Early Intervention IN PSYCHIATRY

Early Intervention in Psychiatry 2018; **12:** 55–65 doi:10.1111/eip.12271

Original Article

Treatment effect with paliperidone palmitate compared with oral antipsychotics in patients with recent-onset versus more chronic schizophrenia and a history of criminal justice system involvement

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Abstract

Aim: Long-acting injectable antipsychotics (APs) are not well studied in recent-onset schizophrenia. This exploratory analysis of a study designed to reflect real-world schizophrenia, as defined by patients, interventions and outcomes, compared relative treatment effect between once-monthly paliperidone palmitate (PP) and daily oral APs in patients with recent-onset or chronic illness

Methods: This randomized, open-label, event monitoring board–blinded study compared treatment response in subjects with schizophrenia and a history of criminal justice system involvement following treatment with PP or oral APs for 15 months (ClinicalTrials.gov identifier, NCT01157351). Event-free probabilities were estimated using Kaplan–Meier method; hazard ratios (HRs) were estimated using Cox proportional hazard models. This subgroup analysis analysed data by disease duration (≤5 (recent-onset) or >5 years (chronic illness) since first psychiatric diagnosis).

Results: Seventy-seven subjects met the criteria for recent-onset illness; 365 for chronic illness. HRs (95% CI) for treatment failure for oral APs versus PP were 1.73 (0.87–3.45; $P = 0.121$) for recent-onset and 1.37 (1.02–1.85; $P = 0.039$) for chronic illness. Most common adverse events for PP versus oral APs were injection site pain (recent-onset, 26% vs. 0%; chronic, 17% vs. 0%), increased weight (14% vs. 6%; 12% vs. 6%), akathisia (14% vs. 9%; 10% vs. 7%), insomnia (12% vs. 17%; 18% vs. 10%) and anxiety (12% vs. 6%; 10% vs. 8%).

Conclusions: Although neither preplanned nor adequately powered, the estimated HRs suggest that the relative advantage of PP over oral APs for reducing the risk for treatment failure may be greater in patients with recent-onset schizophrenia than in those with more chronic illness.

Key words: disease duration, long-acting injectable, oral antipsychotic, paliperidone palmitate, schizophrenia.

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Received 12 June 2015; accepted 17 August 2015

INTRODUCTION

Although schizophrenia is a chronic mental illness affecting approximately 1% of the population,[1,2] innovations in treatment approaches have improved patient outcomes and quality of life. In particular, an increasing body of evidence suggests that treatment of patients with schizophrenia may be more effective when initiated and maintained early in the course of the disease.[3–6] Evidence suggests that treatment response tends to diminish with each successive psychotic episode and that most functional deterioration occurs within 5 years of onset.[1,7] Nevertheless, these patients are particularly vulnerable to incomplete treatment because early in their illness they have poor insight into their illness and their need for

continuous, effective treatment.[8,9] As a result, these patients are often nonadherent to medication regimens,[10,11] thus increasing their risk of relapse and rehospitalization.[1]

Deinstitutionalization of the mentally ill over the past 50 years and changes in health policy have shifted the burden of institutional care for mental illness from hospitals to jails and prisons. These changes have been largely economically based, and continued cost-cutting policies have exacerbated this problem. Consequently, persons with schizophrenia and a history of incarceration represent an important subpopulation requiring public health attention. Persons who are early in their illness may be particularly prone to contact with the criminal justice system (CJS) because their bizarre behaviours, problems with substance abuse and disorganization greatly increase the likelihood of their contact with law enforcement personnel. Furthermore, such patients often have limited, fragile connections with the mental health treatment system and they are more prone to cycle between healthcare facilities, homelessness and the CJS. Therefore, finding better treatments that result in fewer arrests and incarcerations and that reduce recidivism represents a particularly important challenge for the care of younger persons with schizophrenia.[12]

