Profile of paliperidone palmitate once-monthly long-acting injectable in the management of schizophrenia: long-term safety, efficacy, and patient acceptability – a review

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Background and objectives: Short-term studies focused on once-monthly paliperidone palmitate (PP) at doses of 25 mg eq, 50 mg eq, 75 mg eq, 100 mg eq, or 150 mg eq have shown its efficacy and tolerability in the treatment of schizophrenia patients. However, few open-label and long-term studies are available regarding this new pharmacological formulation. Thus, our main aim was to review the scientific evidence on efficacy, safety, tolerability, and preference of PP in these populations.

Method: Electronic searches were conducted by using PubMed and ISI Web of Knowledge databases. All relevant studies published from 2009 until January 2015 were included without any language restriction if patients met diagnostic criteria for schizophrenia, and adequate information on efficacy, safety, and tolerability of once-monthly PP was available.

Results: Nineteen studies were identified irrespective of the study design and duration of the follow-up period. Randomized, double-blind, placebo-controlled trials found that schizophrenia patients receiving PP showed a significant improvement in psychotic symptoms and similar adverse events compared to placebo and suggested that all doses of PP were efficacious and well tolerated. Other studies demonstrated noninferiority of PP compared to risperidone long-acting injectable in recently diagnosed schizophrenia patients, chronically ill patients, as well as in acute and nonacute symptomatic schizophrenia patients, and a similar proportion of treatment-emergent adverse events between both groups were also noted.

Conclusion: Several studies have demonstrated that schizophrenia patients treated with PP show higher rates of improvement of psychotic symptoms compared to placebo, and similar efficacy and tolerability outcomes were noted when comparing PP to risperidone long-acting injectable or oral, paliperidone extended release.

Keywords: once-monthly paliperidone palmitate, long-acting antipsychotics, psychosis, schizophrenia, safety, efficacy, relapses

Introduction

Antipsychotics (understood as dopamine-receptor regulators, antagonists and partial agonists of dopamine and serotonin receptors) represent the cornerstone of the current pharmacological treatment of schizophrenia. Since the initial stages of antipsychotics (chlorpromazine was released in 1953), it was observed that treatment compliance was difficult to achieve and it was directly related with psychotic relapse and readmission. Although the first formulations were for oral administration, the specific characteristics of the disease allowed the development of the concept of long-acting injectables (LAIs) in order to ensure treatment adherence and management of these populations.
Initial studies comparing long-acting injectable antipsychotics (LAIAs) with oral formulations showed that the relapse risk ratio in patients treated with long-term formulations was much lower. A systematic review underlined the inconclusive results but highlighted that mirror-image studies would be better designed and LAIAs might have improved long-term outcome in schizophrenia patients.

Since the introduction of second-generation antipsychotics (SGAs), its oral formulations took over the research in schizophrenia, leaving behind first-generation antipsychotics (FGAs). Its initial promising effects in positive, negative, and cognitive symptoms did not end up with the previous difficulties in improving the final outcomes. Although there is still debate and controversy over efficacy differences between SGA and FGA, overall relapse risk ratio has been described to be lower with SGA compared to FGA, which would imply relevant and beneficial consequences in patient’s performance.

Again, the introduction of long-acting risperidone came after the persistent need in treating patients with schizophrenia and psychotic symptoms, treatment adherence, and the still unresolved problem of treatment-resistance symptoms. Although patient’s difficulties to be compliant to treatments is frequent in general medical practice, its relevance in schizophrenia seems extreme as consequences range from psychotic relapse, hospitalization, disruptive behavior, reduced capacity to recovery, and worse outcome and prognosis. Nevertheless, social and familiar environment also play a role in the adherence, so a multidisciplinary approach is required to improve patient’s adherence and functioning.

LAIA formulations have traditionally been used at later stages of the disorder, for those patients with schizophrenia with most severe symptoms, poorest adherence, higher rates for relapses, and generally poorest outcomes. However, several authors support the notion that patients in early phases may gain from LAIAs, at a time when their disorder is most treatable, in order to avoid recurrences and rehospitalizations and decrease complications associated with noncompliance such as substance abuse, violence, legal conflicts, and treatment resistance.

