

Paliperidone palmitate: effectiveness, safety, and the use for treatment of schizophrenia

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Summary

The aim of the study was to summarize the efficacy and tolerability of paliperidone palmitate, an atypical long-acting antipsychotic drug. Paliperidone is a 9-hydroxy metabolite of risperidone with a slightly different receptor profile and significantly different pharmacokinetic profile. After the short review of its pharmacological properties, the efficacy of the drug in comparison to placebo or to an active comparator was described. The studies revealed the effectiveness of paliperidone palmitate in the treatment of psychotic symptoms, mainly schizophrenia. The drug proved to be efficacious in both acute psychotic symptoms treatment and long-term treatment. Its efficacy in patients with schizophrenia was similar and sometimes even better than the efficacy of other long-acting drugs, such as risperidone or olanzapine. In the pharmaco-economic studies, paliperidone proved to be cost-effective in comparison to risperidone or olanzapine. The review of the literature also underlined that paliperidone palmitate is well tolerated, compared with placebo. Frequency and severity of side-effects such as extrapyramidal symptoms, hyperprolactinemia and weight gain, was similar or less than those found in treatment with other atypical antipsychotics, including long-acting ones.

Key words: efficacy, paliperidone, tolerability

Introduction

The use of long-acting antipsychotics is a therapeutic option in psychiatry [1]. The introduction of paliperidone palmitate (PALI) for the treatment of psychotic disorders constitutes a valuable broadening of therapeutic possibilities for patients who are mainly suffering from schizophrenia. Therefore, it is important to know the characteristics of this drug and its possibilities for use in clinical practice.

Pharmacology of paliperidone palmitate

Even small modifications of the chemical structure may significantly change the receptor profile of a drug, its pathways in the body, including liver metabolism, the biological half-life or the potential interactions with other medications [2]. The example of risperidone and its active metabolite, 9-hydroxy risperidone (paliperidone), demonstrates how a subtle difference in chemical structure can lead to clinically meaningful differences in the formulation, frequency of administration, pharmacokinetics and other pharmacological features [3–6].

The pharmacological differences between the oral forms of risperidone and paliperidone – including serum level fluctuations, biological half-life, and risk of interactions – are visible and underlined by several authors as clinically meaningful [5, 7]. These differences between risperidone and paliperidone are even more visible for long-acting injection forms (LAI). Independent of the method of administration, these differences are the result of different formulations of both drugs. In comparison to risperidone LAI, PLAI is administered as a water solution of nanocrystals [8, 9].

The medications differ by a hydroxyl group in position 9 which means that paliperidone is 9-OH risperidone chemically [4, 10]. Risperidone does not possess the hydroxyl group (–OH), which could be used for the synthesis of fatty acid esters. The chemical structure of PLAI and the presence of a hydroxyl group allows it to be administered as the fatty acid ester – palmitic acid. PLAI is injected as an aqueous solution of nanocrystals of the ester. PLAI is relatively quickly released from nanocrystals into the interstitial fluid. Free paliperidone is derived from the ester by tissue hydrolases breaking ester bonds. The hydrolysis of paliperidone palmitate is relatively rapid; therefore, supplementation with oral antipsychotics is not necessary. Interestingly, one can prolong paliperidone release from PLAI and reduce the frequency of PLAI injections by regulating the structure of nanocrystals [6, 9].

The individual reaction in the injection site, the frequency of administration, and the time taken for the clinically significant serum concentration are some examples of significant differences between risperidone and PLAI which may lead to individual tolerability and efficacy of the drugs [11, 12].

Paliperidone – pharmacodynamic properties in comparison to risperidone

Independent from the method of administration, both risperidone and paliperidone are characterized by similar but not identical receptor profiles. Paliperidone is a rather

weaker 5-HT_{2A} antagonist than risperidone, which causes the lower 5-HT_{2A}/D₂ affinity ratio. The importance of this difference for the clinical practice has not been fully documented [13].