Studies in patients with first-episode schizophrenia have shown strong correlations between early treatment and better outcomes later in the course of the disease.[13,14] Therefore, effective antipsychotic (AP) therapy that begins early in the disease course may help reduce the risk of relapse and hospitalization and preserve the patient's day-to-day functioning.[15–17] Treatment with long-acting injectable (LAI) APs is characterized by certain knowledge of their delivery and a larger window for corrective intervention if they are not taken as prescribed. Consequently, the use of LAIs may be appropriate in younger patients who are more likely to be nonadherent to their AP treatment.[18–20]

The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study (ClinicalTrials.gov identifier, NCT01157351) is a prospective, randomized study that compared the effects of once-monthly paliperidone palmitate (PP) with the effects of daily oral APs on time to treatment failure.[21,22] The study was designed to evaluate response under conditions that reflect real-world treatment.[21] It is unique among schizophrenia treatment trials in that it enrolled patients who are customarily excluded from clinical trials, such as those with a history of incarceration and comorbid substance abuse. The trial compared PP treatment response with that of oral AP medications and allowed clinicians extensive flexibility in making treatment and management decisions during the course of the study. End-points included a range of important real-world consequences of poor treatment response, such as arrest or incarceration, hospitalization and treatment discontinuation.[21] Overall study results showed that median time to treatment failure was significantly delayed by 190 days with PP compared with daily oral APs.[22]

This exploratory analysis of the PRIDE study data examined the relative treatment response between PP and daily oral APs in patients with recent-onset schizophrenia and in patients with more chronic illness.

METHODS

Study design

PRIDE is a prospective, randomized, open-label, event monitoring board (EMB)–blinded, parallel-group, multicentre US study conducted between 5 May 2010 and 9 December 2013 (ClinicalTrials.gov identifier, NCT01157351).[21,22] The study included a screening phase of up to 2 weeks, followed by a 15-month randomized treatment phase. Study participation for the full 15 months was encouraged regardless of whether subjects reached the primary end-point or discontinued their randomly assigned study treatment early. In the current subgroup analysis, the relative treatment response of PP versus daily oral APs (hazard ratios (HRs) and median time to initial treatment failure) was examined in patients who were early in their course of illness (≤5 years since psychiatric diagnosis (recent-onset)) and in patients with more chronic illness (>5 years since psychiatric diagnosis (chronic illness)). Five years was chosen as the cut-off based on previous studies suggesting that most functional disability occurs within the first 5 years of the disease.[1,7] These results have been supported by similar analyses of other trials conducted in PP-treated patients with recent onset of illness.[23,24]

Subjects

The study included men and women aged 18–65 years with a current diagnosis of schizophrenia confirmed by the Mini International Neuropsychiatric Interview, version 6.0.[25] Subjects must have had contact with the CJS (i.e. were previously in custody) at least twice in the previous 2 years, with at least one instance of custody leading to incarceration. Release from the most recent custody must have been within 90 days of screening. Subjects must also

have been willing to receive a once-monthly injectable AP. Subjects were excluded if they had used either oral clozapine within 3 months of screening or an injectable AP within two injection cycles of screening. Substance abuse was not an exclusionary factor at randomization; however, subjects were excluded if they had actively abused intravenous drugs within the 3 months preceding screening or had an opioid dependence disorder.

To help facilitate recruitment, a unique patient outreach strategy was developed that was tailored to each research setting. It focused on patient flow patterns for persons living on the streets, in homeless shelters and in single-residence units. To the extent possible, law enforcement personnel, case managers and behavioural health departments were incorporated into the process.

The study was approved by the institutional review board at each site and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Treatments

Before receiving their randomized treatment assignment, each subject and his or her clinician reviewed the seven commonly prescribed oral APs available for this study (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine and risperidone) to determine their acceptability based on prior experience as potential treatments. Up to six of the seven medications could be deselected. Reasons for deselection were documented. Subjects were then stratified based on their selection of acceptable oral AP treatments and were randomly assigned to either flexibly dosed monthly PP (78–234 mg) or flexibly dosed daily oral AP therapy, which was randomly selected from the subject's list of prespecified acceptable oral APs.

