ABSTRACT - Objective: Summarize and synthesize the current literature regarding long-acting injectable paliperidone palmitate for the treatment of schizophrenia. Methods: A literature search of PubMed, Embase, and Web of Science was conducted in February 2016, using the following search terms in varying permutations: schizophrenia; antipsychotic medication; long-acting injectable; paliperidone palmitate; 3-monthly injectable. Results: Once-monthly injectable paliperidone palmitate (PDP) has demonstrated comparable efficacy as 1st-generation long-acting injectable antipsychotics (LALAs) in reducing disease severity and re-hospitalizations in schizophrenic patients. However, PDP leads to significantly less extrapyramidal symptoms than these older medications indicating a superior safety profile. Compared to oral 2nd-generation antipsychotics, PDP has shown less incidence of disease relapse related to medication non-compliance, particularly in real world populations. It also showed a similar safety profile as oral 2nd-generation antipsychotics, but with greater incidence of mild injection-site pain. A novel 3-monthly formulation of PDP has shown similar safety and efficacy as once-monthly PDP compared to placebo. Conclusions: Overall, both 1-month and 3-month formulations of PDP are safe and effective in the treatment of schizophrenia and schizoaffective disorder. They may be most effective in patients with prior failed treatment of oral antipsychotics or other LALAs, in patients with a history of medication noncompliance, or in patients with an individual preference for less frequent dosing. Psychopharmacology Bulletin. 2017;47(2):42–52.

INTRODUCTION

Schizophrenia is a chronic mental disorder characterized by deficiencies in thought processes, perceptions, and emotions. This disorder is relatively common, affecting roughly 1.1% of the US adult population, more often in men than in women.\textsuperscript{1,2} It can also be severely disabling, making it difficult for those affected to hold jobs, form relationships, and even attend to their activities of daily living. Schizophrenia typically presents in early adulthood and follows a chronic course throughout the patient’s life, significantly affecting quality of life and ultimately leading to an average 10-year reduction in life expectancy.\textsuperscript{3} Due to the prevalence...
and severity of this disease, it remains one of the most burdensome and devastating illnesses in the world today.\textsuperscript{4} Nonetheless, the development of novel pharmacological treatments has dramatically improved our ability to manage this disease.

The advent of antipsychotic medication in the mid-20th century has allowed for good control of positive symptoms of schizophrenia, eliminating or reducing them to a tolerable level in up to 70\% of patients.\textsuperscript{5,6} Maintenance treatment with antipsychotics is recommended indefinitely, even for those who have achieved remission following a first psychotic break. Furthermore, oral formulations of these drugs allowed this treatment to take place in the outpatient setting, thereby reducing the burden of disease on the patient. However, this first generation of antipsychotics carry considerable side effects, most notably extrapyramidal symptoms (EPS), including akathisia, pseudoparkinsonism, and dystonia. These motor symptoms have been shown to be dose-dependent, occurring with greater frequency and severity at higher doses.\textsuperscript{7} Due in part to a combination of poor side effect profiles and patient cognitive dysfunction, noncompliance with these drugs is very common.\textsuperscript{8} Newer medications, collectively termed 2nd-generation (“atypical”) antipsychotics were able to achieve similar suppression of positive symptoms while reducing the incidence and severity of EPS.\textsuperscript{9,10} However, despite improved side-effect profiles, noncompliance continues to be an issue with 2nd-generation antipsychotics. In fact, compliance with oral maintenance therapy for schizophrenia is estimated at merely 40\%–60\% 1-year after discharge from an acute episode.\textsuperscript{7,11}

