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Practical guidelines for the use of long-acting injectable second-generation antipsychotics

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Summary

Long-acting injectable antipsychotics constitute a valuable alternative for the treatment of psychotic disorders, mainly schizophrenia. They assure a more stable drug level, improve treatment compliance, and increase the chances for favorable and long-lasting improvement. Additionally, the long-acting second-generation antipsychotics combine the values of long-acting injectable drugs with the values of atypical antipsychotics. Four second generation long-acting antipsychotics have been described: risperidone, olanzapine, aripiprazole and paliperidone. The indications for their use, treatment strategy, tolerance, and potential interactions are discussed.

Key words: schizophrenia, long-acting antipsychotics, arpiprazole, olanzapine, paliperidone, risperidone, guidelines for use

Introduction

The use of long-acting antipsychotics injections (LAI) constitutes a valuable option for treatment psychotic disorders. For years, this form of treatment has been successfully used to treat psychotic disorders and has gained merit among practicing psychiatrists.

The principal conditions which need to be fulfilled when choosing this form of treatment are:

1. The necessity for antipsychotic treatment;
2. A long period of treatment foreseen;
3. The need for improvement in patient's compliance.

The notion that the LAIs are used solely to improve a patient's compliance is not true. Treatment with LAIs does not only constitute another form of administration of an antipsychotic drug. The use of LAIs provides a stable level of antipsychotics which allows the presumption that the treatment is optimally effective. Fluctuations in drug levels do not foster long-lasting clinical improvement and therefore increase the risk of worsening, including relapse of psychotic symptoms or the risk of hospitalization and the incidence of bothersome side-effects. LAIs assure better bioavailability and a more predictable relationship between a drug's dose and its serum level [1]. The use of LAIs provides a persistent and effective dopaminergic D2 receptors blockade in the range which is needed for the control of psychotic symptoms. Studies including PET and SPECT proved that a blockade of more than 65% of D2 receptors is not necessary for the achievement of this effect [2]. LAIs diminish the risk of abrupt treatment discontinuation and provide the patient with relief from a daily pill taking routine [3]. From a further perspective, irregular intake of medication causes a worsening of the patient's status and also increases the risk of family burden and the worsening of interactions with others, decreases the chances of achieving stable and satisfactory functioning and causes bothersome subjective feelings which accompany the unstable patient's status. An important factor for the use of the LAIs is also the possibility of diminishing family members' doubts regarding the patient following doctor's recommendations [4]. Some psychiatrists claim that the use of LAIs should be considered as a therapeutic option for almost all patients [5].

The French experts suggest the use of the LAIs not only in schizophrenia but also in schizoaffective disorders, delusional disorders and bipolar disorders (BD). [6].

Hamman et al. [7] claim that about half of the patients who receive the antipsychotic treatment in German hospitals seems to be open to the option of the use of LAIs, but only in 30% of them has this treatment been used. One of the reasons for this was the implausible arguments used by psychiatrists when considering this treatment option. The other obstacle to the use of LAIs is physicians' tendency towards the co-administration of the LAIs with other antipsychotics. According to the review done by Wheeler et al. [8], a considerable number of patients treated with risperidone LAI have simultaneously received other antipsychotics, a policy which the authors call bad practice.

LAIs should be used for patients requiring a long-term antipsychotic treatment. The use of LAIs seems to be questionable if the patient does not need antipsychotic treatment for a long period of time. In saying "a long-term" treatment, one should consider at least several months of treatment. This excludes the use of LAIs for *ad hoc* (when necessary) treatment. The need for the temporary use of an oral or short term injectable antipsychotic does not exclude treatment with LAIs; however, LAIs should by no means be used for temporary purposes (sedation for instance). It has to

be underlined that the half-life of an LAI is considerably long (two weeks or even longer) so the sedative effect of the medication will also last far longer than it is needed to tranquillize the patient.

The need for improvement in a patient's compliance is beyond any doubt the most frequently used argument justifying treatment with LAIs. The administration of the LAI every two weeks or so does not guarantee full treatment adherence but it improves treatment compliance substantially. Tandon [9] claims that various antipsychotic agents proved to have a similar effectiveness but the use of a LAI improves the patient's compliance. It has to be mentioned, however, that the use of a LAI also requires the patient's consent. Admittedly, the present administrative regulations allow the forced use of medication (according to article 18 point 6 of the Polish Mental Health Act [10]) but the purpose of such a compulsory use of the medication is the need to avoid aggressive behavior of the patient, and this goal should be achieved by the injection of an antipsychotic or anxiolytic agent. It should be also mentioned that in Poland the use of long-acting injectable second-generation antipsychotics (LAI2G) is partially regulated by the reimbursement policy, which will be discussed later on.