End-point assessments

The primary end-point was time to first treatment failure, defined as any of the following events: arrest or incarceration, psychiatric hospitalization, suicide, discontinuation of treatment because of inadequate effectiveness, treatment supplementation with another AP because of inadequate effectiveness, discontinuation of treatment because of safety or tolerability, or an increase in the level of psychiatric services to prevent imminent psychiatric hospitalization. Primary end-points were determined by an independent EMB that was blinded to individual subject treatment assignment. Time to first psychiatric hospitalization or arrest/incarceration was a key secondary end-point. Safety assessments included monitoring of treatment-emergent adverse events (TEAEs).

Subjects were encouraged to continue in the study to their predefined, 15-month completion date, regardless of early discontinuation of the randomly assigned study treatment or achievement of the primary end-point (i.e. treatment failure).

Statistical analysis

This post-hoc subgroup analysis focused on time to treatment failure in subjects with recent-onset disease (≤5 years since psychiatric diagnosis) and in subjects whose illness was more chronic (>5 years since psychiatric diagnosis). Demographic and baseline characteristics and TEAEs were summarized using descriptive statistics. The intent-to-treat population for this analysis was defined as all randomly assigned subjects who received ≥ 1 dose of study treatment; this definition was used for both efficacy and safety analyses. An explanatory approach was undertaken to determine the relative effects of assigned treatments. Primary and secondary analyses included all data from randomization until the end of the randomly assigned treatment (28 days after the last injection of PP or 1 day after the last dose of oral APs).

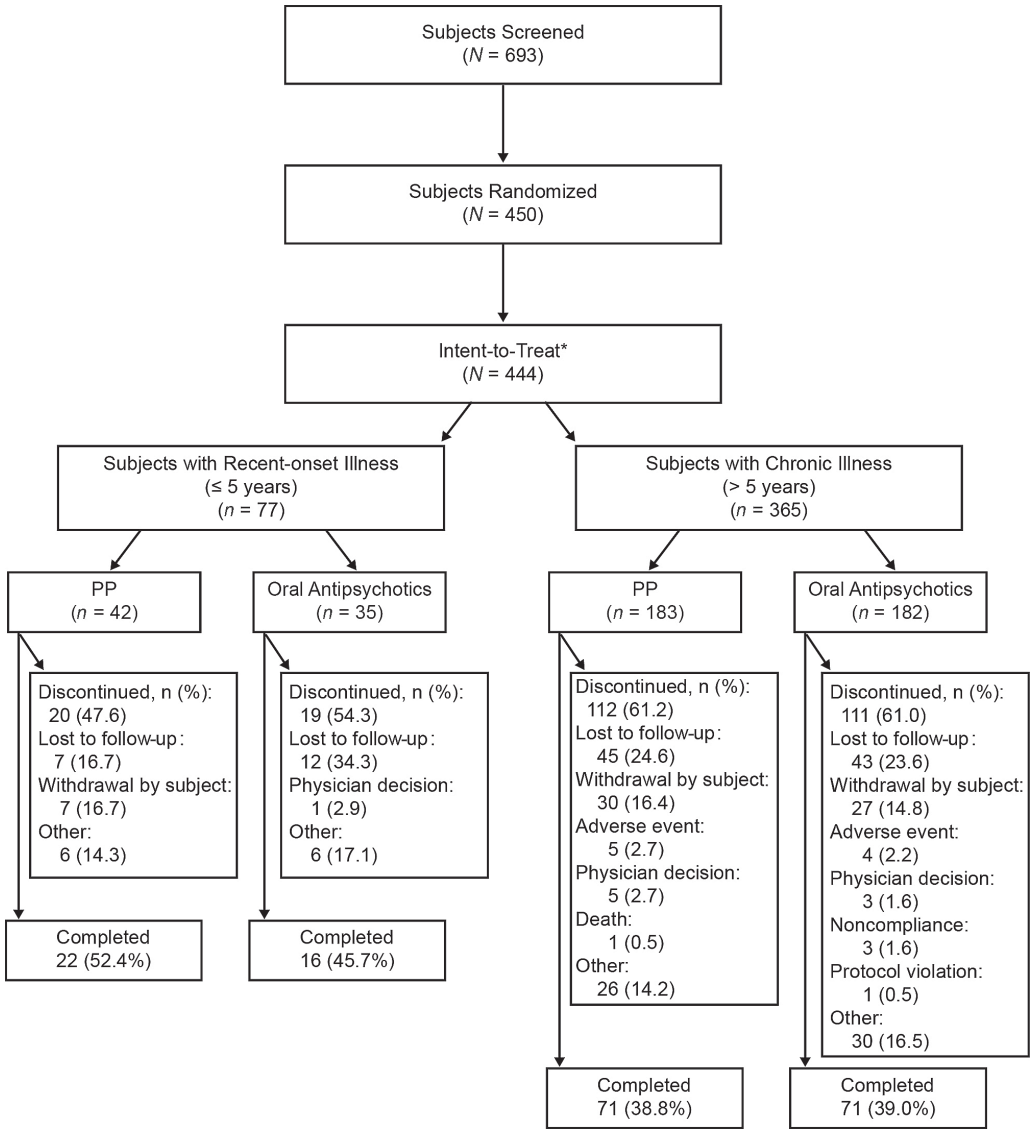
Event-free probabilities of treatment failure and components of treatment failure were estimated using the Kaplan–Meier method. Treatment differences were compared using a log-rank test. HRs and 95% confidence intervals (CIs) were estimated using a Cox proportional-hazards regression model, with randomly assigned treatment as a fixed factor. Median times to treatment failure were not estimable if the estimated probability of treatment failure was less than 50% by end of the study (i.e. > 450 days). Statistical significance was based on a two-sided α of 0.05. All analyses were performed using SAS version 9.2.