A group of authors have tried to clarify whether LAIAs are more effective to prevent relapses in schizophrenia patients in comparison to oral formulations. In a recent meta-analysis of randomized controlled trials, LAIAs did not show to be more effective in reducing relapses compared with oral antipsychotics in schizophrenia patients. But this finding was vulnerable to a cohort bias, as populations included were less representative of real-world patients than naturalistic studies. For instance, population in mirror-image studies better reflect clinical practice for patients receiving LAIAs than randomized controlled trials. Results from mirror-image studies in patients eligible for clinical use of LAIAs showed strong superiority of LAIs compared to oral antipsychotics in preventing hospitalizations.

Paliperidone is a metabolite of risperidone that was previously introduced commercially in an oral formulation. Like risperidone, paliperidone blocks both 5HT2A and dopamine 2 receptors, alpha 1 and alpha 2 adrenoceptors, and histamine 1 receptors, but not beta adrenoceptors, muscarinic cholinceptors, or peptidergic receptors.

In pharmacokinetic trials sponsored by the manufacturer, the maximum paliperidone plasma concentrations were 28% higher when starting treatment in the deltoid muscle, rather than in the gluteal muscle. This difference may be related to the different distribution of muscle and adipose tissue between the two sites. Accordingly, the manufacturer recommends deltoid injections on the first (150 mg) and eighth days ±4 (100 mg) of treatment, to rapidly achieve appropriate plasma concentrations, followed by monthly administration into either the deltoid or gluteal muscles. The manufacturer does not recommend oral supplementation of paliperidone palmitate (PP). The manufacturer reports that oral paliperidone is roughly equivalent to PP on the following doses: 3 mg oral to 50 mg of palmitate, 6 mg to 75 mg, 9 mg to 100–150 mg. In its injectable formulation, PP is combined with inactive substances, so doses of PP can be expressed in terms of milligram equivalents (mg eq) of the active substance, PP, so that the 234 mg dose has 150 mg eq of the active substance, PP, so that the 234 mg dose has 150 mg eq of PP, the 156-mg dose has 100 mg eq, the 117-mg dose has 75 mg eq, the 78-mg dose has 50 mg eq, and the 39-mg dose has 25 mg eq.

In short-term studies, PP is an antipsychotic drug that was shown to be more efficacious than placebo. Related adverse events are similar to those of its related compounds, paliperidone and risperidone, with extrapyramidal movement disorders, weight gain, substantial increases in serum prolactin, and tachycardia all more common with PP than placebo.

We therefore aimed to review the scientific evidence regarding the efficacy, safety, and tolerability of PP in the treatment of schizophrenia patients. As a particular mention, we provide a subsection focused on recently diagnosed schizophrenia patients, as this topic has been of interest in the last years for many clinical reasons.
Methods
We performed electronic searches by using PubMed and ISI Web of Knowledge database. All relevant studies published from 2009 until 2015 were included without any language restriction if patients fulfilled schizophrenia diagnostic criteria according to Diagnostic and Statistic Manual of Mental Disorders and International Classification of Diseases (ICD-10). The following key words were used: “once-monthly paliperidone palmitate and schizophrenia”, “paliperidone palmitate and safety”, “paliperidone palmitate and tolerability”, and “paliperidone palmitate and efficacy”. References of selected articles were carefully searched to identify potential further relevant articles. Psychopathological assessment as efficacy measures was considered when validated scales were used in the reported studies, and adverse events were taken into account when self-reported or measured by specific scales on safety and tolerability. Studies including data on pharmacoeconomics or cost-effectiveness of PP were excluded, as this was not the aim of the present review.

Results
Nineteen studies were identified regarding the efficacy, safety, and tolerability of PP on the treatment of schizophrenia patients. Studies were included irrespective of the study design and follow-up period, as we considered special interest to summarize all the scientific evidence focused on the aforementioned new pharmacological LAI formulation.

A specific subsection on recent-onset schizophrenia patients has been implemented due to the increasing body of evidence in the pharmacological treatment of these patients.