It should be noted that the evaluation of a patient's compliance to antipsychotic treatment is difficult. One option is the measurement of drug serum levels but this is an expensive method and requires the patient's cooperation. Apart from this, we do not have objective measures for treatment adherence. Other methods such as pill counting, package checking, pill distribution by others or MEMS (registration of the opening of the medication bottle) are far more subjective. Some form of compliance improvement is the use of rapidly dissolving pills or medication in solution instead of tablets. The use of a questionnaire prepared by the Polish Psychiatric Association to help the objective evaluation of treatment compliance is a valuable tool [11].

Treatment with the LAI brings a certain value for the patient, but the use of a second – generation antipsychotic in the long-acting injection doubles the advantages of such a treatment. The second-generation antipsychotics differ from the first-generation drugs in terms of effectiveness toward the negative symptoms and the improvement of cognitive functions. They also differ regarding tolerability as well as the risk for tardive dyskinesia [12, 13]. According to Lafeuille et al. [14] the use of long-acting injectable second-generation antipsychotics (LAI2G), compared to atypical oral medication, decreases the risk for hospitalization. Some authors claim that the LAI2G are generally similarly tolerated than the same medications administered in oral form [15], while others suggest that the more favorable toleration of the LAI2G is due to the lower risk of neurological side-effects, more frequently observed during treatment with first-generation antipsychotics [16]. Recent reviews allow consideration of the use of the LAI2G as a valuable therapeutic option not limited solely to patients who do not comply with the treatment [17]. Therefore, the possibilities for the use of LAI2G merit the efforts for their popularization.

For the preparation of present guidelines, Medical Subject Headings (MeSH) were used to search the PubMed database with the following key-words: heading

schizophrenia with the following specifiers: aripiprazole, olanzapine, risperidone, paliperidone, tolerability, drug interactions, indications, treatment with the headings: aripiprazole, olanzapine, risperidone, paliperidone, tolerability, drug interactions, indications, treatment: ("Schizophrenia" [Mesh]) and "above mentioned key-words" [Mesh] with the filters: available full English-language paper, publication within the last 5 years (time frame from January 1, 2009 till December 31, 2013), concerning the clinical trial, written in English. This method revealed several articles referring, with different levels of relevance, to the topic of the treatment of schizophrenia with above mentioned agents.

Risperidone LAI

Indications for use

According to the product characteristics dated September 21, 2012 [18] indications for use risperidone LAI are as follows: "the maintenance treatment of schizophrenia in patients presently treated with oral antipsychotics."

Initiation of treatment

Before the first injection of risperidone LAI (RLAI) the patient has to be treated with an antipsychotic. It is recommended that this should be oral risperidone, however, the use of other antipsychotics is also possible. In the latter case, however, the antipsychotic agent should be switched to oral risperidone in order to be sure that risperidone treatment brings benefits to the patient and there are no contraindications for risperidone administration. The period for oral risperidone treatment has not been strictly defined but in general it should be no shorter that 2 weeks. This obviously does not regard patients already treated with oral risperidone before the switch to RLAI; here the minimum period of treatment is not defined, as it depends on individual needs of the patient.

Dosage

At present the following RLAI doses are available: 25 mg, 37.5 mg and 50 mg. The following scheme for RLAI dosage is recommended (table 1).

Table 1. **Comparison of oral and LAI risperidone dosage**

Oral risperidone dosage	≤ 4 mg daily	4 do 6 mg daily	> 6 mg daily
RLAI dosage	25 mg every 2 weeks	37.5 mg every 2 weeks	37.5 mg every 2 weeks

In the case of treatment with oral antipsychotics other than risperidone, the switch to oral risperidone is required. The suggested dosage of the various most popular antipsychotics in comparison to oral risperidone are presented in table 2.

Table 2. **Comparison of oral risperidone and other antipsychotics dosage**

Oral risperidone dosage	Up to 4 mg daily	from 4 to 6 mg daily
Amisulpride	up to 600 mg	to 800 mg
Aripiprazole	up to 15 mg	to 30 mg
Haloperidol	up to 10 mg	>10 mg
Olanzapine	up to 15 mg	to 25 mg
Perazine	up to 500 mg	to 800 mg
Sulpiride	up to 400 mg	to 800 mg
Ziprasidone	up to 80 mg	to 160 mg
Zuclopentixol	up to 30 mg	to 30 mg