In contrast to other second-generation antipsychotics, risperidone and paliperidone are rather strong dopamine receptor antagonists, which results in a rather high risk for extrapyramidal side-effects (EPS) and hyperprolactinemia. Similarly to risperidone, paliperidone is rather strong alpha-adrenoreceptor antagonist. The affinity of paliperidone and risperidone to cholinergic muscarinic receptors is weak [6, 13].

Paliperidone – pharmacokinetic properties in comparison to risperidone

From the clinical point of view, some significant differences can be seen in the pharmacokinetic properties between risperidone and paliperidone [2, 14, 15]:

- risperidone is rapidly absorbed from the digestive tract while paliperidone is more slowly absorbed; however, food significantly increases the rate of its absorption;
- the bioavailability of orally administered risperidone is 100%, while that of paliperidone < 30%;
- the plasma protein binding of risperidone is 90%; the plasma protein binding of paliperidone is significantly lower (74%);
- risperidone is intensively metabolized in the liver with cytochrome P450 2D6 isoenzyme, by the hydroxylation sites 7 and 9 and by oxidative N-dealkylation; paliperidone is metabolized to a much lower degree – about 60% of the drug is eliminated through the kidneys in an unchanged form;
- the biological half-life, T_{1/2}, of orally administered risperidone ranges from 3 to 24 hours because of clinically meaningful genetically conditioned changes of CYP2D6 activity, while for oral paliperidone, the T_{1/2} change is small, with a mean of about 24 hours;
- the metabolism of risperidone can be significantly changed by drugs which block or induce the activity of cytochrome P450, which in turn indicates the tendency – confirmed in clinical practice – for significant interaction properties, for instance with carbamazepine, SSRI; paliperidone has a low risk (but not zero) for drug-drug interactions which depend on the activity of cytochrome P450 [16].

It is worth mentioning that the 9-OH risperidone (paliperidone) constitutes about 31% of risperidone metabolites. This means that any patient who is treated with risperidone also receives paliperidone. On the other hand, 31% of all metabolites create a mean value. Some of the patients, so-called slow metabolizers, will not produce significant doses of paliperidone, while those patients who are rapid metabolizers, will produce a lot of paliperidone [2, 9].

The above-mentioned differences can pertain the LAI forms of risperidone and paliperidone. The site of administration of the drug plays also an important role because of the different formulations of both drugs.

Clinically significant paliperidone serum levels are already present after the first injection. The release of the drug from the injection site lasts for up to 4 months, with

the maximal serum level noted approx. 12th day after injection. The injections into the deltoid muscle enable serum levels that are 30% higher than after gluteal injection. This difference is used in practice to reach the therapeutic serum level of paliperidone and to achieve a more stable level of the drug. The two first injections of 150 mg and 100 mg paliperidone administered to the deltoid muscle with a 7 day interval lead to the quick achievement of therapeutic levels of the drug. Subsequent administration of the drug requires one-monthly injections. In some countries, the one-3-month formulation (PP3M) is available. This formulation, which is not available in Poland, is used after stabilization of the mental state has been reached with PLAI monthly injections (PP1M) [6, 12]. Taking into consideration the drug absorption, the time to stabilize the serum drug level, the need for oral supplementation and the frequency of administration, risperidone LAI and PLAI can be valuable options for many patients suffering from schizophrenia.

The most important pharmacological properties of PLAI in comparison to risperidone are presented in Table 1.

Table 1. The most important pharmacological differences between risperidone LAI and PLAI