**LONG ACTING INJECTABLE ANTIPSYCHOTIC (LAIA) MEDICATION**

Noncompliance with maintenance treatment in schizophrenic patients is associated with greater rates of disease relapse.\textsuperscript{12} Disease relapse often leads to re-hospitalization, creating potentially immense cost and burden to the patient and their family, as well as poorer long-term outcomes.\textsuperscript{12,13} Long-acting injectable antipsychotics (LAIA) were created largely to address the issue of noncompliance by allowing the medication to be administered only once every 2–4 weeks rather than each day. Also referred to as “depot” injections, these medications are administered via gluteal or deltoid IM injection. In general, LAIA result in more stable serum levels of the drug and fewer dose-related side effects compared to oral medication. For example, Ereshefsky et al. compared pharmacodynamics and pharmacokinetics between comparably bioavailable doses of oral and LAI risperidone. The authors found that, compared to oral risperidone, LAI risperidone showed closer correlation between administered dose and serum levels,
resulting in more precise dosing and less difference between peak and trough serum drug levels.\textsuperscript{7} There is a direct relationship between serum drug levels and EPS, so by reducing peak serum levels, LAIAs can theoretically reduce the occurrence of these side effects, although clinical studies have shown mixed results.\textsuperscript{14–16}

Several studies have shown the efficacy of these drugs in improving outcomes in schizophrenia compared to placebo control. For example, in a double-blind RCT\textsuperscript{7} of 403 patients who had achieved good stabilization of acute schizophrenia, Kane et al administered either aripiprazole-IM-depot injection or placebo every 4 weeks for 1 year. They observed significantly greater improvement in the Positive and Negative Syndrome Scale (PANSS) and lower rates of impending relapse with aripiprazole than with placebo, indicating that LAI aripiprazole is a safe and effective alternative to oral aripiprazole.\textsuperscript{17} Furthermore, other studies have compared LAIAs to their oral equivalent to better establish the case for their use. Chue et al randomized 640 patients with well-controlled schizophrenia to receive either LAI or oral risperidone for 12 weeks, finding similar improvement in PANSS between groups and no reported adverse events.\textsuperscript{15} In a case series of 38 chronically psychotic, hospitalized patients previously receiving oral haloperidol, Deberdt et al injected haloperidol decanoate every 4 weeks at varying doses. They found that LAI haloperidol resulted in equally effective control of psychotic symptoms and no increase in EPS or injection-site pain compared to daily oral administration.\textsuperscript{16} These results suggest comparable efficacy and safety between LAI and oral antipsychotics.

Despite intuitive assumptions that LAIAs can lead to superior compliance rates compared to oral antipsychotics in schizophrenic patients, several studies have found no difference in compliance rates between treatment modalities. For example, Rosenheck et al randomized 369 VA patients with unstable schizophrenia to receive either LAI risperidone or an oral antipsychotic. They found no significant difference between groups in terms of re-hospitalization, reported compliance, psychiatric symptoms, quality of life, and neurological side effects, but patients receiving LAI risperidone reported more injection-site pain and EPS than those receiving oral medication.\textsuperscript{14} In addition, a 2005 meta-analysis of 6 RCTs comparing LAI fluphenazine to oral antipsychotics found no reduction in relapse with injectable medication.\textsuperscript{18} However, some have argued that these results can be confounded by highly compliant study populations that are not representative of the general schizophrenic population. Addressing this source of bias, a claims-based analysis by Marcus et al compared compliance and re-hospitalization rates in Medicaid
patients with recent history of noncompliance who were recently hospitalized for schizophrenia and prescribed either oral or LAI antipsychotics upon discharge. The authors found that LAIAs led to lower rates of both noncompliance and re-hospitalization than oral medication, but that this difference was only significant with 2nd-generation LAIAs. Several other studies have come to similar conclusions, finding improved compliance and long-term outcomes in patients prescribed LAIAs than in patients prescribed oral antipsychotics. Overall, research has demonstrated that LAIAs, particularly 2nd-generation, are as safe and effective for maintenance treatment of schizophrenia as oral antipsychotics, suggesting that compliance can potentially be improved without sacrificing medication efficacy.