Treatment strategy

RLAI should be used in the lowest effective dose, usually given every two weeks. In cases where a lowering of the dose (which is possible in case of doses higher than 25 mg) is required due to side effects or the use of additional treatment (for the correction of the side-effects) is not possible because of the good effectiveness of treatment, the intervals between injections can be extended beyond two weeks. The administration of RLAI less frequently than every four weeks is not recommended. When the RLAI treatment is discontinued it needs to be taken into consideration that the risperidone level will maintain for at least three weeks after the last RLAI injection. In case of the need to increase the RLAI dose this should not be done more often than every four weeks. After the last injection, a period of three weeks should be kept in order to evaluate the need for dose increase. The maximal RLAI dosage is 50 mg every two weeks. In the elderly the usual RLAI dosage is 25 mg every two weeks; maximal dosage of 50 mg every two weeks should be used with caution in this particular population. RLAI is not recommended for patients below 18 years of age.

Tolerability

RLAI is generally well tolerated. The possible side-effects during RLAI administration are the same as during oral risperidone treatment; the only difference is possible side-effects at the site of injection. The most frequently observed side-effects (in >1/10 treated patients) are: insomnia, anxiety, headache, upper respiratory tract infections, Parkinsonism, depression, akathisia, and an increase in prolactin level. In the case of side-effects, it is recommended to consider lowering the RLAI dose and extending the periods between injections; this action should by no means jeopardize the effectiveness of RLAI treatment. Further, the possibility of using correctional treatment should be taken into account. The use of RLAI in patients with dementia or with cerebrovascular

disorders requires caution. There is a higher risk of side-effects or even death in such patients, and the mechanism of this increased risk is unknown. The increased death risk was mentioned earlier in patients treated simultaneously with risperidone and furosemide (data from the product characteristics). The analysis of 64 clinical trials proved the higher risk of cardio-vascular side-effects (syncope, tachycardia, edema, transient ischemic attacks) in patients treated with risperidone or paliperidone than in those receiving a placebo [19]. The analysis of the risk of cardio-vascular events or diabetes among patients treated with risperidone revealed no difference in comparison to patients treated with other drugs (quetiapine or olanzapine); such a risk was lower in patients receiving aripiprazole [20]. These data, however, regard oral risperidone and not RLAI. The contraindication for RLAI use is the hypersensitivity to risperidone or to any of the excipients.

Drug interactions

Simultaneous administration of other drugs frequently used for the treatment of mental conditions and RLAI may have certain consequences (see table 3).

Table 3. **Potential RLAI interaction**

Medication	Influence on RLAI level
L-dopa and DA-agonists	Antagonism
Carbamazepine and other CYP3A4 inductors	Decrease of RLAI level
Fluoxetine, paroxetine and other CYP2D6 inhibitors	Increase of RLAI level
Phenothiazines, tricyclic antidepressants, β-blockers	Increase of RLAI level
Lithium, valproates, donepezil	No influence on RLAI level

All of the discussed LAI (risperidone, olanzapine, aripiprazole and paliperidone) should not be used during pregnancy and lactation; they can also affect driving a motor vehicle.

Reimbursement indications

The conditions that should be fulfilled in order for the RLAI to be reimbursed by the national health care insurance system differ from product characteristics and result from the national reimbursement policy. Treatment with RLAI [13] is reimbursed only in patients who failed to respond to previous treatment with antipsychotics (first – or second-generation drugs) because of the persistent lack of adherence to treatment. The "persistent lack of adherence to treatment" is defined as long-lasting (at least four weeks) and persisting occurrence, regardless of attempts to change the patient's behavior, of at least one of the following:

1. Patient's resistance to follow doctor's instructions regarding the intake of medication in a certain dose and in the given scheme. The doctor's instructions should

include: the necessity for treatment, the choice of the medication, its dosage and form;
2. The use of other medications or doses not recommended by the leading physician.
3. The introduction of intervals in the treatment not recommended by the leading physician and/or medically not justified.
4. Failure to report to the scheduled visits when this causes changes in pharmacological treatment not recommended by the leading physician.

Aripiprazole LAI

Aripiprazole is an antipsychotic agent characterized by a unique mechanism of action; it is serotonergic 5-HT2 antagonist but also 5-HT1A and D2 partial agonist, thus it is called the third-generation antipsychotic drug. Since February 2013, its long-acting form used in injections administered once every four weeks has been registered in the US and, in November 2013, also in Europe, including Poland.

The efficacy of Aripiprazole LAI (ALAI) is similar to that of oral aripiprazole in daily doses of 10–30 mg [21]. It has been shown that the switch from oral antipsychotic to ALAI significantly reduces the need for hospitalization [22]. This is important not only because of the patient's subjective experience – the admission to the psychiatric hospital is always a troublesome experience – but it also significantly reduces the health system burden as well as the treatment costs.