From the 19 selected studies, we found several articles reporting outcomes by using different study designs, as follows: one randomized, cross-over trial,\textsuperscript{17} six randomized, double-blind, placebo-controlled trials,\textsuperscript{18-23} one open-label, noninferiority study comparing PP with risperidone long-acting injectable (RLAI),\textsuperscript{24} five randomized, double-blind, noninferiority clinical trials, four of them comparing PP with RLAI\textsuperscript{25-28} and one comparing PP with oral paliperidone extended release.\textsuperscript{29} Further, six open-label prospective studies were detected: one long-term, 1-year prospective study,\textsuperscript{30} one open-label, double-blind trial comparing PP in recently diagnosed patients versus chronically ill schizophrenia;\textsuperscript{31} one flexible-dose, interventional, single-arm study with 6-month follow-up;\textsuperscript{32} one open-label, 15-month, active-controlled trial;\textsuperscript{33} one open-label, 6-month, prospective study;\textsuperscript{34} and a 18-month, open-label, Phase IIIb study.\textsuperscript{35}

Characteristics, study design, and main findings on efficacy, safety, and tolerability of the reviewed studies can be found in Tables 1 and 2.

Specific studies on recent-onset schizophrenia patients
Poor adherence to oral antipsychotics and high relapse and rehospitalization rates have been extensively found in first episode of psychosis or recent-onset schizophrenia patients. LAIs may improve adherence to treatment and reduce the rate of relapse and rehospitalization in first-episode or recent-onset schizophrenia.\textsuperscript{36-44} For this reason, we have included a specific section regarding this issue.

Bossie and colleagues investigated the efficacy and tolerability of PP by comparing different PP doses with placebo in recently diagnosed schizophrenia patients (≤5 years).\textsuperscript{22} The authors found significant improvement in Positive and Negative Syndrome Scale (PANSS) total scores, but not an improvement in Clinical Global Impression-Severity Scale (CGI-S) and Personal and Social Performance Scale (PSP), in those patients receiving PP compared to those treated with placebo. In this subgroup of patients, PP initiation doses (150 mg eq on day 1, 100 mg eq on day 8) were well tolerated with no unexpected findings.

Long-term tolerability of PP was compared between recently diagnosed schizophrenia patients (≤5 years) and chronically ill patients as a post hoc analysis from an open-label multicenter trial.\textsuperscript{31} Regarding main findings, nasopharyngitis was more common in chronically ill patients compared to recently diagnosed schizophrenia patients, and amenorrhea in recently diagnosed patients. Further, the authors found that prolactin levels were higher in women recently diagnosed when compared to chronically ill female schizophrenia patients.

On the other hand, Fu et al compared the efficacy and tolerability of PP to RLAI in a sample formed by recently diagnosed schizophrenia patients; and over the entire sample, efficacy was found to be similar between both groups as measured by mean PANSS score changes, CGI-S and score changes in functionality, as measured by the PSP, and responder rates to treatment.\textsuperscript{28} Further, rates for adverse events were found to be similar between both LAI groups.