RESULTS

Subjects and disposition

A total of 77 subjects with recent-onset illness and 365 with chronic illness were included in this analysis (Fig. 1). Table 1 summarizes the prerandomization selection and deselection of potential oral APs available to subjects that is described in Methods. No major differences in the proportion of subjects deselecting any given oral AP were noted across the groups. Haloperidol was the most

FIGURE 1. Study flow of subjects with recent-onset or chronic illness in the PRIDE study. *Two subjects did not have data available for the duration of their illness and were not included.



frequently deselected AP, and extrapyramidal symptoms (EPSs) were the most frequently identified reason for its deselection. Study completion rates were 49.4% in subjects with recent-onset illness and 38.9% in those with chronic illness. A subject was considered to have completed the study if he or she completed assessments at the 15-month visit.

Demographic and baseline characteristics for the PP and oral AP treatment arms were generally similar in both the recent-onset and chronic illness subgroups. An exception was 'time since release from last incarceration' in the recent-onset subgroup (Table 2). Mean (SD) duration of illness was 3.0 (1.8) years in the recent-onset group and 18.7 (9.3) years in the chronic illness group. In both treatment cohorts, concurrent substance abuse (including alcohol) was seen in more than 50% of all subjects. Overall, most subjects in both treatment cohorts were male and black/African American, with a mean age of 32 years in the recent-onset population and 39 years in the chronic illness population. The mean (SD) dose of PP in the recent-onset and chronic illness subgroups was 178.5 (35.2) mg and 181.8 (34.1) mg, respectively.