**Paliperidone Palmitate**

Paliperidone palmitate (PDP) is a LAI formulation of the atypical antipsychotic paliperidone, the primary active metabolite of risperidone. It was approved by the FDA for acute and maintenance therapy of schizophrenia and schizoaffective disorder in 2009. This drug is a palmitate ester of paliperidone, prepared in an aqueous suspension of nanocrystals equipped with a sustained-release mechanism, resulting in slow dissolution in vivo. These nanocrystals are roughly 10 times smaller than the particles that one would find in a standard drug powder, creating substantially increased drug-solution surface area. Therefore, the drug solution is both able to more rapidly achieve steady state and maintain this steady state for a longer period of time than other LAIAs. Effects of the drug are usually seen roughly 8 days following injection, and peak plasma level is reached roughly 13 days after injection. Serum half-life is roughly 25–49 days, and standard dosing schedule is induction therapy with 2 injections one week apart, followed by maintenance dose every 4 weeks.

**PDP in Acute-Phase Therapy**

PDP injection has proven to be effective in improving psychotic symptoms in both acute and maintenance phases of schizophrenia. In a double-blind RCT of 652 patients with acutely exacerbated schizophrenia, Pandina et al administered either PDP 150 mg or placebo injection on day 1, followed by a set dose of PDP on placebo on day 8 and monthly thereafter. They found significantly greater improvement in PANSS with PDP over placebo, and sufficient serum levels of drug to exert effects by day 8. The most common side effects they observed in
the PDP group were injection-site pain (7.6%), dizziness (2.5%), and sedation (2.3%). Several other studies were performed with similar designs, and unanimously observed that monthly PDP injections significantly improved PANSS outcomes over placebo. The PDP groups generally experienced higher rates of headache, nausea, and extremity pain than placebo, as well as slightly elevated BMI and weight in a dose-dependent fashion. Some studies reported higher levels of patient-evaluated injection-site pain with PDP injection, but others reported no difference. There was generally no difference observed between PDP and placebo groups in terms of extrapyramidal symptoms, although parkinsonism was the most commonly occurring movement disorder in the treatment groups. Overall, numerous double-blind RCTs of LAI PDP are in agreement that it constitutes a safe and effective treatment for acutely exacerbated schizophrenia with relatively few side effects.

**PDP in Maintenance-Phase Therapy**

PDP injection has also been demonstrated to be effective in maintenance therapy for schizophrenia. Hough et al transitioned 410 patients with schizophrenia from previous oral antipsychotic to PDP injection therapy, stabilized them on PDP maintenance therapy, and subsequently randomized them to either continue receiving PDP or switch to placebo for the remainder of the study. They found that a majority of patients in the placebo group experienced disease relapse, with a median time-to-relapse of 163 days, while less than 25% of patients in the PDP group relapsed. Mean PANSS outcomes were similar between groups at baseline, but at 40 weeks were significantly lower in the PDP group. There was no difference between groups with respect to adverse events, but the PDP group experienced a mean 1.9 kg weight-gain while the placebo group experienced none. Moreover, many patients in which LAI therapy is indicated have experienced persistent symptoms despite oral antipsychotic medications. In a double-blind RCT, Silwa et al evaluated the use of monthly PDP injections versus placebo in schizophrenic patients who remained symptomatic after a trial of oral risperidone therapy. They found that PDP significantly improved PANSS, global illness ratings, and functional outcomes over placebo. The most commonly observed adverse events were insomnia, anxiety, and headache. Similar to its primary use in acute-phase schizophrenia, use of PDP in maintenance-phase and persistent schizophrenia has been shown to yield positive outcomes, with the most consistently observed adverse effects being weight gain and insomnia.
**PDP in Relation to Oral Antipsychotics**