Risperidone LAI	PLAI
Chemical structure and its consequences for pharmacokinetic characteristics	
No hydroxyl group in position 9	Hydroxyl group in position 9
No fatty acid esters which could be used in LAI	Esterification possible in position 9; ester with palmitic acid used in LAI
LAI forms based on unchanged drug molecules encapsulated in polymer to form microspheres with delayed onset of drug release	LAI based on nanocrystals of paliperidone palmitate – ester of paliperidone and fatty acid
Drug release delayed for a couple of weeks until microspheres break; relatively short-lasting drug release from microspheres	Fast onset of drug release, long-term drug release from nanocrystals of paliperidone palmitate
Supplementation with oral forms necessary	No supplementation with oral forms needed
Frequent injections, every 2 weeks	Injections every 4 weeks
Other pharmacokinetic characteristics of drugs independent of pharmaceutical form	
Risperidone	Paliperidone
Intense hepatic metabolism to active and inactive metabolites	Risperidone metabolite – limited hepatic metabolism; dose reduction in patients with hepatic insufficiency not necessary*
High genetic variability of hepatic metabolism	No genetic variability of hepatic metabolism
High risk of drug-drug interactions	Low risk of drug-drug interactions
High variability of drug concentrations, half-life, and response to the drug	Low variability of drug concentrations

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Drug receptor profile	
Risperidone	Paliperidone
high affinity for serotonin 5-HT _{2A} receptors	Weaker, compared to risperidone, affinity for serotonin 5-HT _{2A} receptors

* dose modification of paliperidone is recommended in patients with renal failure [5–7].

Effectiveness in comparison to placebo

The methodologically correct, double-blind, randomized clinical trials of 9 to 13 weeks have proved the efficacy of PLAI in doses 25 to 100 mg in comparison to placebo, in terms of improvement of acute schizophrenia symptoms. Similarly, PLAI proved to be efficacious in comparison to placebo in the maintenance treatment of schizophrenia, causing significant elongation of the stable period of the illness until the moment of worsening [17]. The analysis of two placebo-controlled clinical trials with PLAI or oral paliperidone showed better efficacy of PLAI than of the oral form, both in terms of a decrease in the severity of symptoms measured by the PANSS and an improvement of patient's functioning. The risk of relapse after the discontinuation of oral paliperidone was higher than the risk of relapse when switching from PLAI to placebo [18]. The review of 19 placebo-controlled or active comparator vs. PLAI clinical trials showed that patients who received PLAI demonstrated significant improvements of psychotic symptoms, while the treatment tolerance was similar to that found in the placebo group [19]. The new formula of paliperidone administered every 3 months (means four times a year) also proved to be efficacious in elongation of the period to relapse in schizophrenia, in comparison to the administration of placebo [20].

Efficacy of PLAI, compared to active comparator

The selection of an active comparator in the majority of studies was aimed at those antipsychotics which possess good clinical efficacy.

The analysis of 19 clinical trials shows the efficacy of PLAI to be non-inferior to treatment of schizophrenia with risperidone LAI [19]. The PRIDE study was based on the 15-month observation of 450 schizophrenic patients receiving PLAI once monthly or oral antipsychotic medication (randomized to: aripiprazole, haloperidol, olanzapine, oral paliperidone, perphenazine, quetiapine, and risperidone); the results showed the longest period to relapse in PLAI group, and the percentage of therapeutic failures in the PLAI group was also lower than in the group of orally treated patients (39.8% vs. 53.7%) [21]. In another large study (353 schizophrenic patients who were ill for 1 to 5 years), the efficacy of PLAI was compared to that of various orally administered antipsychotics. The relapse rate was significantly lower in the PLAI group (14.8%) than in orally treated patients (20.9%). Those who received PLAI treatment showed significantly better clinical improvement (measured by the PANSS) already by the 8th day of treatment [22].

In 212 acute schizophrenia patients who were unsuccessfully treated with oral antipsychotics, the clinical improvement after switching to PLAI at doses from 50 to 150 mg daily was observed by the 8th day of treatment. After 6 months of therapy, 66.7% of PLAI treated patients showed at least a 30% improvement in the PANSS vs. baseline, and 43.5% showed even better improvement of 50% of the PANSS basal score. The improvement regarded the severity of schizophrenia symptoms, the subjective feelings of patients under PLAI treatment, and patients' functioning [23]. In more than 300 schizophrenia patients with a high risk of worsening, the treatment with PLAI at doses from 39 to 234 mg daily vs. haloperidol decanoate in the dose range from 25 to 200 mg daily, showed similar outcomes: 33.8% in the PLAI group and 32.4% in the haloperidol group suffered from treatment failure [24].