The most recent study evaluating the efficacy and safety of PP in recent-onset schizophrenia patients was carried out by Zhang and colleagues.\textsuperscript{35} This 18-month open-label Phase IIIb study found that patients unsuccessfully treated with oral antipsychotics and switch to PP showed a significant improvement in psychotic symptoms (measured by PANSS scale and
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Topic</th>
<th>Sample (n)</th>
<th>Study design</th>
<th>Aims</th>
<th>Severity of patients</th>
<th>Comparison groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hough et al 2009</td>
<td>Efficacy, safety, and preference</td>
<td>252</td>
<td>25-week randomized, multicenter, cross-over trial</td>
<td>To evaluate the safety and tolerability of PP in the injection sites (deltoid – gluteus)</td>
<td>Mild</td>
<td>1:1:1</td>
</tr>
<tr>
<td>Hough et al 2010</td>
<td>Efficacy, safety, and tolerability</td>
<td>849</td>
<td>Two phases 9-week open label</td>
<td>To assess efficacy and tolerability of PP in delaying time-to-relapse</td>
<td>Mild</td>
<td>1:1:1</td>
</tr>
<tr>
<td>Nasrallah et al 2010</td>
<td>Efficacy, safety, and tolerability</td>
<td>514</td>
<td>13-week multicenter, randomized, double-blind, placebo-controlled trial</td>
<td>To assess the efficacy and safety of three fixed doses of PP</td>
<td>Mild</td>
<td>1:1:1:1</td>
</tr>
<tr>
<td>Pandina et al 2010</td>
<td>Efficacy and safety</td>
<td>652</td>
<td>13-week randomized, double-blind, placebo-controlled multicenter study</td>
<td>To assess the efficacy and safety of higher doses of PP</td>
<td>Acute patients</td>
<td>1:1:1:1</td>
</tr>
<tr>
<td>Alphs et al 2011</td>
<td>Efficacy, safety, and tolerability</td>
<td>312</td>
<td>Post hoc analysis of a 13-week randomized, double-blind, placebo-controlled, multicenter clinical trial</td>
<td>To assess onset of efficacy and tolerability</td>
<td>Acute (markedly to severely ill)</td>
<td>1:1:1:1</td>
</tr>
<tr>
<td>Bossie et al 2011a</td>
<td>Efficacy and tolerability</td>
<td>652</td>
<td>Post hoc analysis of a 13-week randomized, double-blind, placebo-controlled, clinical trial</td>
<td>To examine the tolerability of the initiation doses for PP and efficacy</td>
<td>Acute, mild</td>
<td>1:1:1:1</td>
</tr>
<tr>
<td>Bossie et al 2011b</td>
<td>Efficacy and tolerability</td>
<td>652</td>
<td>13-week randomized, double-blind, placebo-controlled, clinical trial</td>
<td>To investigate the time of onset of efficacy and tolerability of PP</td>
<td>Mild</td>
<td>1:1:1:1</td>
</tr>
<tr>
<td>Li et al 2011</td>
<td>Efficacy, safety, and tolerability</td>
<td>452</td>
<td>13-week open-label, rater-blinded, parallel-group, noninferiority study</td>
<td>To evaluate the noninferiority of PP to RLAI</td>
<td>Acute</td>
<td>1:1:1:1</td>
</tr>
<tr>
<td>Pandina et al 2011</td>
<td>Efficacy, safety, and tolerability</td>
<td>1,220</td>
<td>13-week randomized, double-blind, double-dummy, active-controlled, parallel-group multicenter noninferiority comparative study</td>
<td>To assess noninferiority of PP versus RLAI</td>
<td>Acute</td>
<td>1:1:1:1</td>
</tr>
<tr>
<td>Study</td>
<td>Title</td>
<td>Year</td>
<td>Study Design</td>
<td>Primary Objective</td>
<td>Patient Characteristics</td>
<td>Treatment Details</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Coppola et al 2012</td>
<td>Safety and tolerability</td>
<td>2012</td>
<td>1-year open-label, long-term prospective, multiple-dose, multicenter study</td>
<td>To evaluate the long-term safety and tolerability of PP 150 mg eq</td>
<td>Mild</td>
<td>Treatment A (fixed doses of PP 150 mg eq)</td>
</tr>
<tr>
<td>Sliwa et al 2012</td>
<td>Efficacy and tolerability</td>
<td>2012</td>
<td>Post hoc analysis from an open-label, double-blind, multiphase trial</td>
<td>To investigate long-term tolerability according to duration of illness</td>
<td>Mild-severe</td>
<td>Treatment B (50–150 mg eq)</td>
</tr>
<tr>
<td>Fleischhacker et al 2012</td>
<td>Efficacy, safety, and tolerability</td>
<td>2012</td>
<td>53-week double-blind, noninferiority trial</td>
<td>To assess the safety and tolerability of PP in maintenance therapy</td>
<td>Mild</td>
<td>Recently diagnosed</td>
</tr>
<tr>
<td>Alphs et al 2013</td>
<td>Efficacy and tolerability</td>
<td>2013</td>
<td>Post hoc analysis of a 13-week randomized, double-blind clinical trial</td>
<td>To evaluate clinical response to treatment with PP and RLAI</td>
<td>Mild</td>
<td>Chronic ill</td>
</tr>
<tr>
<td>Fu et al 2014</td>
<td>Efficacy, safety, and tolerability</td>
<td>2014</td>
<td>Post hoc safety and efficacy analyses of a 13-week, double-blind, double-dummy, multicenter comparative study</td>
<td>To compare efficacy and tolerability of PP with oral risperidone (and RLAI) during the first month of treatment</td>
<td>Mild</td>
<td>Flexible dosing</td>
</tr>
<tr>
<td>Gopal et al 2014</td>
<td>Safety and tolerability</td>
<td>2014</td>
<td>6-month, post hoc analysis of randomized, controlled, long-term, clinical research studies</td>
<td>To determine the incidence of tardive dyskinesia in PP and PER</td>
<td>Mild</td>