In comparison with oral antipsychotic medications, LAI PDP therapy has shown positive results, both in terms of efficacy and safety. Alphs et al investigated PDP therapy in a “real world” schizophrenic population, defined as those with complicated disease, a history of incarceration, and previous oral antipsychotic use. They designated these patients to receive open-label treatment with either LAI paliperidone or one of seven different daily oral antipsychotics. No differences were seen between groups in terms of social functioning or severity of illness, but medication compliance was higher and treatment failure rate was significantly lower with PDP than with oral medication. In terms of adverse events, only injection-site pain was seen more frequently in the PDP group. These results support previous findings that disease relapse is associated with medication noncompliance, and suggest that PDP may be a particularly suitable treatment option for patients with a high likelihood of noncompliance. In their previously mentioned Medicaid claims-based study, Marcus et al observed a lower rate of rehospitalization in patients receiving PDP than in those receiving any other available drug formulation, further supporting its efficacy at maintaining disease remission. Furthermore, many patients initiated on PDP therapy are transitioned from 2nd-generation oral antipsychotics, and must be instructed when to discontinue their previous medication to avoid both over-dosing and gaps in therapy. Doshi et al examined current approach to this issue in an observational claims-based study by looking for simultaneous prescription of LAI and oral antipsychotics in recently-discharged schizophrenic patients. They found that, of all available LAIAs, PDP was least frequently prescribed with an oral antipsychotic, likely due to its fast-achievement of steady-state and subsequent therapeutic effect. However, they note that when co-prescription occurred, in a majority of instances it overlapped substantially with time therapeutically covered by the LAI medication. These results suggest that some degree of over-dosing exists during the transition from oral to LAI antipsychotic therapy following hospitalization for acute exacerbation of schizophrenia. However, more research must be done to determine the clinical consequences of such over-dosing, and ultimately to determine an optimal transition-dosing schedule based on clinical evidence.

**PDP in Relation to Other LAIAs**

While PDP therapy appears superior to placebo and at least non-inferior to oral antipsychotics, we still must determine its relative safety
and efficacy compared to other available LAIAs to make recommendations regarding its use. Gopal et al conducted a meta-analysis of RCTs investigating LAIAs versus placebo to calculate relative number-needed-to-treat (NNT) and number-needed-to-harm (NNH) for these medications. In the acute phase of schizophrenia, they found NNT to be 6, defined as a 30% improvement in PANSS, and found NNT in maintenance phase to be 2, defined as prevention of relapse for 12 months. These values were similar to those calculated for first-generation LAIAs, such as haloperidol-decanoate (HPD), indicating similar efficacy. In terms of developing movement disorders, such as akathisia, tremor, and tardive dyskinesia, NNH varied considerably, but was significantly higher with PDP than with first-generation drugs. These same results were observed with regard to anticholinergic use, indicating a lower propensity for movement disorders to occur with PDP injections. McEvoy et al corroborated these findings in a double-blind RCT comparing PDP to HPD injections in schizophrenic patients deemed to be at risk of relapse, and therefore good candidates for LAIA use. They observed similar rates of efficacy failure with PDP (33.8%) as with HPD (32.4%), but observed greater weight gain (+2.17 vs −0.96 kg) and serum prolactin levels with PDP and greater rates of akathisia with HPD. Furthermore, although primary clinical research comparing PDP to other 2nd-generation LAIAs is lacking, Einarson et al conducted a cost-effectiveness analysis of PDP, LAI risperidone, and LAI olanzapine in acute and maintenance schizophrenia. In their analysis, they conclude that PDP exhibits superior clinical outcomes, determined using Quality-Adjusted Life-Years, days in remission, hospital re-admissions, and emergency room visits as outcomes measures. They also found that PDP costs significantly less overall when the aforementioned clinical factors are taken into account, resulting in the conclusion that PDP is more cost effective than either LAI 2nd-generation antipsychotic. However, to make a recommendation regarding their relative safety and efficacy, further research must directly compare their clinical use.