In the study of Li et al. [25], the efficacy of PLAI vs. the active comparator was evaluated in 452 adult Chinese acute schizophrenia patients. In this open, rater-blinded, randomized trial of parallel patients, the one monthly deltoid injection of PLAI was compared to gluteal muscle injections of risperidone LAI (RLAI). The doses of drugs were 50, 100, or 150 mg daily of PLAI and 25, 37.5 or 50 mg daily risperidone LAI. Similar efficacy was shown in both studied groups, which also reflected patients' functioning.

Fleischhacker et al. [26] conducted a study of 747 adult US acute schizophrenia patients, with both positive and negative symptoms evaluated with the use of the PANSS. Patients were randomly assigned to the groups of treatment with PLAI 50 mg gluteal injection on the first and 8th day of treatment, and subsequent doses of 25 to 100 mg PLAI injected monthly. In the risperidone LAI group, doses of 25 to 50 mg every two weeks were administered and oral supplementation of risperidone at the beginning of the treatment was allowed. The PLAI doses of less than 150 mg monthly proved to be optimal. While the study of Li et al. [25] demonstrated the non-inferiority of PLAI vs. risperidone LAI, in the study of Fleischhacker et al., the non-inferiority criterion was not fulfilled [26]. This might be due to the low initiation dose of PLAI (50 mg), which did not assure the proper drug level. Nevertheless, the efficacy of PLAI and risperidone LAI, evaluated with the use of the PANSS, was similar. The only difference was the lower decrease of schizophrenia positive symptoms in the PLAI vs. risperidone LAI groups. The drug tolerance was similar and did not jeopardize patient safety. A similar efficacy of PLAI and RLAI was showed by Pandina et al. [27]. The mean decrease of the PANSS score after PLAI treatment was 18.6 points while this was 17.9 points in the risperidone LAI group.

In another study, the outcome of switching from risperidone LAI to PLAI or an oral antipsychotic was studied. Those patients who switched to PLAI had fewer events (e.g., out-patient visits, hospitalizations) than patients treated orally. The mean time to such an event was longer in the PLAI group than in orally treated patients (70 vs. 47 days). A lower risk of relapse was also seen in the PLAI group [28].

Kim et al. [29] proved the beneficial effect of PLAI on patients' cognitive functioning. Schizophrenia patients were treated for 12 weeks with risperidone; some of them were then switched to PLAI while the others continued on risperidone. A number of cognitive functions (verbal learning test) and patients' global functioning improved in the PLAI group.

The results of the above-mentioned studies indicate higher efficacy of PLAI in comparison to other antipsychotic drugs; some studies indicate similar efficacy. This is important because there is a perspective of the administration of paliperidone once every three months instead of monthly injections. This kind of treatment is recommended for patients who have been previously treated for at least 4 months with once monthly injections of PLAI. The doses of paliperidone administered every 3 months range from 175 to 525 mg. It is also important to note that this kind of dosing regimen allows deviation from the injection schedule for up to two weeks, which gives a certain amount of freedom when the treatment is planned [6].

Cost-effectiveness of PLAI treatment

For a couple of years, the pharmacoeconomic aspects of the use of long-acting atypical antipsychotics (LAI) have been analyzed, and this analysis also applied to paliperidone palmitate. In a study conducted in Sweden, paliperidone palmitate (75 mg/month) was compared with risperidone LAI (37.5 mg/2 weeks) and with olanzapine LAI (150 mg/2 weeks or 300 mg/month). During the 5 year observational period, the better effectiveness of PLAI in comparison to the other drugs was shown: this concerned the lower number of relapses and higher QALY (quality-adjusted life years) [30]. A similar 5-year observational period was used in Germany: PLAI proved to be superior to risperidone or olanzapine in terms of the number of relapses and the number of QALY, but the costs of the use of PLAI were slightly higher than those of olanzapine [31]. In Norway, PLAI was compared to olanzapine embonate during a 1-year period and a slight advantage of PLAI was demonstrated [32]. During a 1-year study in the Czech Republic, lower costs of the treatment with PLAI compared to risperidone or olanzapine were demonstrated with similar QALY indexes but a lower number of relapses [33]. In a systematic analysis by Achilla and McCrone [34] of 28 studies including LAI risperidone, olanzapine and paliperidone, the latter demonstrated the best cost-effectiveness. In the newly published American study, the pharmacoeconomic aspects of PLAI were evaluated in comparison to aripiprazole LAI. This study showed a greater reduction of relapses as well as slightly lower treatment costs in patients treated with aripiprazole LAI vs. PLAI (0.181 and 0.277, respectively) [35].

