Long Term Efficacy of the Treatment with Olanzapine Pamoate, Risperidone and Aripiprazole Monohydrate

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The use of long-acting injectable antipsychotics (LAIs) is considered to be an important treatment option, especially in early stages of schizophrenia. The aim of this study was to evaluate the efficacy, safety and sustained remission in schizophrenia patients treated with three of the available LAIs substances: olanzapine pamoate, risperidone microspheres and aripiprazole monohydrate. A retrospective chart review study evaluating the efficacy of LAIs compared to oral antipsychotics during a five years period was performed. Of the 102 patients included in the study, 52 (50.9%) continued LAIs: olanzapine pamoate (n = 20, 38.4%), risperidone microsphere (n = 22, 42.3%), aripiprazole monohydrate (n = 10, 19.3%). In the LAIs group the number of relapses was smaller than in the oral antipsychotics group (12 vs. 23, P < 0.05) as well as the number of admissions (15 vs. 30, P < 0.05). In conclusion, relapse in schizophrenia is strongly related to nonadherence. LAIs prescription overall was underutilized despite their efficacy. Future randomized studies are needed to evaluate the long term efficacy of LAIs compared to oral treatment.

Keywords: LAIs substances, olanzapine pamoate, risperidone, aripiprazole monohydrate, oral antipsychotic, relapse

Nonadherence rates in patients with schizophrenia are known to be high in comparison to patients with other diseases [1-3]. Estimates in the literature range between 40 and 50%, but can be as high as 89% [4]. The use of long-acting injectable antipsychotics (LAIs) is considered to be an important treatment option [5]. Current guidelines recommend LAIs when adherence is inadequate [6, 7].

Side-effects and pregnancy are considered the main causes of treatment abandon in schizophrenia [8, 9]. The consequence of nonadherence is the evolution and progression of schizophrenia with relapses, admissions, and finally with institutionalization [10, 11].

LAIs represent a newer formula of antipsychotics, with different pharmacokinetics, so that they can be administered via intramuscular injection, once every two weeks, once a month or once every three months.

Olanzapine pamoate formula is: 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b] benzodiazepine 4,4’-Methylenebis[3-hydroxy-2-naphthalenecarboxylate] Monohydrate [1, 6]. Olanzapine’s main characteristics are a high affinity for dopamine receptors types I, II and IV; 5-hydroxy-tryptamine receptors, type 2A, 2C and 3; α2 adrenergic, H1 histaminergic and five muscarinic receptors, and a low affinity for type 5 5-hydroxy-tryptamine receptors, adrenergic receptors type α1 and β, gamma-aminobutyric acid type A receptors and benzodiazepine receptors [12].

The vehicle used in olanzapine LAI is olanzapine pamoate. The organic salt dissolves slowly intramuscularly, releasing acidic and basic molecules: olanzapine-free base, and pamoic acid. Subsequent absorption into muscle tissue is rapid. Olanzapine is metabolized in the liver by conjugation and oxidation; the major circulating metabolite is 10-N-glucuronon conjugate, which does not cross the blood-brain barrier. The cytochrome P450-CYP1A2 and CYP2D6 isoenzymes contribute to the formation of N-dimethyl and 2-hydroxymethyl metabolites which, in animal studies, showed in vivo pharmacological activity significantly lower than olanzapine. Mainly untransformed olanzapine is responsible for the pharmacological effects. After a single intramuscular injection of olanzapine LAI, the slow release of the olanzapine pamoic salt immediately begins in muscle tissue and ensures a slow and continuous release of olanzapine for more than 4 weeks. Olanzapine release gradually decreases in the following 8 to 12 weeks [13, 14]. Risperidone, as well as its active metabolite, 9-hydroxy-risperidone, is a potent antagonist of the 5-hydroxytryptamine type IIA and of type II dopamine receptors, and with a low affinity for muscarinic and β adrenergic receptors [3, 5]. Risperidone formula is 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropryrido[1,2-a]pyrimidin-4-one [15].

As a vehicle, the product uses risperidone coated in polymer microspheres. The microsphere formula contains risperidone or 9-hydroxy-risperidone or salts, and a polymer blend with a first uncapped lactide-glycolide copolymer and a second uncapped lactide-glycolide copolymer, in which the first uncapped lactide-glycolide copolymer is a copolymer with a high intrinsic viscosity and the second uncapped lactide-glycolide copolymer is a copolymer with a low intrinsic viscosity. It is metabolized by CYP 450-2D6 enzyme. Risperidone LAI has a half-life of 3-6 days. The releasing period is approximately 7-8 weeks after the last
Experimental studies have shown that aripiprazole acts as an antagonist of the post-synaptic, and agonist of presynaptic dopaminergic autoreceptors; this demonstrates that, psychopharmacologically, this antipsychotic has dual agonist-antagonist properties. Another important target for aripiprazole is serotonergic neurotransmission; this antipsychotic is an important antagonist of the 5-hydroxytryptamine IIA receptor, which is associated with an additional efficacy on negative and cognitive symptoms and with low extrapyramidal side effects. On the 5-hydroxytryptamine IA receptor, the interaction is agonist type, which results in an improvement of depression and anxiety [17-24].