Indications for use

ALAI is indicated for maintenance treatment of patients with schizophrenia who have been stabilized by oral antipsychotic treatment. ALAI is not indicated for elderly demented patients. Similarly as in the case of other atypical antipsychotic drugs there is an increased risk of death, mainly from cardio-vascular causes. It is not indicated for patients under 18 years of age as no data for the efficacy and safety in this population are available.

Dosage

Patients who have not been treated with aripiprazole before the initiation of ALAI should at first be treated with aripiprazole administered orally. Those who have already been treated with oral aripiprazole should receive 400 mg of ALAI with the simultaneous continuation of oral aripiprazole for 14 days in order to assure stable serum aripiprazole levels. This strategy (the continuation of oral aripiprazole after the first ALAI injection) also refers to those patients who have been previously treated with oral aripiprazole, but immediately before the switch to ALAI, they have received a drug other than oral aripiprazole. After the period of 14 days, oral aripiprazole should be discontinued, and the ALAI injections should be given every four weeks.

Treatment strategy

The recommended dose of ALAI is 400 mg, administered every four weeks. In case of intolerance, the dose can be decreased to 300 mg, every four weeks. In the case that one ALAI injection is missed and the interval from the last injection is longer than six weeks, the next ALAI injection should be given along with supplementation with oral aripiprazole for 14 days. If the ALAI is discontinued it has to be remembered that the aripiprazole level will be maintained for a long period of time; the half-life (T1/2) of ALAI given in a dose of 400 mg is 47 days, and for 300 mg, 30 days. For elderly patients (> 65 years of age) the efficacious and safe dose has not been established; however, it seems to be reasonable to start the treatment with a lower ALAI dose (300 mg).

Tolerability

The safety profile of ALAI treatment is similar to that of oral aripiprazole. According to Fleischhacker et al. [21] the most common ALAI side-effects were insomnia, akathisia and body mass change (increase or decrease) which were observed in 9–12% of patients treated with ALAI. In 7.5% of patients who received 400 mg of ALAI a pain of moderate severity was observed at the injection site; the severity of this symptom diminished with subsequent ALAI injections. In the study of Kane et al. [23] the most common side-effects of ALAI were: insomnia (27% of patients), tremor (16%) and headache (16%). No hyperprolactinemia, QTc prolongation, orthostatic hypotonia, or metabolic changes have been noted. The contraindication for ALAI use is the hypersensitivity to aripiprazole or to any of the excipients.

Drug interactions

Aripiprazole is metabolized with the use of isoenzymes 3A4 and 2D6 of the cytochrome P450. Below some important interactions between the ALAI and other drugs are presented (table 4).

Table 4. **Potential ALAI interactions [24]**

Medication	Influence of ALAI level
Carbamazepine and other CYP3A4 inductors	Decrease of ALAI level
Ketokonazole and other CYP3A4 inhibitors	Increase of ALAI level
Chinidine and other CYP2D6 inhibitors	Increase of ALAI level
Lithium, valproates,	No influence on ALAI level

Reimbursement indications

At the moment of preparation of this text the ALAI is not reimbursed in Poland.

Olanzapine LAI

Olanzapine is an antipsychotic drug of the second-generation with multireceptor affinity: to the serotonergic receptors (5-HT2A and 2C, 5-HT3, 5-HT6), dopaminergic (D1, D2, D3, D4, D5), muscarinic (M1–M5), adrenergic (α-1) and histaminergic H1 [25]. This multireceptor profile is probably linked to its antipsychotic effectiveness, which has been proved in clinical trials comparing olanzapine with other antipsychotic drugs [26, 27]. Olanzapine also exerts a favorable effect on the affective symptoms.

Indications for use

Olanzapine long-acting injections (OLAIs) have been registered in Poland for the maintenance treatment of adult schizophrenic patients who have been stabilized on oral olanzapine. Because of the lack of adequate data, OLAIs have not been recommended for patients older than 65 years of age, nor for children and adolescents. They are also not recommended for patients with renal and/or liver failure [25].

Initiation of treatment

When the patient had already been stabilized on oral olanzapine, the OLAI should be given at the lowest possible dosage, usually at the intervals of four weeks. The drug should be administered deeply into the gluteal muscle. The administration of the drug should take place under conditions which allow for observation of patient after the injection has been given and also ensure the proper medical care in case of post-injection syndrome (see Tolerability).

Dosage

OLAI is available in three doses: 210 mg, 300 mg and 405 mg of olanzapine pamoate monohydrate powder and solvent for prolonged-release suspension for injections. The calculation of the proper olanzapine dose in the switch from oral olanzapine to OLAI is presented in table 5.