**Paliperidone Palmitate 3-Monthly Injections**

Paliperidone palmitate 3-monthly injectable (PDP3M) is a novel formulation of IM injectable paliperidone palmitate with a significantly longer half-life than the once-monthly formulation. It was approved by the FDA in 2015 for use in schizophrenia and schizoaffective disorders. Ravenstijn et al completed a phase 1 pharmacokinetics study of the novel drug, finding that peak serum concentration was reached at 23–34 days post-injection, and half-life in vivo was roughly 2–4 months. Of note,
while the half-life of PDP is equivalent between gluteal and deltoid injection sites, the half-life of PDP3M is slightly greater with gluteal injection. The most commonly occurring adverse events that they noted were headache and nasopharyngitis, followed by weight-gain and back pain. Due to the extremely long half-life of PDP3M, it is recommended to only begin treatment in patients who have received at least 4 months of PDP, in order to assess individual tolerability. When switching these patients from PDP to PDP3M, it is important to give the first dose of PDP3M at the time of their next scheduled dose of PDP, and to initiate treatment with a dose 3.5 times greater than scheduled dose. Following that induction dose, a regular maintenance dosing schedule of one injection every 3 months should be followed.

Berwaerts et al evaluated the clinical safety and efficacy of this drug in a double-blind RCT comparing the use of PDP3M to placebo in patients diagnosed with schizophrenia. They initially administered monthly injections of PDP during a 17-week transition phase, subsequently administered 1 dose of PDP3M in a 12-week maintenance phase, and finally randomized patients to receive a fixed dose of PDP3M or placebo for the remainder of the study. The authors observed significantly greater rates of disease relapse with placebo than with PDP3M, supporting its efficacy in maintaining remission in schizophrenia. In terms of treatment-emergent adverse events, the PDP3M group experienced greater incidence of headache (9%), weight gain (9%), nasopharyngitis (6%), and akathisia (4%) than the control group. In a phase 3 non-inferiority study, Savitz et al stabilized 1,016 schizophrenic patients on monthly PDP injections for 17 weeks, and subsequently randomized these patients to either switch to PDP3M or continue receiving PDP injections. The authors observed similar disease relapse rates and clinical measures of disease severity between groups. They also observed similar safety/tolerability profiles between groups, with the most common treatment-emergent adverse event being weight gain, experienced by 21% of patients in each group. Therefore, PDP3M has demonstrated equal safety and efficacy as PDP, and may be preferable to select patients due to less frequent dosing schedule.

**Conclusions**

Schizophrenia is an incredibly devastating and relatively common disease, but advancements in antipsychotic medication has proved to dramatically lessen the burden of this disease. However, due to cognitive and judicial compromise of those who suffer from it, medication non-compliance commonly leads to poorer outcomes for patients. Compared to oral antipsychotics, LAIAs have been shown to improve compliance
and lead to lower disease relapse and re-hospitalization rates in real-world populations. PDP, a once-monthly LAIA, has demonstrated good efficacy in reducing disease severity and re-hospitalizations in schizophrenic patients, with a similar safety profile as many 2nd-generation oral antipsychotics. PDP exhibits similar efficacy as 1st-generation LAIAs, such as haloperidol-decanoate, but is associated with significantly less EPS and greater metabolic effects. PDP3M, a once-three-monthly LAIA, is a recently-approved formulation of paliperidone palmitate that exhibits similar efficacy and safety as PDP in preliminary trials. Overall, both 1-month and 3-month formulations of PDP are safe and effective in the treatment of schizophrenia and schizoaffective disorder. They may be most effective in patients with prior failed treatment of oral antipsychotics or other LAIAs, in patients with a history of medication noncompliance, or in patients with an individual preference for less frequent dosing. However, further research directly comparing both PDP formulations to other 2nd-generation LAIAs to make a definitive recommendation.

**Disclosures of Potential Conflicts of Interest**

On behalf of both authors, the corresponding author states that there are no conflicts of interest or sources of funding to declare.

**References**


Paliperidone Palmitate in Schizophrenia