Features which differentiate paliperidone from other atypical LAI antipsychotics

To date, the position of long-acting injections of paliperidone among antipsychotic treatments seems to be favorable. Above-mentioned clinical studies have shown its effectiveness in schizophrenia. The switch from other antipsychotic drugs which have not proven to be as effective as paliperidone palmitate results in both clinical and subjective improvement [36, 37]. Paliperidone palmitate is well tolerated and the percentage of patients who demonstrate extrapyramidal side-effects or weight gain is low. The drug is conveniently administered (once monthly) and the clinical effect is visible within the first days of treatment; also, contrary to risperidone LAI, oral supplementation within

the first weeks of treatment is not necessary. The drug can be administered both to the deltoid or gluteal muscle, and the observation of patient's reactions during the first hours after injection (as it is recommended after olanzapine LAI injection) is also not needed. In comparison to risperidone LAI or olanzapine LAI, paliperidone palmitate treatment is characterized by favorable pharmacoeconomic indices.

Paliperidone in the early stage of schizophrenia

During the last few years, atypical LAIs have been more frequently recommended for the long-term treatment of the early stages of schizophrenia [38, 39]. Approximately 80% of patients with a first schizophrenia episode experience symptomatic remission when atypical antipsychotics are used, but in the majority of them, the relapse occurs within 2 years. The rationale for the use of LAIs in those patients continues to be more obvious; however, some psychiatrists are still skeptical of such a procedure. More recently, a randomized 1-year clinical trial was published in "JAMA Psychiatry", comparing the effects of risperidone LAI vs. risperidone oral treatment in first episode patients. The percentage of relapses was significantly lower in the LAI group (5% vs. 33%). Among patients treated with risperidone LAI, the mean severity of psychotic symptoms was significantly lower, and the drop-out rate was also lower in this group [40]. Üçok et al. [41] published the results of a 1-year study of 80 patients who were hospitalized up to 3 years previously and underwent treatment with PLAI. The results indicated the effectiveness of such a treatment in terms of the reduction of psychotic symptoms, both positive and negative, and the improvement in patients' functioning.

Safety of use of paliperidone palmitate

For evaluation of the safety of PLAI, those studies which included a thorough analysis of drug tolerance were selected: 4 open studies, 4 placebo-controlled randomized trials, and 3 double-blind PLAI vs. risperidone LAI intramuscular injection trials. The analysis of drug tolerance also included the rare side-effects, for instance post-injection syndrome, tardive dyskinesia, and studies comparing PLAI vs. first-generation antipsychotics (3 studies). In general, 20 published papers (15 clinical trials, 5 descriptive studies and meta-analyses) were considered (Table 2).

The safety of treatment was evaluated with regard to the duration of treatment, most frequently on the 1st day after administration of the drug, on the 8th day of treatment, and then monthly afterwards, with the possible range of ± 7 days.