Table 5. **Recommended calculations scheme of doses in the switch from oral olanzapine to OLAI [25]**

Oral olanzapine dose	Recommended initial OLAI dose	Maintenance OLAI dose (after 2 months of OLAI treatment)
10 mg daily	210 mg every 2 weeks or 405 mg every 4 weeks	150 mg* every 2 weeks or 300 mg every 4 weeks
15 mg daily	300 mg every 2 weeks	210 mg every 2 weeks or 405 mg every 4 weeks
20 mg daily	300 mg every 2 weeks	300 mg every 2 weeks

* ½ of the 300 mg dose

After intramuscular administration, the dissolution process of olanzapine pamoate starts immediately and lasts continuously for more than four weeks. Subsequently, within eight to twelve weeks, the release of olanzapine gradually decreases. Six to eight months after the injection, the compound is completely eliminated; the half-life of OLAI is 30 days.

Treatment strategy

For maintenance treatment in schizophrenia usually the lowest possible dose of OLAI is administered every four weeks. In clinical trials with OLAI the oral supplementation with olanzapine was not required. If the physician decides so, olanzapine in both oral and LAI form can be administered simultaneously for a short period of time; however, the cumulative olanzapine dose should not exceed the maximal dose of 20 mg daily. The decrease of olanzapine dose should be considered in the presence of one or more factors which can slow down the olanzapine metabolism, (e.g. female gender, older age, non-smoking patient, polytherapy) [25].

Tolerability

Because olanzapine shows a stronger affinity to the serotonergic 5-HT2A receptors than to the dopaminergic D2 receptors, the risk of extrapyramidal side-effects is low, a property which favors olanzapine among other antipsychotics. The limitations for olanzapine use include the risk of body weight gain and metabolic syndrome. In patients treated with olanzapine, abnormal lipids levels as well as hyperglycemia have been observed. This may lead to the development or exacerbation of diabetes, including rare complications like ketoacidosis and coma. This is why every patient should be carefully examined before and during olanzapine treatment in order to avoid metabolic changes. The recommendations of the Polish expert panel are included in table 6 [28].

Table 6. **Recommendations for the elimination of the risk of metabolic syndrome in patients treated with antipsychotics [28]**

Medical history (including genetic load).
The control of metabolic parameters:
before treatment: waist circumference, BMI, glucose (fasting), lipids, blood pressure;
After 4 weeks: BMI, blood pressure;
After 8 weeks: BMI;
After 12 weeks: BMI, blood pressure, glucose, lipids;
Quarterly: BMI, waist circumference.
In the case of abnormal values: the tests should be repeated and the antipsychotic treatment should be re-evaluated.
In the case that the abnormal values are still present or the BMI or waist circumference has increased: control dietary and life style habits, exclude any medical conditions, decrease the antipsychotic dose, switch to another antipsychotic with less potential for metabolic changes (aripiprazole, ziprasidone, sertindole).

Post-injection syndrome is a rare complication of OLAI treatment which has been noted less frequently that one in a thousand OLAI injections. Because of its symptoms: sedation (with various levels of severity: from somnolence to coma) and/or delirium (including amentia and disorientation), agitation, anxiety and cognitive dysfunctions, after every OLAI injection the patient has to be under the close supervision of medical personnel for three hours. Before the patient leaves the facility, it has to be certain that he/she is conscious and properly oriented and that no symptoms of olanzapine overdose are present. In the case of olanzapine overdose the careful medical supervision of the patient is necessary until the symptoms of post-injection syndrome resolve. Activities aimed at the acceleration of drug elimination are not recommended. In all reported cases of post-injection syndrome the spontaneous resolution of all symptoms was seen within 24–72 hours [25].

Other OLAI side-effects are similar to those of oral olanzapine. The most common are: somnolence, hyperprolactinemia, eosinophilia, orthostatic hypotension, constipation, dry mouth, transient symptomless increase of AST and ALT activity, rash, asthenia, fatigue. Due to producing stable serum levels, the OLAI may be better tolerated in terms of somnolence, fatigue and orthostatic hypotension than oral olanzapine. Side-effects at the injection site were seen in about 8% of patients. The most common injection site side-effect was pain – 5% [25].The contraindication for OLAI use is the hypersensitivity to olanzapine or to any of the excipients.

Drug interactions

Olanzapine is metabolized in the liver with the use of CYP1A2. Its metabolism can be induced by tobacco smoking and carbamazepine taking which may result in lowering olanzapine levels. Fluvoxamine causes a significant inhibition of olanzapine metabolism, on average by 54% in non-smoking women and by 77% in smoking men, as does an antibiotic, ciprofloxacin. Olanzapine causes neither inhibition nor induction of main CYP450 isoenzymes thus no interaction with the majority of drugs is expected [25]. Caution in OLAI administration should be applied for patients who use alcohol or drugs which cause central nervous system sedation such as benzodiazepines and other antipsychotics. This is also true for the simultaneous use of olanzapine with drugs which can cause QTc prolongation (table 7).