The formula for the long acting injection solution is crystalline aripiprazole monohydrate, with the formula: 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one hydrate [25].

Both molecules, aripiprazole parent molecule and its main metabolite, dehydro-aripiprazole, are active. This metabolite accounts for 29% of the activity. The key to its long acting property is the low solubility of aripiprazole particles. Aripiprazole is extensively metabolized by the liver, particularly by three biotransformation pathways: dehydrogenation, hydroxylation and N-dealkylation.

This study focuses on olanzapine, risperidone and aripiprazole, atypical antipsychotics with LAI formulation, in the treatment of schizophrenia.

**Experimental part**

**Objectives**

The aim of this study was to evaluate the efficacy, safety and sustained remission in schizophrenia patients treated with three of the available LAI substances: olanzapine pamoate, risperidone microspheres and aripiprazole monohydrate.

**Study subjects**

The patients enrolled in this study were recruited from the patients admitted to the Clinic of Psychiatry, part of the Clinical Psychiatry and Neurology Hospital Brasov, Romania. The clinic is composed of two 60-bed units, each self-organized. Patients are admitted, on alternate days, to one of the two units. The clinical care is coordinated by board-certified psychiatrists.

Five hundred sixty patients diagnosed with schizophrenia, according to DSM-V criteria [26] were admitted in the clinic between January 1, 2012 to December 31, 2013. Within this cohort, 52 patients, representing 9.28 % agreed LAIs treatment (LAIs group). This group was compared to a control group, enrolling 50 patients who refused treatment with LAIs, so they received oral second-generation antipsychotics (SGA) (SGA group).

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After the index admission the patients were followed-up for 60 months. The Consent for treatment was obtained in instances of elsewhere hospitalization. The lack of information on past admissions in other setting may likely have resulted in underestimation of the true adherence rate.

**Conclusions**

We found that the majority of patients with schizophrenia admitted to our hospital had adherence-related problems. LAIs prescription overall was underutilized when indicated on the basis of our criteria. LAIs prescription resulted in significantly less relapses and admission with better outcome.

Results and discussions

Of the 102 patients included in this study, 52 (50.9%) continued LAIs: olanzapine pamoate (n = 20, 38.4%), risperidone microsphere (n = 22, 42.3%), aripiprazole monohydrate (n = 10, 19.3%). Demographics and results of the switch are shown in table 1.

The results show a strong benefit of the LAIs treatment in prevention of relapses compared to oral antipsychotics. The distribution of antipsychotics in each group is presented in figure 1. The lack of information on past admissions in other setting may likely have resulted in underestimation of the true adherence rate.

**References**

### Table 1
DEMOGRAPHIC DATA OF THE TWO STUDY GROUPS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LAIs GROUP n = 52</th>
<th>SGA GROUP n = 50</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male [n (%)]</td>
<td>22 (43.3%)</td>
<td>24 (48%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Time evaluation [months, mean±SD]</td>
<td>55±5.6</td>
<td>52±7.8</td>
<td>0.62</td>
</tr>
<tr>
<td>Reason for admission</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- nonadherence [n (%)]</td>
<td>36 (69.2%)</td>
<td>33 (66%)</td>
<td>0.89</td>
</tr>
<tr>
<td>- alcohol abuse [n (%)]</td>
<td>12 (23.1%)</td>
<td>11 (22%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Age [years, mean±SD]</td>
<td>44.7±11.22</td>
<td>42.3±4.12</td>
<td>0.76</td>
</tr>
<tr>
<td>Age of onset [years, mean±SD]</td>
<td>23.4±4.17</td>
<td>24.2±4.78</td>
<td>0.88</td>
</tr>
<tr>
<td>Duration of illness [years, mean±SD]</td>
<td>16.3±13.33</td>
<td>17.2±16.65</td>
<td>0.92</td>
</tr>
<tr>
<td>Number of hospitalization (lifetime)</td>
<td>10.67 (5.38)</td>
<td>12.60 (3.55)</td>
<td>0.7</td>
</tr>
<tr>
<td>Days of hospitalizations (lifetime)</td>
<td>456.56 (120.20)</td>
<td>444.20 (140.76)</td>
<td>0.11</td>
</tr>
<tr>
<td>Olanzapine before [n (%)]</td>
<td>44 (84.16%)</td>
<td>43 (86%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Risperidone before [n (%)]</td>
<td>10 (19.22%)</td>
<td>12 (24%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Aripiprazol before [n (%)]</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous antipsychotic number [mean]</td>
<td>4.3</td>
<td>5.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Relapse [n (%)]</td>
<td>12 (24.24%)</td>
<td>23 (75.76%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hospitalization [n]</td>
<td>15</td>
<td>30</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Fig. 1. Distribution of LAIs, respectively, SG oral antipsychotics used in the treatment of schizophrenia patients enrolled in the study [n (%)]


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