Editorial

How Would You Like to Take Your Medicine 2 Times a Year? Paliperidone Palmitate Every 6 Months for the Maintenance Treatment of Schizophrenia

A 6-month formulation of paliperidone palmitate was approved for the treatment of schizophrenia in September 2021. The availability of a treatment administered twice a year is a new approach for this chronic and often difficult to manage illness.

The purpose of maintenance treatment with antipsychotics is to reduce the intensity and frequency of acute exacerbations of the illness, typically manifested by positive symptoms, such as hallucinations and delusions. With these symptoms minimized as optimally as possible, other psychological and psychosocial interventions, such as vocational rehabilitation and cognitive remediation, can also be used to assist in the patient's recovery journey. Of note, the early phase of treatment after an individual's first psychotic episode is a critical time because after each relapse response to antipsychotic medication may be less robust and take longer to respond to treatment.[1] Relapse is thought to be associated with neuropathological brain changes, including diffuse gray matter atrophy and microglia abnormalities, and each decompensation can result in a stepwise decrease in global functioning.[2] Moreover, other consequences of symptom relapse can include strained interpersonal relationships, additional hospitalization, deteriorating medical comorbidities, and death (including suicide).[3] Treatment adherence is a way to minimize relapse, and continuous treatment is superior to intermittent treatment targeted toward acute episodes only.[4,5]

Unfortunately, as with many chronic medical conditions, in schizophrenia the rates of partial and complete nonadherence to treatment are high. Poor adherence can be inadvertent or unintentional, such as when an individual's living situation is chaotic or if they have cognitive impairments that get in the way. Covert intentional nonadherence is another possibility when insight into illness fluctuates and the person with schizophrenia makes the decision not to take their prescribed medication and (usually) not to tell their health care practitioner. One solution to enhance adherence and mitigate covert nonadherence is the use of long-acting injectable (LAI) antipsychotics, which eliminate the need for daily dosing and ensure stable plasma levels. Several lines of evidence indicate that LAI antipsychotics leads to better consistency with medication treatment and a longer time to treatment discontinuation than oral antipsychotics.[6,7]

The choice of LAI antipsychotics available in the United States is limited to 2 first-generation antipsychotics (haloperidol decanoate and fluphenazine decanoate) and 3 second-generation antipsychotics (risperidone-paliperidone, aripiprazole, and olanzapine), but ease of use and the amenities of care (such as injection frequency) differ from formulation to formulation, regardless of the molecule.[8] The most commonly prescribed oral second-generation antipsychotic for the treatment of schizophrenia is risperidone, whose principal active metabolite is paliperidone. There are a variety of available risperidone-paliperidone LAIs, including risperidone microspheres (administered every 2 weeks), subcutaneous risperidone (administered monthly, with another agent pending US Food and Drug Administration approval that may offer the option of administration every 2 months), and paliperidone palmitate administered monthly (PP1M) or every 3 months (PP3M).[9] To date, every 3 months was the longest interval available for an injectable treatment for schizophrenia. That interval has now been doubled.

Paliperidone palmitate every 6 months (PP6M) is the only twice-yearly LAI antipsychotic. Because of the large injection volume (3.5 mL [1092-mg dose] or 5 mL [1560-mg dose]), PP6M must be administered in the upper outer quadrant of the gluteal muscle. Before receiving the injection, patients must have been adequately treated with PP1M for at least 4 months or with PP3M for at least one 3-month injection cycle.[10,11] PP3M can only be administered after the patient has been adequately treated with PP1M for at least 4 months.

Although many patients prefer LAI antipsychotics and clinicians may consider LAI antipsychotics as a potential useful option for patients who have difficulties with medication adherence, these agents are not necessarily offered and, generally speaking, this modality of treatment is underused.[12–15] For patients who are ambivalent about LAI

antipsychotics, education and demystification of the injection process can potentially increase patient acceptance.[16] Many different treatment guidelines from around the world, including the recently revised guidance offered by the American Psychiatric Association in 2020, now include patient preference, independent of adherence status, as a recommended rationale for using an LAI antipsychotic.[17,18]

The efficacy of PP6M was established in a Phase III, randomized, double-blind, active-controlled, interventional, parallel-group, noninferiority study.[11] Study participants (702 randomized participants) were adults with schizophrenia stabilized with PP1M for at least 4 months or PP3M for at least one 3-month injection cycle. The primary outcome measure was time to first relapse, defined as psychiatric hospitalization, suicidal or homicidal ideation, self-injurious or violent behavior, or a significant increase in Positive and Negative Syndrome Scale (PANSS) score. The mean baseline PANSS score was approximately 51 for each group. PP6M (n = 478) was noninferior to PP3M (n = 224) on the primary end point after 12 months in the intention-to-treat population. In the intention-to-treat analysis, 36 patients (7.5%) in the PP6M group and 11 (4.9%) in the PP3M group relapsed. Because of low rates of relapse, the median time to relapse was not able to be estimated. After 12 months, the Kaplan-Meier estimate of the difference between the PP6M and PP3M treatment groups in the percentages of patient who remained relapse free was −2.9% (95% CI, −6.8% to 1.1%).