Treatment failure outcomes

Among subjects with recent-onset schizophrenia, the observed rate of treatment failure was 33.3% (n = 14/42) in the PP group and 54.3% (n = 19/35) in the oral AP group. For those with chronic illness, observed rates were 41.5% (n = 76/183) and 53.8%

TABLE 1. Summary of prerandomization selection and deselection of potential oral antipsychotics available to subjects with recent-onset or chronic illness (intent-to-treat population)

Selection of oral APs, *n* (%)	Recent-onset illness (≤5 years)		Chronic illness (>5 years)	
	PP (*n* = 42)	Oral APs (*n* = 35)	PP (*n* = 183)	Oral APs (*n* = 182)
Aripiprazole				
Yes	34 (81.0)	27 (77.1)	127 (69.4)	135 (74.2)
No	8 (19.0)	8 (22.9)	56 (30.6)	47 (25.8)
Haloperidol				
Yes	25 (59.5)	14 (40.0)	64 (35.0)	73 (40.1)
No	17 (40.5)	21 (60.0)	119 (65.0)	109 (59.9)
Olanzapine				
Yes	29 (69.0)	25 (71.4)	118 (64.5)	123 (67.6)
No	13 (31.0)	10 (28.6)	65 (35.5)	59 (32.4)
Paliperidone				
Yes	40 (95.2)	32 (91.4)	167 (91.3)	169 (92.9)
No	2 (4.8)	3 (8.6)	16 (8.7)	13 (7.1)
Perphenazine				
Yes	29 (69.0)	22 (62.9)	108 (59.0)	108 (59.3)
No	13 (31.0)	13 (37.1)	75 (41.0)	74 (40.7)
Quetiapine				
Yes	30 (71.4)	28 (80.0)	117 (63.9)	123 (67.6)
No	12 (28.6)	7 (20.0)	66 (36.1)	59 (32.4)
Risperidone				
Yes	33 (78.6)	28 (80.0)	140 (76.5)	151 (83.0)
No	9 (21.4)	7 (20.0)	43 (23.5)	31 (17.0)

AP, antipsychotic; PP, paliperidone palmitate.

TABLE 2. Baseline demographics and clinical characteristics (intent-to-treat population)

	Recent-onset illness (≤5 years)		Chronic illness (>5 years)	
	PP (*n* = 42)	Oral APs (*n* = 35)	PP (*n* = 183)	Oral APs (*n* = 182)
Age, years, mean (SD)	30.8 (9.7)	32.8 (10.9)	39.2 (10.1)	39.7 (9.9)
Male, *n* (%)	38 (90.5)	33 (94.3)	154 (84.2)	156 (85.7)
Race, *n* (%)				
White	11 (26.2)	11 (31.4)	61 (33.3)	63 (34.8)†
Black/African American	31 (73.8)	22 (62.9)	114 (62.3)	107 (59.1)
Other	0 (0)	2 (5.7)	8 (4.4)	11 (6.0)
Hispanic or Latino, *n* (%)	9 (21.4)	5 (14.3)	21 (11.5)	31 (17.0)
BMI, kg m^{-2}, mean (SD)	26.7 (5.6)	27.4 (4.9)	28.1 (5.5)	27.9 (5.1)
Time since release from last incarceration, days, mean (SD)	31.9 (30.7)	56.9 (64.1)	40.5 (53.9)	43.3 (50.6)
Age at first psychiatric diagnosis, years, mean (SD)	27.9 (10.1)	29.6 (11.0)	20.7 (8.9)	20.7 (9.0)
No. of psychiatric hospitalizations in lifetime, mean (SD)	3.5 (4.0)	5.0 (5.8)	8.1 (17.9)	5.8 (5.6)
No. of psychiatric hospitalizations in the past 12 months, mean (SD)	0.9 (1.1)	1.7 (2.1)	1.3 (8.3)	0.9 (1.3)
Concurrent substance abuse (including alcohol), *n* (%)				
Yes	21 (50.0)	22 (62.9)	109 (59.6)	112 (61.5)
No	21 (50.0)	13 (37.1)	74 (40.4)	70 (38.5)
Homelessness, *n* (%)‡	1 (2.4)	5 (15.2)	27 (15.2)	29 (16.5)
PSP total score, mean (SD)	53.3 (12.3)	53.5 (10.3)	55.1 (12.9)	55.2 (13.2)
CGI-S score, mean (SD)	3.8 (0.9)	4.1 (0.7)	3.9 (0.8)	3.8 (0.7)

†*n* = 181. ‡At baseline, subjects were considered to be homeless if they had been on the streets or in an emergency shelter for the homeless. AP, antipsychotic; BMI, body mass index; CGI-S, Clinical Global Impressions-Severity scale; PP, paliperidone palmitate; PSP, Personal and Social Performance scale; SD, standard deviation.