<td>1:1</td>
</tr>
<tr>
<td>Schreiner et al 2014</td>
<td>Efficacy, safety, and tolerability</td>
<td>2014</td>
<td>6-month prospective flexible-dose, interventional, single-arm, international, unblinded</td>
<td>To explore the tolerability, safety, and treatment response</td>
<td>Nonacute</td>
<td>1:1</td>
</tr>
<tr>
<td>Alphs et al 2014</td>
<td>Efficacy, safety, and tolerability</td>
<td>2014</td>
<td>15-month, randomized, active-controlled, open-label, board-blinded, parallel-group, flexible-dose, multicenter study</td>
<td>To assess the efficacy, safety, and tolerability of PP in both explanatory and pragmatic approaches</td>
<td>Severe</td>
<td>PP versus oral antipsychotics</td>
</tr>
<tr>
<td>Mao et al 2014</td>
<td>Efficacy, safety, and tolerability</td>
<td>2014</td>
<td>6-month prospective, multicenter, nonrandomized, single-arm, open-label study</td>
<td>To explore treatment outcomes and suggest recommendations for use of PP</td>
<td>Acute</td>
<td>PP (50–150 mg eq)</td>
</tr>
<tr>
<td>Hargarter et al 2015</td>
<td>Efficacy, safety, and tolerability</td>
<td>2015</td>
<td>18-month, nonrandomized, single-arm, open-label, mirror-designed, multicenter, Phase-IIIb study</td>
<td>To assess the effectiveness and safety of PP and impact on hospitalization in patients previously treated with oral AP</td>
<td>Mild-severe</td>
<td>PP (50 mg eq, 75 mg eq, 100 mg eq, or 150 mg eq; flexible dosing)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AP, antipsychotics; PER, paliperidone extended release; PP, paliperidone palmitate; RLAI, risperidone long-acting injection.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Efficacy assessment</th>
<th>Safety and tolerability assessment</th>
<th>Efficacy outcomes</th>
<th>Safety and tolerability outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hough et al 2009</td>
<td>PANSS, CGI-S</td>
<td>TEAEs</td>
<td>(Efficacy assessments were presented at baseline)</td>
<td>Similar reporting of TEAEs in both injection sites during the last 8 weeks after switching</td>
<td>Local tolerability weekly better with gluteal injections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAS, BARS, AIMS, Medication, Preference Questionnaire</td>
<td></td>
<td>Differences in the deltoid injection site preference between countries and sex</td>
<td>Patients from US countries preferred deltoid site versus non-US, and men preferred deltoid site</td>
</tr>
<tr>
<td>Hough et al 2010</td>
<td>PANSS, CGI-S, PSP</td>
<td>TEAEs</td>
<td>Time-to-relapse was higher in PP treated schizophrenia patients</td>
<td>Injection-site pain was similar between both groups</td>
<td>Schizophrenia patients receiving PP showed a delay in psychotic relapses and similar tolerability than placebo treated patients</td>
</tr>
<tr>
<td>Nasrallah et al 2010</td>
<td>PANSS, CGI-S, PSP</td>
<td>SAS, BARS, AIMS, Laboratory tests</td>
<td>Significant improvement in psychotic symptoms in all PP groups</td>
<td>Similar TEAEs frequencies in PP groups and placebo</td>
<td>All doses of PP were efficacious and well tolerated</td>
</tr>
<tr>
<td>Pandina et al 2010</td>
<td>PANSS, CGI-S, VAS for insomnia</td>
<td>TEAEs, SAS, BARS, AIMS, Laboratory tests</td>
<td>Psychotic symptoms improved significantly in all PP dose groups versus placebo</td>
<td>Injection-site pain and dizziness were the TEAEs most commonly encountered</td>
<td>PP at doses of 25 mg eq, 100 mg eq, or 150 mg eq was efficacious compared to placebo</td>
</tr>
<tr>
<td>Alphs et al 2011</td>
<td>PANSS, CGI-S, PSP</td>
<td>TEAEs</td>
<td>Improvement of psychotic symptoms after receiving 234 mg PP</td>
<td>TEAEs (most frequently): headache, insomnia, schizophrenia exacerbation, injection site pain, agitation</td>
<td>Acute treatment with PP is effective and well tolerated for markedly to severely schizophrenia patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAS, BARS, AIMS, Laboratory tests</td>
<td></td>
<td>No differences in benzodiazepine use</td>
<td>No differences in SAS, BARS and AIMS scores</td>
</tr>
<tr>
<td>Bossie et al 2011a</td>
<td>PANSS, CGI-S, PSP</td>
<td>TEAEs</td>
<td>Improvement of psychotic symptoms (PANSS) after initiation doses in all PP groups</td>
<td>Injection site pain, headache, and agitation more common in PP versus placebo</td>
<td>Initiation doses of PP in recently diagnosed schizophrenia demonstrated improvement in psychotic symptoms</td>
</tr>
<tr>
<td>Bossie et al 2011b</td>
<td>PANSS, Responder rates</td>
<td>TEAEs</td>
<td>After the day 8 injection, PP groups showed greater improvement than placebo, that continued at day 22 and 36</td>
<td>No unexpected tolerability findings</td>
<td>Initiation doses of PP were associated with significant improvement in psychotic symptoms by day 8, 22, and 36</td>
</tr>
<tr>
<td>Li et al 2011</td>
<td>PANSS, CGI-S, PSP</td>
<td>TEAEs</td>
<td>Similar improvement in psychotic symptoms between both groups (PP, RLAI)</td>
<td>TEAEs rates were similar between groups</td>
<td>PP demonstrated noninferiority compared to RLAI</td>
</tr>
</tbody>
</table>
Similar decrease in psychotic symptoms in both groups

