STUDY ON TOLERABILITY AND EFFICACY OF PALIPERIDONE PALMITATE, OLANZAPINE PAMOATE AND RISPERIDONE LONG ACTING INJECTION IN A ROMANIAN SAMPLE OF PATIENTS WITH SCHIZOPHRENIA

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Abstract

Due to its debilitating character and the propensity to chronicity, schizophrenia is one of the most important psychotic disorder of modern times. Recent studies have emphasized the superiority of depot long-acting antipsychotics (LAIs) versus oral antipsychotics in terms of remission maintenance and the prevention of relapses and (re)hospitalization events. Here we designed a mirror-image study meant to analyse the efficacy of one-year long LAI therapy for 21 patients admitted to the “Eduard Pamfil” Psychiatry Clinic Timișoara for which a previous one-year long oral antipsychotic therapy didn’t provide satisfactory results. To further strengthen our analysis, we have also compared the mirror-image data set with the results of a parallel analysis of a control group of 11 patients under therapy with the same oral antipsychotics for an equivalent period (two years) of time. Both analyses have shown a significant reduction of re-hospitalization accompanied by a substantial alteration of PANSS scores dynamics in the group of patients treated with LAIs, thus proving the overall superiority of LAIs in comparison with oral antipsychotics. Last but not least, we critically discuss two rather sensitive issues in schizophrenia therapy, the high level of polypharmacy and a hidden bias of clinical psychiatrists in selecting the patients suitable for therapeutic switch from oral to depot antipsychotics.

Rezumat

Studiile existente au evidențiat superioritatea antipsohticelor depot (LAI) față de antipsihoticele orale, în menținerea remisunii, prevenirea recidivilor și implicit a rehospitalizărilor. Am efectuat o cercetare de tip mirror-image study, care a inclus 21 de pacienți ce au fost inițiați în cadrulClinicilui de Psihiatrie „Eduard Pamfil” Timișoara pe unul din antipsihotice disponibile în țara noastră, după eșecul tratamentului cu antipsihotice orale ce a avut o durată de minim un an de zile anterior acestei inițiieri. Pentru a reconfirma eficacitatea măsurată prin numerul mediu de spitaliizări a fost făcută și o a doua analiză comparativă folosind datele unui grup de control format din 11 pacienți ce au beneficiat de tratament cu un același antipsihotic oral pe o durată de minim 2 ani de zile. Atât analiza de tip mirror-image efectuată în cadrul grupului cu antipsihotice depot, cât și compararea acestuia cu grupul de control a evidențiat o reducere semnificativă a numărului de spitaliizări sub tratamentul cu antipsihotice depot. Mai mult, evoluția medielor scurilor în scala PANSS și a celor din subscalele acesteia a fost una semnificativă în favoarea eficacității tratamentului cu antipsihotice depot. Prezența evenimentelor adverse legate de tratament este o realitate clinică și apare la o majoritate covârșitoare a pacienților tratați cu antipsihotice LAI. Nivelul crescute de polipragmazie în tratamentul schizofreniei în ambele grupuri luate în considerare, precum și existența unui anumit subiectivism al practicienilor în alegerea cazurilor pentru tratamentul cu antipsihotice depot, au constituit alte două rezultate valoroase ale cercetării noastre.

Keywords: long-acting injection, antipsychotics, efficacy

Introduction

Considered the most disabling major psychiatric disorder, schizophrenia is affecting more than 23 million people worldwide, although with a lower prevalence in comparison with other mental health conditions [1]. Moreover, a retrospective matched cohort study for German society in 2008 revealed that the total annual costs attributable to schizophrenia (including service utilization and premature mortality) ranged between €9.63 billion and €13.52 billion. It was estimated that therapy optimization might lower the financial
burden associated with this disorder with up to 22% [2, 3]. One of the main issues related to schizophrenia therapy is the rather low (around 50%) rates of adherence to medication plan (in comparison to other chronic illnesses), which leads not only to high rates of discontinuity, but also to a twofold increase in the risk of relapse in comparison with continuous maintenance therapy [4, 5]. This also translates into an increased frequency and duration of hospitalizations, poorer quality of life and social functioning, disease chronicity and increased health costs [6, 7]. It has been shown that patients on long-term, maintenance antipsychotic therapy experience fewer relapses and require less hospitalization compared to those on intermittent therapy regimens [7].