Table 2. Studies considered in the analysis of the safety of PALI

Number of subjects (PLAI)	PLAI Dose (mg eq)	Comparator	Type of study	Time of evaluation	Comments	Author
N = 212 (104)	Range 50–150	-	Open, prospective	12 months		Coppola et al. [42]
N = 231 (231)	50–150	-	Open, prospective	6 months	Treated earlier with RLAI or "depots"	Schreiner et al. [43]

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N = 521 (474)	150–100	-	Open	18 months	Ineffective oral treatment	Zhang et al. [44]
N = 212 (212)	150–100	-	Open	6 months	Ineffective oral treatment	Hargarter et al. [23]
N = 652 (163)	Range 150–25	Placebo	Randomized, double-blind	13 weeks		Pandina et al. [27]
N = 652 (652)	150–100	Placebo	Randomized, double-blind	13 weeks		Bossie et al. [45]
N = 645 (645)	50–150	Placebo	Randomized, double-blind	52 weeks		Sliwa et al. [46]
N = 324 (162)	150–100	Placebo	Randomized, double-blind	13 weeks		Takahashi et al. [47]
N = 1,214 (456)	Range 150–25	RLAI	Randomized, double-blind	13 weeks		Pandina et al. [27]
N = 749 (379)	Range 25–100	RLAI	Randomized, double-blind	53 weeks		Fleischhacker et al. [26]
N = 292 (181)	150–100	RLAI/ Placebo	Randomized, double-blind	13 weeks		Fu et al. [48]
N = 506 (160)	175–525	Placebo	Randomized, open	29 weeks	PLAI every 3 months	Berwaerts et al. [20]

RLAI – risperidone long-acting injections

Side-effects profile

In all of the analyzed studies, similar effectiveness of PLAI in terms of the reduction of psychotic symptoms and also similar side-effect profile has been underlined. The type and severity of side-effects depended on the selected patient groups: first-episode patients, subjects with a duration of illness of less than 5 years vs. those who are chronically ill, the type of the comparator used, e.g., placebo or antipsychotic drug – first – or second-generation, and also the duration of observational period (from 13 to 72 weeks).

Both in the open studies and in randomized placebo-controlled trials, the most commonly observed PLAI side-effects were: nasopharyngitis (17.5%), insomnia (10.8%–15.2%), injection-site pain (13.7%–18.6%), headache (6.1%–13%), and tachycardia (13%) [23, 42, 44]. Less frequently observed side-effects were: dizziness (PLAI/placebo: 2.5% vs. 1.2%), sedation (PLAI/placebo: 2.3% vs. 0.6%), limb pain (PLAI/placebo: 1.6% vs. 0%), and muscle pain (PLAI/placebo: 1% vs. 0%) [27, 45–47].

When PLAI injections were located only in the deltoid muscle, injection-site pain was less frequently reported than in patients who received the drug injection in the gluteal muscle.

Among the rarely reported treatment side-effects (less than 10% of subjects), the following were noted: psychotic exacerbation (3%–7% of subjects) and slight weight gain (< 7%) in 22% of patients. The elevation of prolactin level was observed in both

female and male patients, but a significant increase in PRL level was observed in women: 32.8% W, 14.3% M – the PRL increase was found in an average of 19% of treated subjects [42]; in 3% [43]; 25.6% W; 4.7% M; in 11.9% of treated subjects [44]. In the study of Hargarter et al. [23], the hyperprolactinemia-induced side-effects were reported in 5.7% of patients treated with PLAI. Nevertheless, amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction have been reported only in less than 2% of patients. In general, the hyperprolactinemia-induced side-effects were rarely reported, but were more frequently seen in patients with a short duration of illness (7.9%) than in chronic schizophrenia patients (3.5%); amenorrhea was noted in 3.2% of females [45].

The extrapyramidal side-effects were seen during the consecutive injections of PLAI in 24–31% of treated patients. The most frequently observed were akathisia (13.4%) and parkinsonism (16%). Other symptoms (dyskinesia, tremor, restlessness, muscle stiffness, and dystonia, were seen in less than 7% of subjects [42, 44]. In chronic schizophrenia patients, extrapyramidal symptoms were less frequently observed (PLAI/placebo: 2.3%/4.6%), but akathisia was seen more frequently (PLAI/placebo: 3.3%/1.9%). When the antiparkinsonian drugs were used, extrapyramidal symptoms showed a tendency toward decreasing severity during consecutive PLAI injections. Significant changes of glucose level and changes in body weight were not found for individuals under PLAI treatment [42, 47].