Proportion of TEAEs and EPS-related TEAEs similar in both groups

Noninferiority of PP to RLAI was demonstrated in acutely ill schizophrenia patients

The most frequent TEAEs: nasopharyngitis, insomnia, injection-site pain, headache, tachycardia, akathisia, and tremor

Safety results of PP 150 mg eq and other doses were consistent with previous studies

Nasopharyngitis rates were higher in chronically ill patients compared to recently diagnosed

TEAEs associated with prolactin levels were similar in both groups, but higher in recently diagnosed women than chronically ill female schizophrenia patients

Insomnia most common adverse event, similar in both groups

Both treatments showed a similar tolerability

PP did not show comparable efficacy to RLAI (design dependent)

PP: Insomnia, headache, injection-site pain

RLAI: insomnia, headache

Treatment with PP or RLAI contributes to improvement of treatment response and adherence

For the completed study, tolerability after initiation of treatment with PP or RLAI was similar in early diagnosed schizophrenia patients

TD appears to be similar in both groups (PP and PeR)

Time of onset of TD was highest in the first month

Nonacute symptomatic schizophrenia patients switched to PP showed an improvement in psychotic symptoms

Certain clinical features might be associated with increased risks of arrests (preliminary results, final results not published)
The efficacy and tolerability of delirious and glutel injections of PP were investigated in stable schizophrenia patients by Hough et al by means of adverse event rates and scores of the main rating scales for extrapyramidal symptoms (Tables 1 and 2). The authors highlighted that at initiation doses of PP, both injection sites had a similar reporting of adverse events, as well as during the last 8 weeks after switching from site. However, several findings should be taken into consideration. Differences in the injection site differ between US and non-US countries and men preferred deltoïd site in contrast with women who reported the preference of glutel site. Further, local tolerability was better with gluele injections than deltoïd sites.

The efficacy and tolerability of three fixed doses of PP versus placebo were investigated by Nasrallah et al. The authors found that patients treated with all PP groups showed a significant improvement in psychotic symptoms, but no differences in functionality were detected compared to placebo. Regarding safety and tolerability, it should be taken into consideration that prolactin levels were higher in PP groups than placebo. The efficacy and tolerability of three fixed doses of PP versus placebo were investigated by Nasrallah et al. The authors found that patients treated with all PP groups showed a significant improvement in psychotic symptoms, but no differences in functionality were detected compared to placebo. Regarding safety and tolerability, it should be taken into consideration that prolactin levels were higher in PP groups than placebo. The increase was dose-dependent.

On the other hand, Hough et al confirmed the efficacy of PP in delaying time-to-relapse in adult schizophrenia patients. The authors also found that injection-site pain was similar in those treated with PP, as well as those receiving placebo.