Despite the contradictory findings (randomized control trials – RCTs - vs. mirror-image studies) regarding their efficiency in comparison to oral antipsychotics [8, 9], long-acting injectable antipsychotics (LAIs) are currently considered an important options meant to ensure the adherence to therapy. The particularity of mirror-image studies resides in the comparison of the same subjects for the same period of time before and after initiation of the researched intervention (also known as pre-post comparison), thus limiting the differences related to the metabolizing profiles of different compounds which varies among individuals. The limitations of RCTs reside in the inclusion of patients with better treatment adherence and, hence, better illness evolution, while the limitations of mirror studies are the expectancy effect, the natural course of disease, and the possibility of time bias. Nevertheless, the mirror-image studies compare, for the same patients, a period of oral antipsychotics with a period with LAIs treatment and are expected to reflect more precisely the true status of therapy response and the hospitalization risk for the period of the 6 months after LAI discontinuation in the same patients [10]. Although the 2014 guidelines of the National Institute for Health and Care Excellence, as well as the American and Australian guidelines, recommend LAI from the very first psychotic episode and for patients that explicitly opt for this therapy, there is an inexplicable reluctance of psychiatry clinicians in our country to adhere to this recommendation, LAI being considered merely an option for patients who fail oral antipsychotic therapy [11-13].

The present mirror-image study aimed to evaluate the efficacy of LAIs compared to oral antipsychotics medication in patients with schizophrenia, in terms of number of hospitalizations, and changes in PANSS scores within the 12 months following LAIs initiation. The LAIs used in this study were of risperidone, paliperidone palmitate and olanzapine pamoate. Major active metabolite of risperidone (9-hydroxy-risperidone), paliperidone is a benzisoxazole LAI (atypical) antipsychotic, serotonin 5HT2A and dopamine D2 receptor antagonist. Paliperidone is also known for its increased affinity for 5HT7 receptor, whose inhibition would lead to mood and cognitive improvement. Olanzapine pamoate is a thienobenzodiazepine derivative LAI (atypical) antipsychotic, 5HT2A and D2 antagonists, olanzapine is also known for its affinity for 5HT2C and 5HT6 receptors whose inhibition would improve cognitive function and act as antidepressant [14, 15].

Materials and Methods

Population and study design

Our one-year mirror-image study included 21 schizophrenia patients on oral antipsychotics regimens, with at least one hospitalization in the “Eduard Pamfil” Psychiatry Clinic Timișoara, Romania with mirror periods of 365 days either side of the first LAIs injection. The control group included 11 schizophrenia patients on the same oral antipsychotics regimen for two years and with at least one hospitalization in the same clinic, for which retrospective data from the medical records were used. The sampling method was by convenience. All patients enrolled provided a written informed consent. Within the one-year follow-up, the patients were assessed using the PANSS scale at baseline, 6 months, and 12 months. The study was carried out in accordance with the Code of Ethics of the Declaration of Helsinki and was approved by the institutional review board.

Inclusion criteria

For the study group: the age at onset between 18 to 65 years, diagnosis of schizophrenia according to ICD 10, at least 1 year of oral antipsychotic treatment before the initiation of LAIs regimen, ability to provide a written informed consent, lack of psychiatric comorbidities, participation to all periodical psychiatric evaluations scheduled within the 365 days following the LAI initiation.

For the control group: the age at onset between 18 to 65 years, diagnosis of schizophrenia according to ICD 10, at least 2 years of the same oral antipsychotic therapy, ability to provide a written informed consent, lack of psychiatric comorbidities, medical records for all periodical psychiatric evaluations scheduled within the two years taken into consideration.

Measures

The primary outcome is represented by the total number of psychiatric hospitalizations in the mirror periods and during the two years prior to the hospitalization, for the study group and control group, respectively. PANSS total scale and subscales assessments’ scores at baseline, 6 months and 12 months were analysed comparatively in both the study and the control group. PANSS scale is a psychiatric rating scale consisting of 30 items which can be divided into 3 subscales: positive symptoms (7 items), negative symptoms (7 items), general psychopathology (16 items). Each item includes a set of carefully written anchors for each level of severity, from 1 (absent) to 7 (extreme). [16].
The following abbreviations related to the PANSS scale were used in figures and tables: P.LAI - positive subscale mean score of LAI group; P.OA - positive subscale mean score of control group; N.LAI - negative subscale mean score of LAI group; N.OA - negative subscale mean score of control group; G.LAI - general psychopathology subscale mean score of LAI group; G.OA - general psychopathology subscale mean score of control group; PANSS.LAI - PANSS mean total score of LAI group; PANSS.OA - PANSS mean total score of control group; P.Base - positive subscale mean score of LAI group at baseline; P.6M - positive subscale mean score of LAI group at 6 month; P.12M - positive subscale mean score of LAI group at 12 month; N.Base - negative subscale mean score of LAI group at baseline; N.6M - negative subscale mean score of LAI group at 6 month; N.12M - negative subscale mean score of LAI group at 12 month; G.Base - general psychopathology subscale mean score of LAI group at baseline; G.6M - general psychopathology subscale mean score of LAI group at 6 month; G.12M - general psychopathology subscale mean score of LAI group at 12 month; PANSS.Base - mean total score of LAI group at baseline; PANSS.6M - mean total score of LAI group at 6 month; PANSS.12M - mean total score of LAI group at 12 month.

