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 antispychotics 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 treatment may be most appropriate for patients in early stages of the disease, when poor adherence occurs. Nevertheless, there are few data regarding the long-term efficacy, safety and sustained remission in patients treated with LAIs.

LAIs represent a newer formula of antipsychotics, with a 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 type I, II and IV; 5-hydroxi-tryptamine receptors, type 2A, 2C and 3; α1 adrenergic, H1 hystaminergic and five muscarinic receptors, and a low affinity for type I 5-hydroxi-tryptamine receptors, adrenergic receptors type α2 and β, gamma-amino-butyric 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-glucuronoconjugate, 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-hydroxi-risperidone, is a potent antagonist of the 5-hydroxi-tryptamine type IIA and of type II dopamine receptors, and with a low affinity for muscharinic 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-tetrahydropyrido[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

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injection [16].

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 serotoninergic neurotransmission; this antipsychotic is an important antagonist of the 5-hydroxitryptamine IIA receptor, which is associated with an additional efficacy on negative and cognitive symptoms and with low extrapyramidal side effects. On the 5-hydroxitryptamine 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*). After the index admission the patients were followed-up for 60 months. The Consent for treatment was obtained in accordance with the procedures stipulated by the hospital's Ethics Committee. The retrospective chart review was approved by the hospital's Ethics and Research Committees, in accordance to some published models [27].

Parametres and laboratory assessments

Blood pressure, temperature, heart rate, as well as height, weight, abdominal circumference were measured. A complete blood count, metabolic panel, hepatic panel, renal, inflammatory and electrolytic panels, as well as prolactin levels were assessed. 12-lead ECG was also performed. The severity of the illness was ascertained using the Clinical Global Impression Scale (CGI) [28]. Since the study was retrospective, adverse drug effects such as extrapyramidal symptoms were assessed by the use of anticholinergic drugs.

Statistical analysis

Demographic, clinical and biochemical characteristics of the schizophrenia patients treated with the targeted LAIs and SGA oral antipsychotics were compared using analysis of variance. The primary outcome was the time interval until relapse (in months) in LAIs group compared to SGA group.

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.

We performed a chart review to examine the impact of clinically determined and documented nonadherence on clinical practice and to explore factors associated with LAIs prescription. The originality of the study is the long period of observation. The main finding can be resumed in three aspects.

First, we found that a large proportion of patients (66.1%) were admitted because of nonadherenece or partial adherence to treatment, our results being in accordance with another published data [29, 30].

Second, LAIs were prescribed in less than 20% of patients who had clear indications for LAIs [31].

Third, patients in whom a LAI was indicated (LAIs group) compared to those in whom it was not (SGA group) presented significantly less relapses and less hospitalization. In a recent study the author reported a beneficial effect of olanzapine LAI in prevention of catatonia [32].

The results of our study need to be interpreted in the context of several limitations. First, the study was a retrospective chart review. Second, the relative small number of patients, and third, accurate information failed to be 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.

It is important to focus on the patients who are less likely to receive a LAI antipsychotic, as they may derive considerable benefit from LAIs. Future randomized studies are needed to evaluate the long term efficacy of LAIs compared to SG oral antipsychotics.

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Characteristics	*LAIs GROUP* n = 52	*SGA GROUP* n = 50	*P* value
Gender male [n (%)]	22 (43.3%)	24 (48%)	0.93
Time evaluation [months, mean±SD]	55±5.6	52±7.8	0.62
Reason for admission - nonadherence [n (%)] - alcohol abuse [n (%)]	 36 (69.2%) 12 (23.1%)	 33 (66%) 11 (22%)	 0.89 0.91
Age [years, mean±SD]	44.75±11.22	42.32±4.12	0.76
Age of onset [years, mean±SD]	23.44±4.17	24.20±6.78	0.88
Duration of illness [years, mean±SD]	16.22±15.33	17.29±16.65	0.92
Number of hospitalization (lifetime)	10.67 (5.38)	12.60 (3.65)	0.7
Days of hospitalizations (lifetime)	456.56 (120.20)	444.20 (140.76)	0.11
Olanzapine before [n (%)]	44 (84.16%)	43 (86%)	0.96
Risperidone before [n (%)]	10 (19.23%)	12 (24%)	0.15
Aripiprazol before [n (%)]	3 (6%)	4 (8%)	0.12
Previous antipsychotic number [mean]	4.3	5.2	0.8
Relapse [n (%)]	12 (24.24)	23 (75.76)	< **0.05**
Hospitalization [n]	15	30	< **0.05**

Table 1
DEMOGRAPHIC DATA OF THE TWO STUDY GROUPS

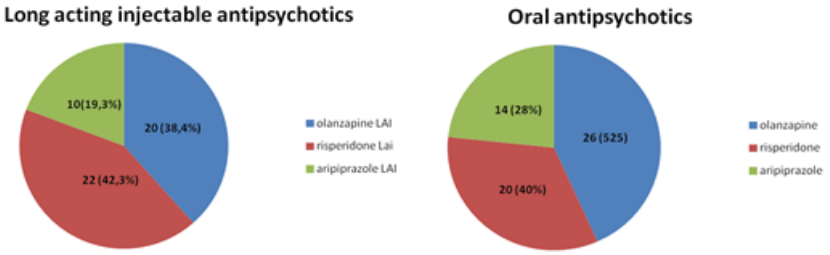

Fig. 1. Distribution of LAIs, respectively, SG oral antipsychotics used in the treatment of schizophrenia patients enrolled in the study [n (%)]

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