psychiatry 2017; 8: 148.
60. Serafini G, De Berardis D, Valchera A, et al. Alexithymia as a possible specifier of adverse outcomes: clinical correlates in euthymic unipolar individuals. J Affect Disord 2020; 263: 428-36.
61. De Berardis D, Vellante F, Fornaro M, et al. Alexithymia, suicide ideation, affective temperaments and homocysteine levels in drug naive patients with post-traumatic stress disorder: an exploratory study in the everyday 'real world' clinical practice. Int J Psychiatry Clin Pract 2020; 24: 83-7.