The educational level was categorized as follows: 1 - primary school, 2 - gymnasium (secondary education), 3 - high school, 4 - at least university studies. The level of social network support was evaluated as follows: 1 - lives alone, 2 - lives together with friends/acquaintances, 3 - lives together with a close relative (father, mother, siblings, children), 4 - lives with his/her partner/spouse. Alcohol and tobacco consumption were assessed based on patients’ self-evaluation and medical recordings.

In accordance to previously published studies, we conceived a 7-item checklist regarding the first 7 treatment-emergent adverse events (TEAEs) observed in the LAI study group.

All demographic and clinical data of the recruited subjects were unitary standardized and collected from medical patients’ records.

**Statistical analysis**

Statistical analyses were performed using STATA version 15 for Windows. Descriptive statistics were conducted contingent on analysis demands. In order to compare the frequencies of categorical variables, the Chi-squared test was performed. A two-tailed parametric t-test was used for continuous data analyses and a non-parametric rank test (Mann-Whitney U-Test) was performed to analyse categorical variables originating from two independent subsamples. The Wilcoxon signed-rank test was used to compare repeated measurements of the PANSS scale and subscales mean scores of the studied group.

**Results and Discussion**

**Sociodemographic and anamnestic data**

In line with previously published data, there are no statistically significant differences between the study group and control group regarding the age at the moment of enrolment (38.52 vs. 36.45; p = 0.583) and the age at the onset of symptoms (27.19 vs. 23.45; p = 0.113) ([17, 18] (Table I).

There is no statistical difference between the sex ratios in the two groups of patients (57.1% vs. 63.6%; p = 0.722), which both exhibit a prevalence of males vs. females. This bias versus males has been also reported in previous studies on schizophrenia, based on much wider cohorts of patients [18, 19] (Table I).

**Table I**

| Sociodemographic data                              | Patients on LAI antipsychotics | Patients on oral antipsychotics | Statistical significance |
|-----------------------------------------------------|--------------------------------|---------------------------------|--------------------------|
| Average current age (SD)                           | 38.52 (10.472)                 | 36.45 (9.004)                   | t = 0.556; p = 0.583     |
| Average age at the onset (SD)                      | 27.19 (6.653)                  | 23.45 (5.007)                   | t = 1.631; p = 0.113     |
| Gender, male                                       | 12 (57.1%)                     | 7 (63.6%)                       | χ² = 0.126; p = 0.722    |
| Educational level, mean ranks                      | 17.50                          | 14.59                           |                         |
| Residency - Urban area, n (%)                      | 16 (76.2%)                     | 8 (72.7%)                       | χ² = 0.046; p = 0.830    |
| Professional status - Employed or Student, n (%)   | 11 (52.4%)                     | 0 (0.0%)                        | Fischer’s Exact Test;    |
| Marital status - with intimate partner, n (%)      | 7 (33.3%)                      | 2 (18.2%)                       | χ² = 0.820; p = 0.365    |
| Smoking, n (%)                                     | 10 (47.6%)                     | 8 (72.7%)                       | χ² = 1.849; p = 0.174    |
| Occasional alcohol consumption, n (%)              | 6 (28.6%)                      | 4 (36.4%)                       | χ² = 0.204; p = 0.652    |
| Positive family history for psychiatric conditions, n (%) | 15 (71.4%)                    | 10 (90.9%)                      | χ² = 1.603; p = 0.205    |
| Quality of social support network, mean ranks      | 17.40                          | 14.77                           | Mann Whitney U = 96.500; p = 0.394 |

The level of significance for all analyses was set at α = 0.05; The listed percentages are reported to either strata considered separately.