Table 7. **Potential OALI interactions**

Medication	Effect on OLAI level
Carbamazepine	Decrease of OLAI level
Fluvoxamine	Increase of OLAI level
Ciprofloxacin	Increase of OLAI level
Tobacco smoking	Decrease of OLAI level

Reimbursement indications

In Poland OLAI is reimbursed for schizophrenia patients who have been previously stabilized on oral olanzapine and whose symptoms reappeared because of the persistent lack of adherence to treatment. The definition of this "lack of adherence" is given in the chapter dedicated to risperidone LAI.

Paliperidone

Paliperidone blocks the monoamine activity with a strong affinity to serotonergic 5-HT2 receptors and dopaminergic D2 receptors. It also blocks the α-1, H1 and α-2 receptors. It does not bind to cholinergic receptors. Although it is a strong D2 antagonists – the property which probably relates to the decrease of positive schizophrenia symptoms – it rarely causes cataleptic states and blocks motor functions to a lower degree than the classic neuroleptics. The central antagonistic action toward the serotonin system may be responsible for the lower incidence of extrapyramidal side-effects. Risperidone given orally or intramuscularly is to a various degree metabolized to papliperidone [29].

Indications for use

Adult schizophrenia patients after at least one relapse or exacerbation of symptoms in the patient's history caused by the persistent lack of adherence to treatment, who respond to treatment with risperidone and paliperidone. It has to be noted that paliperidone is available in both oral and long-acting injection form (PLAI). In the next section of this text long-acting injection form of paliperidone will be discussed.

Initiation of treatment

PLAI should be used for adult schizophrenia patients who have been stabilized under risperidone or paliperidone treatment. In selected patients who have previously shown a favorable response to oral paliperidone or risperidone, PLAI can be used without the previous stabilization of patients with oral antipsychotic treatment, when psychotic symptoms are of mild to moderate severity and there are indications for the use of long-acting injections. If the patient has been treated previously with another antipsychotic he/she should be switched to oral risperidone or paliperidone and afterwards to PLAI.

Dosage

PLAI is available in the doses of (suspension for injection with prolonged release) 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg. The initiation of treatment is recommended with the 150 mg dose and after a week (eight days after first injection) a dose

of 100 mg should be given. Both injections should be given into the deltoid muscle in order to reach the therapeutic serum level of paliperidone as quickly as possible. The recommended maintenance dose is 75 mg monthly; some patients may benefit from the lower or higher doses in the range from 25 mg to 150 mg, depending on individual tolerability and/or efficacy. Obese or overweight patients may require higher doses. After the second injection of PLAI is given, the subsequent administration of PLAI may be administered to the deltoid or to the gluteal muscle. Adjustment of the treatment dose may be done in monthly intervals. During the dose adjustment, the prolonged release of the active substance should be taken into consideration as the final therapeutic effect of the treatment may be seen only after a couple of months. Exceptionally a deviation from the expected date of drug administration of 1–2 days is possible. In stable patients the next monthly dose of PLAI may be administered with a deviation of several days.

Treatment strategy

The simultaneous administration of resperidone or paliperidone orally and PLAI should by applied with caution. At the time of the first PLAI injection, the oral paliperidone or risperidone can be discontinued. Treatment with PLAI should start with 150 mg on the first day and 100 mg on the eighth day of treatment. In the case that the patient is being treated with risperidone LAI and is switched to PLAI, the PLAI may be administered instead of the next RLAI injection. Subsequent doses of PLAI should be given at monthly intervals. In this case, the second PLAI injection takes place one month after the first PLAI injection, and not eight weeks after as has been previously described. In patients who have been stabilized on RLAI, the following PLAI doses are recommended (table 8).

Table 8. **Comparison of RLAI and PLAI doses [29]**

Former RLAI dose	PLAI dose
25 mg every 2 weeks	50 mg every month
37.5 mg every 2 weeks	75 mg every month
50 mg every 2 weeks	100 mg every month

In the case of discontinuation of PLAI treatment, the prolonged phenomenon of paliperidone release should be considered. According to the recommendation regarding the majority of other drugs, the requirement for continuation of treatment aimed at the elimination of extrapyramidal symptoms should be evaluated. The PLAI should not be used for patients with acute psychoses and/or those who require immediate sedation. The use of PLAI in the population of elderly patients has not been studied [30].