In the same line of the study aforementioned, Pandina et al confirmed the efficacy and tolerability of lower doses of PP (25 mg eq, 100 mg eq) and observed positive results at higher doses of PP (150 mg eq) in acutely exacerbated schizophrenia patients.

The same authors evaluated the noninferiority of PP flexible dosing versus RLAI. After 13 weeks of treatment, changes in psychotic symptoms showed a similar decrease in both groups, and similar frequency of adverse events.

Alpha et al carried out a randomized placebo-controlled trial in acutely schizophrenic patients by comparing efficacy and tolerability of PP dosing to placebo. The study included markedly to severely ill schizophrenia patients defined as 5 or more scores of the CGI-S at baseline, and the authors concluded that active treatment with PP was an effective and
well-tolerated treatment in this kind of clinical populations when compared to placebo.

In this line, Bossie and colleagues investigated the onset of efficacy and tolerability of PP by comparing different doses with placebo in schizophrenia patients.\textsuperscript{22,23} The authors found that PP was associated with higher psychopathological improvement by days 8, 22, and 36 when compared to placebo and found no unexpected tolerability findings.

An open-label, parallel-group noninferiority study evaluating the efficacy and safety of PP versus RLAI was conducted by Li and colleagues.\textsuperscript{24} The authors found both treatment groups to be similar in terms of adverse events and improvement in psychotic symptoms, as measured by the CGI-S and the PANSS Scale, suggesting that PP demonstrated noninferiority compared to RLAI.

The first long-term, open-label, prospective study in schizophrenia patients treated with PP was conducted by Coppola and collaborators, who aimed to assess the long-term safety of PP at 150 mg eq.\textsuperscript{25} In this study, all patients did not receive injectable antipsychotic formulations previously, and the authors concluded that safety results of this PP dosing were consistent with previous results recently published.

In a similar study design, long-term tolerability of PP was investigated in an open-label, double-blind, multicenter trial in recently diagnosed schizophrenia.\textsuperscript{31} Main findings of this study are mentioned in Specific Studies on recent Schizophrenia patients subsection.

The noninferiority of PP to RLAI was assessed in a sample of acutely symptomatic schizophrenia patients in a 53-week, double-blind study.\textsuperscript{26} The authors concluded that insomnia was the adverse event most commonly encountered, and tolerability of PP and RLAI was found to be similar in both groups. However, probably due to the initial dosing strategy, PP did not show less efficacy when compared to RLAI. In agreement with the previous study, a recent one reporting response to treatment with two, long-acting, injectable atypical antipsychotics (PP, RLAI) also indicated that individuals diagnosed with schizophrenia previously treated with oral antipsychotics showed a significant reduction of psychotic symptoms.\textsuperscript{27}

When focusing on safety and tolerability profile of PP, it should be highlighted that Gopal et al focused their investigations in schizophrenia patients receiving PP or oral paliperidone extended release by comparing rates of tardive dyskinesia measured by two well-established methods: the Schooler–Kane standardized research criteria, based on the Abnormal Involuntary Movement Scale, and the spontaneous reporting of this particular adverse event.\textsuperscript{29} Frequency and incidence of tardive dyskinesia were similar in both treatment groups being low the observed risk ($<$0.2\%) in the entire sample. In this study, dyskinesia rate was higher within the first month of treatment and clearly decreased over time.

A prospective, flexible-dose, interventional, 6-month study was carried out by Schreiner and colleagues in nonacute but symptomatic adult schizophrenia patients who were unsuccessfully treated with oral antipsychotics.\textsuperscript{32} This pragmatic study found that more than two-thirds of the nonacute patients switched to PP showed an improvement in psychotic symptoms and functionality after 6 months of treatment. Furthermore, satisfaction with medication and sleep quality, as measured by the Treatment Satisfaction Questionnaire for Medication Scale, showed a relevant and significant improvement in patients receiving PP.