Educationally, the study group patients ranked higher (17.50 vs. 14.59; p = 0.352) compared to the control group ones, although this difference did not reach statistical significance. Moreover, half of the study group patients were still active professionally, while in the control group all patients were retired, socially
assisted or without a job (p = 0.005). This might point towards a psychiatrists’ bias on selection of patients for switch from oral antipsychotics to LAI therapy; it might also be worth noting that patients on LAI have better (but statistically not significant) social network support compared to patients on oral antipsychotics (17.40 vs. 14.77; p = 0.394), despite their very similar place of residence status (76.2% vs. 72.7%; p = 0.830). Taking into consideration that all patients were covered by national health insurance (thus benefiting of 100% reimbursement of LAIs), this suggests that LAIs prescription is not influenced by the accessibility of the injectable therapy. Altogether, our data indicate a remarkable socio-demographic homogeneity between the two groups (see Table I).

Self-reported alcohol and tobacco use was higher in the control group compared to study group (72.7% vs. 47.6%, p = 0.174 for tobacco and 36.4% vs. 28.6%, p = 0.652 for alcohol). Noteworthy, as previously reported, the incidence of smokers in both schizophrenia groups was higher when compared to the general population (28%) [20-22] (Table I).

The pharmacological variables of the compared groups LAI antipsychotic group

Paliperidone palmitate has been prescribed to 10 patients (47.6%), 115 mg was the average dosage at 28 ± 4 days interval. Of note, paliperidone therapy was initiated after a previous clinical stabilization with oral antipsychotics: risperidone 6mg daily (5 patients), amisulpride 300 mg daily (3 patients), olanzapine 13.75 mg orally/daily (8 patients), in accordance with clinical therapy guides [25] and risperidone 12 mg daily (one patient) (Table II).

Risperidone LAI has been prescribed to 2 patients (9.5%), 100mg was the average monthly dosage fractionated at 14 days interval (Table II); both patients have been previously clinically stabilized with oral risperidone 9 mg daily, in accordance with clinical therapy guides [26] (Table II).

Descriptive analysis of the study group reveals a high level of polypharmacy, the most frequent association being with hypnotics (76.2%) mood stabilizers (57.1%), benzodiazepines (57.1%), anticholinergics (47.6%) and antidepressants (28.6%) (Table II). This indicates a trend among clinical psychiatrists to combine multiple psychotropic medications in order to contain all schizophrenia associated symptoms in this group of patients, similar to previous results [27]. It is also possible that nowadays oral and LAI antipsychotics do not address the entire spectrum of schizophrenia symptomatology, including insomnia, anxiety, psychomotor unrest [28].

### Table II

| Antipsychotics LAI group, n (%) | The average dose (per 30 days) | Previous oral antipsychotic - n (%) | Other associated psychotropics to LAI antipsychotics, n (%) |
|---------------------------------|-------------------------------|-----------------------------------|----------------------------------------------------------|
| Paliperidone palmitate - 10 (47.6%) | 115 mg                         | Risperidone - 5 (50%), 6 mg       | Mood stabilizers - 12 (57.1%) Anticholinergic (trihexyphenidylum) - 10 (47.6%) Benzodiazepines - 12 (57.1%) |
|                                 |                               | Amisulpride - 3 (30%), 733.33 mg  |                                                         |
|                                 |                               | Olanzapine - 1 (10%), 10 mg      |                                                         |
|                                 |                               | Haloperidol - 1 (10%), 10 mg     |                                                         |
| Olanzapine Pamoate - 9 (42.9%)  | 535 mg                        | Olanzapine - 8 (88.9%), 13.75 mg | Hypnotics - 16 (76.2%) Antidepressants - 6 (28.6%) |
|                                 |                               | Risperidone - 1 (11.1%), 12 mg   |                                                         |
|                                 |                               | Risperidone - 2 (100%), 9 mg     |                                                         |
| Risperidone - 2 (9.5%)          | 100 mg                        |                                   |                                                         |