Tolerability

The drug is generally well tolerated. Possible side-effects are similar to those of risperidone (see above). During paliperidone treatment, the following side-effects have been observed: insomnia, headache, body weight increase, injection site reactions, agitation, somnolence, akathisia (dose-dependent), nausea, constipation, dizziness, tremor, vomiting, upper respiratory tract infections, diarrhea, tachycardia. Caution should be given to patients who suffer from cardio-vascular diseases or have prolonged QTc, also to those who take medication which can prolong the QTc interval. Like other drugs which act as dopamine receptor antagonists, the risk of tardive dyskinesia should be considered. In the case that the symptoms of tardive dyskinesia are present, the discontinuation of the antipsychotic drug should be considered. This also regards paliperidone.

Paliperidone should be administered with caution to patients with elevated prolactin levels during treatment. Paliperidone can cause orthostatic hypotension in some patients. PLAI should be used with caution in patients with cardio-vascular conditions (such as cardiac insufficiency, myocardial infarction or ischemia, or with disturbances of heart conduction), disturbances of cerebral circulation or conditions predisposing them to hypotension (e.g. dehydration or hypovolemia). In patients with a previous history of seizures or states which decreased the seizure threshold, PLAI should be used with caution. The drug is not recommended for patients with moderate to severe renal conditions (creatinine clearance < 50 ml/min) or with serious liver failure (Child-Pugh class C). Caution is also recommended in elderly patients with dementia who are at risk of brain insult. The contraindication for PLAI use is hypersensitivity to paliperidone, risperidone or to any excipient.

Drug interactions

Significant drug–drug interactions of PLAI and other drugs metabolized with the use of CYP450 are not expected (table 9) [1].

Table 9. **Potential PLAI interactions [1]**

Drug	Influence on PLAI level
Paroxetine	No change
Carbamazepine	Decrease of PLAI level
Valproates	Increase of PLAI level (clinically non-significant)
Risperidone	Increase of PLAI level

Caution is recommended when PLAI is used with drugs that may prolong the QTc interval, for instance with class IA antiarrhythmic drugs (e.g. chinidine, disopyramide) or class III drugs (such as amiodarone or sotalol), as well as with some antihistaminic drugs and antipsychotics. Special attention should be paid to patients who receive

PLAI and centrally acting drugs, such as anxiolytics, the majority of antipsychotics, sleep-inducers, opioids and alcohol.

Caution should also be given to those who receive paliperidone with medications which lower the seizure threshold, such as phenothiazines or butyrophenones, tricyclic antidepressants or SSRIs and tramadol [29].

Reimbursement indications

At the time the manuscript is under preparation, PLAI is not reimbursed in Poland.

References

1. Graffino M, Montemegni C, Mingrone C, Rocca P. *Long acting injectable antipsychotics in the treatment of schizophrenia: a review of literature*. Riv. Psichiatr. 2014, 49: 115–123.
2. Uchida H, Suzuki T. *Dose and dosing frequency of long-acting injectable antipsychotics: a systematic review of PET and SPECT data and clinical implications*. J. Clin. Psychopharmacol. 2014; 34(6): 728–735.
3. Bera RB. *Patient outcomes within schizophrenia treatment: a look at the role of long-acting injectable antipsychotics*. J. Clin. Psychiatry 2014; 75(supl. 2): 30–33.
4. Kane J, Kishimoto T, Correl CU. *Assessing the comparative effectiveness of long-acting injectable vs oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry*. J. Clin. Epidemiol. 2013; 60: S37–S41.
5. Malla A, Tibbo P, Chue P, Levy E, Manchanda R, Teehan M. et al. *Long-acting injectable anitpsychotics: recommendations for clinicians*. Can. J. Psychiatry 2013; 58(supl. 1): 30S–35S.
6. Lorca PM, Abbar M, Courtet P, Guillaume S, Lancrenon S, Samalin L. *Guidelines for the use and management of long-acting injectable antipsychotics in serious mental illness*. BMC Psychiatry 2013; 13: 340–357.
7. Hamann J, Kissling W, Heres S. *Checking the plausibility of psychiatrists' arguments for not prescribing depot medication*. Eur. Neuropsychopharmacol. 2014; 24: 1506–1510.
8. Wheeler A, Vanderpyl J, Carswell C, Sojkovic M, Robinson E. *Explicit review of risperidone long-acting injection prescribing practice*. J. Clin. Pharm. Ther. 2011; 36: 651–663.
9. Tandon R. *Antipsychotics in the treatment of schizophrenia: an overview*. J. Clin. Psychiatry 2011; 72(supl. 1): 4–8.
10. Dz.U. (Journal of Laws) 1994 No 111 item 535. *Ustawa z dnia 19 sierpnia 1994 r. o ochronie zdrowia psychicznego*.
11. Jarema M. *Leki przeciwpsychotyczne II generacji w terapii schizofrenii*. Terapia 2005; 11: 39–45.
12. Jarema M. *Strategies of long-term treatment of psychotic disorders*. In: Jarema M, Sartorius N. ed. *Aspects of long-term treatment of psychotic disorders*. Neuroendocrin. Let. 2007; 28 (supl 1): 13–26.