Part of the analyses also included those randomized, double-blinded studies which used risperidone LAI as a comparator. The profile and the severity of drug-induced side-effects were similar in both groups. Similar was also the percentage of treatment drop-out patients (PLAI/RLAI: 6.8%/4.8%). Extrapyramidal symptoms were observed in about 7% of patients treated in both groups. The most frequent extrapyramidal symptoms were: akathisia and hyperkinesia (PLAI/RLAI: 6%/10%) [26, 27].

Although worsening of schizophrenia symptoms under antipsychotic treatment was rarely seen, it was among the most common symptoms and ranged from (PLAI/RLAI) 2.5%/2.1% to 14%/12% of subjects. The studies did not reveal the impact of the studied drugs on the cardiovascular system or on the glucose serum level. High PRL levels were seen more frequent among risperidone LAI – than PLAI-treated patients: (PLAI/RLAI: 31%/53% of males and 42%/51% of females) [26].

The analysis of safety indicated that during long-term PLAI treatment, metabolic and extrapyramidal symptoms may be the most crucial. The meta-analysis of 3-month trials aimed at the evaluation of metabolic syndrome revealed that weight gain under PLAI treatment was less pronounced than after treatment with other second-generation antipsychotics, e.g., aripiprazole or iloperidone [49]. However, body mass changes were not significant. The changes of blood cholesterol were similar in patients treated with various antipsychotics. Statistically, but not clinically, the blood glucose changes were greater after PLAI than after aripiprazole treatment.

In the meta-analysis aimed at investigating the presence of tardive dyskinesia (TD) in oral paliperidone – and paliperidone palmitate-treated patients, the frequency of TD after PLAI treatment was slightly higher than after oral paliperidone treatment (0.18% vs. 0.10%), but decreased in both groups along with the duration of treatment (-0.12% vs. -0.05%) [50]. The frequency of TD during PLAI treatment was lower

than during treatment with the second-generation antipsychotics: 1-year risk of TD in second-generation antipsychotics – 3.9%, in first-generation antipsychotics – 5.5%. In general, the number of extrapyramidal symptoms during long-term (> 3 months) oral paliperidone treatment was higher than in patients treated with PLAI. As a result, antiparkinsonian drugs were less frequently used in PLAI-treated patients (12% vs. 17%) [51]. During the treatment with PLAI, the post-injection delirium/sedation syndrome was not observed [52, 53].

The safety of PLAI treatment was confirmed in the 29-week study (including an open phase) of Berwaerts [20], where 605 schizophrenia patients were studied. During the study, where PLAI was administered every three months, stabilization of the mental state and diminution of treatment-emergent side-effects were seen in the PLAI-treated group. During the double-blind phase of the trial, the side-effects were observed in 63% of patients in PLAI group vs. 58% of patients in the placebo group. Among the side-effects which were more frequent in the PLAI group were: headache (PLAI/placebo: 9%/4%), weight gain (PLAI/placebo: 9%/3%), nasopharyngitis (PLAI/placebo: 6%/1%) and akathisia (PLAI/placebo: 4%/1%) [54]. In a recently published meta-analysis, it was demonstrated that because of good drug tolerance, PLAI is better accepted by the patients than other antipsychotics [19].

Conclusions

Paliperidone is an active metabolite of risperidone, which is a widely-used antipsychotic drug that has been used for years in the treatment of psychoses. Paliperidone palmitate is a long-acting formulation which possesses certain features that are important from the pharmacological and clinical point of view, differentiating the drug from other antipsychotics, and also from those which are available in long-acting injection forms. The effectiveness of paliperidone palmitate in the recommended doses, measured by a decrease in the severity of symptoms and an elongation of the duration of improvement period has been proved in many methodologically correct clinical trials. Paliperidone palmitate is recommended for the treatment of schizophrenia and is also recommended for early stages of the illness. The frequency and tolerance of paliperidone palmitate side-effects is similar to those found in placebo groups or in patients treated with an active comparator. Because of the good tolerance, paliperidone palmitate was better accepted by the patients than other antipsychotic drugs.

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