Will a longer interval between injections result in better real-world outcomes? Theoretically, longer injection intervals allow for more therapeutic work to be performed during the regular follow-up appointments (often monthly) rather than the focus be on the injection process. Moreover, reformulating an agent so it can be administered less frequently essentially extends its effective $t_{½}$ and can potentially extend the degree of protection against relapse should there be a delay in dose administration. A post hoc analysis addressed this question by comparing when relapse occurred after discontinuation of 3 distinct formulations of paliperidone: oral ($t_{½}$ of approximately 23 hours), PP1M ($t_{½}$ of 25–49 days), and PP3M ($t_{½}$ of 84–95 days and 118–139 days for deltoid and gluteal injection respectively).[5] Median time to relapse differed significantly: 58 days for oral paliperidone, 172 days for PP1M, and 395 days for PP3M.[5] Intuitively, these findings should translate into a longer time to relapse for PP6M given a prolonged $t_{½}$ of 148 to 159 days. Of additional interest is a retrospective cohort study of 3-month vs 1-month dosing intervals among people with schizophrenia enrolled in a Medicaid program who were otherwise evenly matched. Overall, 179 people (15.7%) in the PP1M cohort and 45 (10.5%) in the PP3M cohort had a relapse, and the risk of relapse was 35% higher in the PP1M cohort (hazard ratio = 0.65; 95% CI, 0.47–0.90). Treatment adherence (receiving injections) was also significantly higher ($P < 0.0001$) in the PP3M cohort compared with the PP1M cohort.[19]

A key concern in the prescription of a 6-month LAI antipsychotic are adverse effects, especially motoric symptoms, such as drug-induced parkinsonism, dystonia, and akathisia, as well as the longer-term risk of tardive dyskinesia. In the aforementioned 12-month noninferiority study, the tolerability of PP6M was similar to that of PP3M. The most common adverse events occurring in ≥5% of patients (PP6M vs PP3M) included weight increase (8.4% vs 7.6%), injection site pain (7.7% vs 4.0%), headache (6.7% vs 5.4%), upper respiratory tract infection (5.0% vs 4.0%), and nasopharyngitis (4.6% vs 5.8%).[11] The adverse events that led to stopping medication use were low in each group (3.3% for PP6M vs 2.7% for PP3M). The rates of akathisia (3.6% vs 3.6%), dystonia (0.2% vs 0%), and tremor (0.2% vs 0%) were similar for PP6M and PP3M, respectively. Cumulatively, anticholinergic medications were used by 15.5% of patients receiving PP6M and 12.9% of patients receiving PP3M in the double-blind treatment phase. No cases of neuroleptic malignant syndrome were reported.[10,11]

It remains to be seen whether these efficacy and tolerability results are applicable to real-world patients. At double-blind baseline, the mean PANSS total scores of 51.9 for PP6M and 51.4 for PP3M are considerably lower than expected in outpatients with chronic schizophrenia. For example, in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, the mean PANSS total score was 75.6 at baseline and 68.1 after 6 months of treatment.[20] Tolerability outcomes may also be different in nonresearch clinical settings, where clinically relevant psychiatric and somatic comorbidities may be present. Hesitancy may exist in the prescription of PP6M because of the lack of an option to stop use of the medication in case of a tolerability or safety concern,

although the requirement that a patient must have been treated with PP1M first can help in determining whether the PP6M option is worth considering.

PP6M can be a potential game-changer when used earlier in the disease course. Robust evidence supports the early use of LAI antipsychotics.[4] A recent cluster-randomized trial reinforced that LAI antipsychotics in early-phase schizophrenia can significantly delay time to hospitalization.[21] The early phase might be an optimal time to consider the use of PP6M after establishing that risperidone or paliperidone is efficacious and tolerable for that individual. If young patients accept PP6M, the adherence gains could be transformative and thus paradigm shifting, but only time will tell. More information is needed in comparing PP6M in patients with differing degrees of schizophrenia chronicity and illness severity.

PP6M is not generic, and cost is a potential limiting factor. The estimated cost of $18,000 for a 6-month injection is considerably more than the cost of oral antipsychotics and other LAI antipsychotic options.[22] Commercial and government payers may be hesitant to cover this treatment. Nonetheless, an argument can be made if a person with schizophrenia prefers fewer injections then the offer of such a treatment should be considered for this chronic and debilitating illness, particularly if it can have a tangible effect on avoiding partial adherence or nonadherence and break the cycle of recurrent decompensations.

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DECLARATION OF INTEREST

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