### Antipsychotics LAI group, n (%) | The average dose (per 24 h) | Other associated psychotropics to oral antipsychotics, n (%) | Mood stabilizers - 8 (72.7%) Anticholinergic (trihexyphenidylum) - 3 (27.3%) Benzodiazepines - 8 (72.7%) Hypnotics - 9 (81.8%) Antidepressants - 2 (18.2%) |

| Antipsychotics oral group, n (%) | The average dose (per 24 h) | Other associated psychotropics to oral antipsychotics, n (%) |
|----------------------------------|----------------------------|-------------------------------------------------------------|
| Paliperidone - 2 (18.2%)         | 6 mg                      |                                                             |
| Risperidone - 2 (18.2%)          | 6 mg                      |                                                             |
| Amisulpride - 1 (9.1%)           | 800 mg                    |                                                             |
| Clozapine - 1 (9.1%)             | 150 mg                    |                                                             |
| Ziprasidone - 1 (9.1%)           | 120 mg                    |                                                             |
| Sulpiride - 1 (9.1%)             | 600 mg                    |                                                             |
| Aripiprazole - 1 (9.1%)          | 30 mg                     |                                                             |
| Haloperidol - 1 (9.1%)           | 10 mg                     |                                                             |
| Quetiapine - 1 (9.1%)            | 400 mg                    |                                                             |

Note: The listed percentages are reported to either strata considered separately.

### Oral antipsychotic group

The control group patients received oral, mostly atypical antipsychotics: paliperidone (two patients), risperidone (two patients), amisulpride (one patient), clozapine (one patient), ziprasidone (one patient), aripiprazole (one patient), quetiapine (one patient), sulpiride (one patient).
and haloperidol (one patient) (Table II). The wide range of antipsychotics used reflects decisions based on evaluation of efficacy, but, most probably, also tolerance and patients’ safety [29, 30].

The associated psychotropic medication received by the control group of patients included hypnotics (81.8%), mood stabilizers (72.7%), benzodiazepines (72.7%), anticholinergics (27.3%) and antidepressants (18.2%) (Table II). Although the comparison with LAI group does not lead to statistical significance, one can notice a tendency of their association with oral therapy, most probably reflecting a tendency to polypharmacy among clinical psychiatrists dealing with schizophrenic patients.

The efficacy of long-acting injectable antipsychotics

Primary outcomes: number of hospitalizations

Wilcoxon signed-rank test analysis of hospitalizations in the mirror-image study group showed a statistically significant decrease of hospitalization events after the onset of LAI therapy (p = 0.003) (Figure 1A).

![Figure 1](image)

**Figure 1.**
The difference between the average number of psychiatric hospitalizations before and after the LAI antipsychotic initiation in the studied group (Figure 1A) and the difference between the two compared groups regarding the average numbers of psychiatric hospitalizations during the entire period of 2 years (Figure 1B) (LAI – studied group of patients on LAI antipsychotics; OA – control group of patients on oral antipsychotics)

Further stratification of the LAI cohort (after exclusion of risperidone-treated patients) failed to find statistically significant changes in the hospitalization events between paliperidone palmitate and olanzapine pamoate subgroups (Mann-Whitney U Test; p = 0.780), suggesting the two compounds have comparable efficacies. Furthermore, LAI therapy significantly reduced the number of hospitalization events in the entire two years mirror-image in the study group compared to hospitalization events during an equivalent period of time in the controls (p < 0.001) (Figure 1B). Our results regarding the superior efficacy of LAI in preventing re-hospitalization in schizophrenic patients are in line with previous results [31]. An ample meta-analysis of 25 mirror-image studies on 5940 patients from 28 countries found that LAIs are superior to oral antipsychotics in terms of prevention of re-hospitalizations of schizophrenic patients [9]. It is generally accepted nowadays that an increase in the number and duration of hospitalization events is usually associated with non-adherence to therapy and psychotic symptoms resistance to therapy with oral antipsychotics [32]. Furthermore, several studies have shown that, despite their side effects, paliperidone palmitate and olanzapine pamoate therapies show similar cost-efficiency characteristics [33-35].