(n = 98/182), respectively. The corresponding HRs (95% CI) for recent-onset illness was 1.73 (0.87–3.45; P = 0.121) and for chronic illness it was 1.37 (1.02–1.85; P = 0.039). Thus, in this post hoc analysis, the risk for treatment failure was lower for PP than for oral APs in both subpopulations (Fig. 2) with a lower relative risk observed in the recent-onset group; however, statistical significance was only observed in the much larger group of subjects with chronic illness. In the recent-onset population, median time to first treatment failure was not estimable (>450 days) in the PP group and 270 days in the oral AP group. For subjects with more chronic illness, median time to first treatment failure was 416 days (PP) and 210 days (oral APs).

Reasons for first treatment failure are summarized in Table 3 by subpopulation. No major differences in reasons for treatment failure were identified between the recent-onset and chronic illness cohorts. The HR (95% CI) for either form of institutionalization was 1.79 (0.88–3.62; log-rank P = 0.107) for recent-onset and 1.38 (0.99, 1.92;

FIGURE 2. Kaplan–Meier estimate of time to first treatment failure for subjects with (a) recent-onset (≤5 years) and (b) chronic illness (>5 years). AP, antipsychotic; CI, confidence interval; HR, hazard ratio; PP, paliperidone palmitate.

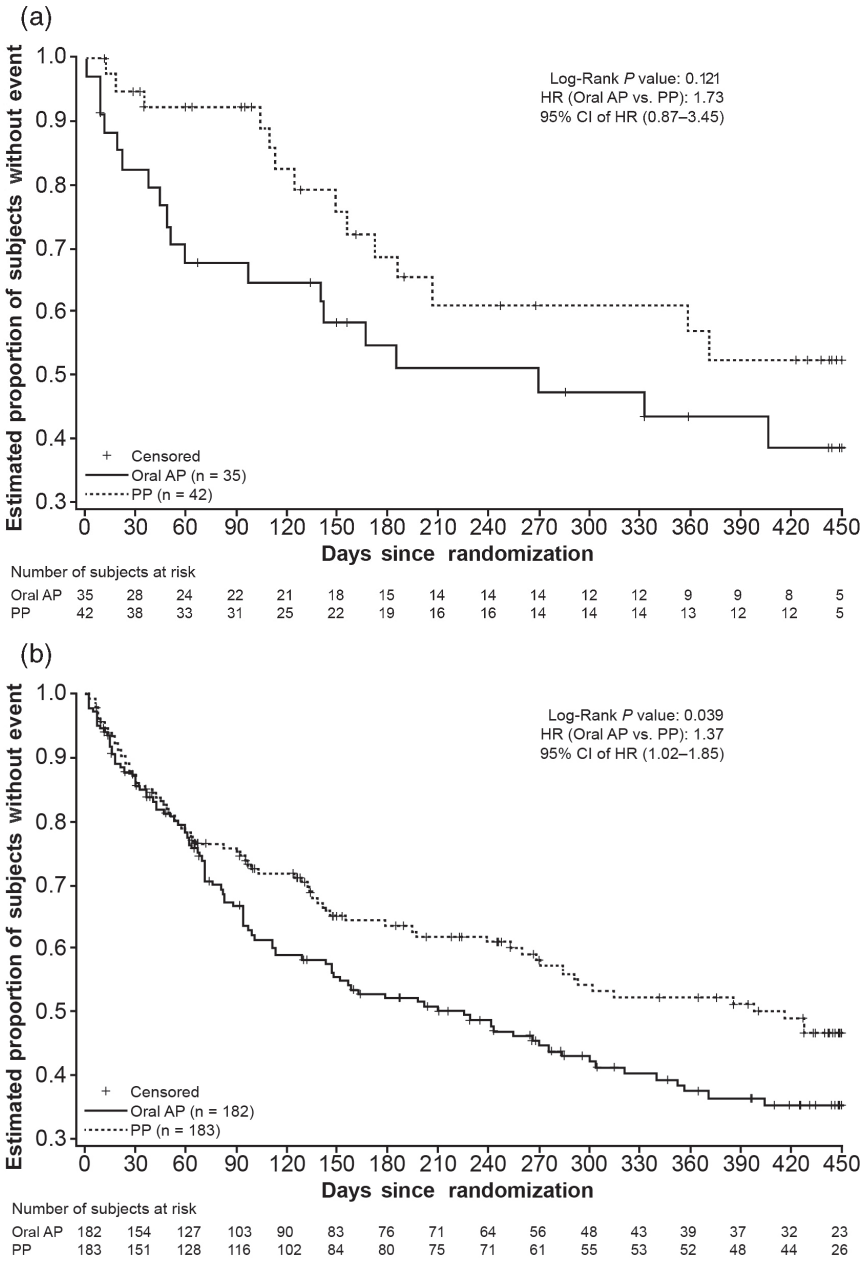


TABLE 3. Reasons for first treatment failure (intent-to-treat population)

Reason, *n* (%)	Recent-onset illness (≤5 years)		Chronic illness (>5 years)	
	PP (*n* = 42)	Oral APs (*n* = 35)	PP (*n* = 183)	Oral APs (*n* = 182)
Any	14 (33.3)	19 (54.3)	76 (41.5)	98 (53.8)
Arrest/incarceration	9 (21.4)	13 (37.1)	39 (21.3)	51 (28.0)