13. Jarema M. *Zalecenia w sprawie stosowania leków przeciwpsychotycznych II generacji*. Farmakoter. Psychiatr. Neurol. 2012; 28: 51–57.

14. Lafeuille MH, Dean J, Carter V, Duh MS, Fastenau J, Dirani R. et al. *Systematic review of long-acting injectables versus oral atypical antipsychotics on hospitalization in schizophrenia*. Curr. Med. Res Opin. 2014; 30: 1643–1655.

15. Gentile S. *Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comparative schematic review*. Pharmacotherapy 2013; 33: 1087–1106.

16. Park EJ, Amatya S, Kim MS, Park JH, Seol E, Lee H. et al. *Long-acting injectable formulations of antipsychotic drugs for the treatment of schizophrenia*. Arch. Pharm. Res. 2013; 36: 651–659.

17. Rauch AS, Fleischhacker WW. *Long-acting injectable formulations of new-generation antipsychotics: a review from a clinical perspective*. CNS Drugs 2013; 37: 637–652.

18. *Rispolept Consta. Charakterystyka produktu leczniczego*. The Office for Registration of Medicinal Products letter dated 21.09.2012. http://leki.urpl.gov.pl/files/Rispolept Consta _proszek_3dawki.pdf [retrieved: 20.03.2015].

19. Gopal S, Hough D, Karcher K, Naumah I, Palumbo J, Berlin JA. et al. *Risk of cardiovascular morbidity with risperidone or paliperidone treatment: analysis of 64 randomized, double-blind trials*. J. Clin. Psychopharmacol. 2013; 33: 157–161.

20. Citrome L, Collins JM, Nordstrom BL, Rosen EJ, Baker R, Nadkarni A. et al. *Incidence of cardiovascular outcomes and diabetes mellitus among users of second-generation antipsychotics*. J. Clin. Psychiatry 2013; 74: 1199–1206.

21. Fleischhaker WW, Sanchez R, Perry PP, Jin N, Peters-Stricland T, Johnson BR. et al. *Aripiprazol once-monthly for treatment of schizophrenia: double-blind, randomized, non-inferiority study*. Br. J. Psychiatry 2014; 205(2): 135–144.

22. Kane JM, Sanchez R, Zhao J, Duca AR, Johnson BR, McQuade RD. et al. *Hospitalization rates in patients switched from oral antipsychotics to aripiprazole once-monthly for the management of schizophrenia*. J. Med. Econ. 2013; 16(7): 917–925.

23. Kane JM, Sanchez R, Perry PP, Jin N, Johnson BR, Forbes RA. et al. *Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomised, double-blind, placebo-controlled study*. J. Clin. Psychiatry 2012; 73(5): 617–624.

24. Tourian L, Margolese HC. *Extended-release intramuscular aripiprazole for maintenance pharmacotherapy in schizophrenia and related disorders*. Neuropsychiatry 2013; 3: 345–354

25. *Zypadhera. Charakterystyka produktu leczniczego*. The Office for Registration of Medicinal Products letter dated 10.11.2014. http://leki. urpl.gov.pl/files/ZypAdhera.pdf [retrieved: 20.03.2015].

26. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP. et al. *Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial*. Lancet 2008; 371: 1085–1097.

27. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO. et al. *Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*. N. Engl. J. Med. 2005; 353: 1209–1223.

28. Jarema M, Rabe-Jabłońska J, Pupek-Musalik D, Ostrowska L, Wożakowska-Kapłon B, Heitzman J. *Zaburzenia metaboliczne w psychiatrii – raport*. Farmakoter. Psychiatr. Neurol. 2011; 1: 1–43.

29. *Xeplion. Charakterystyka produktu leczniczego*. http://ec.europa.eu/health/documents/ community-register/2011/2011030497289/anx_97289_pl.pdf [retrieved: 20.03.2015].

30. Newton R, Hustig H, Lakshmana R, Lee J, Motamanrri B, Norrie P. et al. *Practical guidelines on the use of paliperidonepalmitate in schizophrenia*. Curr. Med. Res. Opin. 2012; 28(4): 559–567.

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