Secondary outcomes: mean differences in PANSS total and subscale scores

Comparative overall analysis of PANSS scores in the study group (from the onset of LAI therapy) and control group (retrospective, from the last hospitalization) showed no significant changes in the severity of the symptoms (Figure 2A). Therefore, the two groups of patients could be considered equivalent in terms of the severity and complexity of clinical symptomatology. However, analysis of PANSS scores’ dynamics shows a significant change starting with the sixth month and continuing at 12 months after LAI therapy onset (Figure 2B), thus confirming the efficacy of LAI therapy versus oral antipsychotics, proving to be a feasible approach even from the first episode of psychosis. Moreover, LAI efficacy resides also in improving both the positive and especially the negative symptomatology, and also the associated symptoms as well.
The differences of PANSS subscales and total mean scores between the two researched groups, at the time of LAI initiation and at the beginning of last hospitalization respectively (Figure 2A) and the dynamic of PANSS subscales and total mean scores in LAI group after the switch from oral antipsychotics (Figure 2B) (mean ± S.D., ** = p < 0.01, *** = p < 0.001; P LAI - positive subscale mean score of LAI group; P OA - positive subscale mean score of control group; N LAI - negative subscale mean score of LAI group, N OA - negative subscale mean score of control group; G LAI - general psychopathology subscale mean score of LAI group, G OA - general psychopathology subscale mean score of control group; PANSS LAI - PANSS mean total score of LAI group, PANSS OA - PANSS mean total score of control group; P Base - positive subscale mean score of LAI group at baseline; P 6M - positive subscale mean score of LAI group at 6 month; P 12M - positive subscale mean score of LAI group at 12 month; N Base - negative subscale mean score of LAI group at baseline; N 6M - negative subscale mean score of LAI group at 6 month; N 12M - negative subscale mean score of LAI group at 12 month; G Base - general psychopathology subscale mean score of LAI group at baseline; G 6M - general psychopathology subscale mean score of LAI group at 6 month; G 12M - general psychopathology subscale mean score of LAI group at 12 month; PANSS Base - mean total score of LAI group at baseline; PANSS 6M - mean total score of LAI group at 6 month; PANSS 12M - mean total score of LAI group at 12 month).

**Treatment-emergent adverse events (TEAEs)**

After excluding the two risperidone LAI treated subjects (due to the low number in this subgroup), TEAEs were observed in 16 (84.2%) subjects, of which 1 (5.3%) had 4 TEAEs, 2 (10.5%) had 3 TEAEs, 7 (36.8%) had 2 TEAEs and 6 (31.6%) presented 1 TEAE.

Among the patients receiving paliperidone palmitate, the following TEAEs were noted in decreasing frequency order: injection site pain in 4 subjects (40.0%), tremor in 3 subjects (30.0%), insomnia in 3 subjects (30.0%), akathisia in 2 subjects (20.0%) and headache and somnolence in one patient each (10.0%), respectively (Table III).

**Treatment-emergent adverse events in patients treated with LAI antipsychotics**

| TEAEs                  | Paliperidone Palmitate (N = 10), n (%) | Olanzapine Pamoate (N = 9), n (%) |
|------------------------|---------------------------------------|-----------------------------------|
| Injection site pain    | 4 (40.0%)                             | 1 (11.1%)                         |
| Somnolence             | 1 (10.0%)                             | 3 (33.3%)                         |
| Insomnia               | 3 (30.0%)                             | 1 (11.1%)                         |
| Weight increased > 10% | 2 (20.0%)                             | 5 (55.6%)                         |
| Headache               | 1 (10.0%)                             | 2 (22.2%)                         |
| Tremor                 | 3 (30.0%)                             | 1 (11.1%)                         |
| Akathisia              | 2 (20.0%)                             | 1 (11.1%)                         |

N – total number of patients; n – number of affected patients; TEAEs – treatment-emergent adverse events.

In the group of patients treated with olanzapine pamoate the frequency of TEAEs was: weight increase of over 10% in 5 subjects (55.6%), somnolence in 3 subjects (33.3%), headache in 2 subjects (22.2%), and tremor, akathisia and injection site pain in 1 subject each (11.1%) (Table III).

It is worth mentioning that the above results, even though in line with previously published data, the frequency of TEAEs was higher possibly due to the relative low number of subjects included and the sampling method [36-37].

**Conclusions**

Our data demonstrate for the first time the efficacy of LAI antipsychotics in a Romanian population, in terms of hospitalization events and improvement of the polymorphic clinical symptomatology of schizophrenia. Unequivocally, when consistently administered, LAI antipsychotics prove to be superior to oral antipsychotics.
mainly by improving therapy non-adherence. Furthermore, by reducing the level of cumulative side effects and of possible drug interactions, consistent administration of LAIs might contribute to the reduction of polypharmacy, a practice much too common in schizophrenia therapy.

The high prevalence of TEAEs is part of the clinical reality that should be considered by psychiatric practitioners especially due to the fact that they represent the most common cause of non-adherence towards antipsychotic treatment.

Last but not least, the socio-demographic data of the present study indicate a possible bias in clinical psychiatrists practice related to the decision to switch to injectable antipsychotics, an issue deserving further, more in depth analysis.

Conflict of interest
The authors declare no conflict of interest.

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