Recently, Alphs et al published the study design and rationale of the Paliperidone Palmitate Research in Demonstrating Effectiveness study, a 15-month, open-label, and prospective study carried out between 2010 and 2013.\textsuperscript{33} The study aimed to compare PP and oral antipsychotics in schizophrenia patients in a pragmatic and explanatory approach. Preliminary results in a sample of schizophrenia patients with history of arrests or incarceration were presented at the 167th Annual Meeting of the American Psychiatric Association.\textsuperscript{43}

Hargarter et al carried out an open-label, prospective study with a 6-month follow-up in acutely schizophrenia patients and suggested several recommendations for the use of PP.\textsuperscript{34} The authors found that the vast majority of the sample receiving PP showed improvement in psychotic symptoms, and PP was well tolerated, with the treatment-emergent adverse event most commonly found being injection-site pain.

Discussion

LAIA have demonstrated to be useful regarding patients’ tolerability and adherence either in FGA or SGA formulations.\textsuperscript{46} Although symptom recognition or treatment resistance still underlie the difficulties expressed by many patients, the evaluation of LAIA in clinical practice and the possibility of discussing the formulation with patients and family reflects a new paradigm in treatment management.\textsuperscript{8}

The current state of knowledge favors the introduction of LAIA at different stages of the illness reflecting a change of paradigm toward new treatment options not only from the patient’s personal view but also and most important from the mental health care providers themselves.\textsuperscript{47}

LAIA formulations have traditionally been used at latter stages, but some authors defend that early-phase patients
may have the most to gain from them.\textsuperscript{9,39-42} Some clinical guidelines, like the Canadian one, are beginning to include the recommendation to use LAIAs in patients in early stages of the disorder.\textsuperscript{45,48} This proportion could also be increased with the recent appearance of new second-generation LAIAs, such as olanzapine pamoate, PP, and aripiprazole depot.\textsuperscript{49}

Results from naturalistic studies, such as mirror-image studies, showed strong superiority of LAIs compared to oral antipsychotics in preventing hospitalizations.\textsuperscript{13}

Thus, our main goal was to review the available scientific literature focused on the efficacy, safety, and tolerability of once-monthly PP in schizophrenia patients.

We identified 19 studies reporting data on efficacy, safety, tolerability, or preference of PP in the treatment of schizophrenia patients. From those selected, several study designs can be identified.

In a first step, it should be noted that gluteal injections have demonstrated better local tolerability than deltoid administrations in a randomized cross-over trial.\textsuperscript{17} However, this is the unique study specifically investigating tolerability in both types of administration, so results should not be generalizable.

Regarding the efficacy and safety of different doses of PP, six randomized, double-blind, placebo-controlled trials found that schizophrenia patients receiving PP showed a significant improvement in psychotic symptoms and similar adverse events compared to placebo,\textsuperscript{18-23} suggesting that all doses of PP were efficacious and well tolerated. Further, time-to-relapse was higher in those patients treated with PP.\textsuperscript{18}

In spite of the evidence previously mentioned, several noninferiority studies have compared PP with other LAI formulations or oral paliperidone.\textsuperscript{24-29} These studies demonstrated noninferiority of PP compared to RLAI in early diagnosed schizophrenia patients and chronic schizophrenic patients independent of severity of illness. Further, a similar proportion of treatment-emergent adverse events was noted between both the groups. On the other hand, nonacute symptomatic schizophrenia patients, PP has also demonstrated its efficacy in terms of psychotic improvement, and lower rates of mild to moderate adverse events compared to RLAI.

The most recent studies investigating this field were conducted by Hargarter et al and Zhang et al\textsuperscript{34,35} who found that PP in acute schizophrenia was well tolerated and associated with improvement in psychotic symptoms. On the other hand, it should be mentioned that Sliwa et al found higher prolactin levels in those women suffering from an acute recent-onset schizophrenia in comparison with chronically ill female schizophrenia patients.\textsuperscript{31}

Conclusion

Short-term studies based on PP at doses of 25 mg eq, 50 mg eq, 75 mg eq, 100 mg eq, or 150 mg eq have shown its efficacy and tolerability in the treatment of schizophrenia.

Several studies have demonstrated that schizophrenia patients treated with PP show higher rates of improvement of psychotic symptoms compared to placebo and similar efficacy and tolerability outcomes when comparing PP to RLAI or oral paliperidone extended release.

However, in the present review, several limitations should be taken into consideration. To date, no studies have compared the efficacy and tolerability of PP with other LAI formulations, except for RLAI. It would be of interest, and further research is needed, to compare PP with typical antipsychotics and other formulations to date not studied.

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