Psychiatric hospitalization	1 (2.4)	2 (5.7)	17 (9.3)	24 (13.2)
Discontinuation of AP treatment because of inadequate effectiveness	0	1 (2.9)	1 (0.5)	8 (4.4)
Discontinuation of AP treatment because of safety or tolerability	2 (4.8)	1 (2.9)	13 (7.1)	7 (3.8)
Treatment supplementation with another AP because of inadequate effectiveness	0	2 (5.7)	5 (2.7)	4 (2.2)
Increase in level of psychiatric services to prevent imminent psychiatric hospitalization	2 (4.8)	0	1 (0.5)	4 (2.2)
Suicide	0	0	0	0

AP, antipsychotic; PP, paliperidone palmitate.

log-rank $P = 0.058$) for chronic illness (Fig. 3). Median time to first psychiatric hospitalization or arrest/incarceration was > 450 days in the PP group for both the recent-onset and chronic illness subpopulations, whereas the median time to first psychiatric hospitalization or arrest/incarceration in the oral AP group was 270 and 274 days for the recent-onset and chronic illness subpopulations, respectively.

Safety

TEAEs are summarized by treatment group and disease chronicity subpopulation in Table 4. In these subpopulations, the overall incidence of TEAEs (PP vs. oral APs) was 90.5% versus 77.1% for recent-onset schizophrenia and 84.7% versus 80.2% for chronic illness. The incidence of serious TEAEs (PP vs. oral APs) was 11.9% versus 20.0% for recent-onset schizophrenia and 18.6% versus 22.0% for chronic illness. The most common TEAEs (≥10%) across treatment groups and subpopulations were injection site pain (PP only), increased body weight, akathisia, insomnia, anxiety, sedation, back pain and headache (Table 4). Prolactin-related TEAEs and weight increases of ≥ 7% were more frequent in the PP group than in the oral AP group for both the recent-onset and chronic illness subpopulations (Table 4).

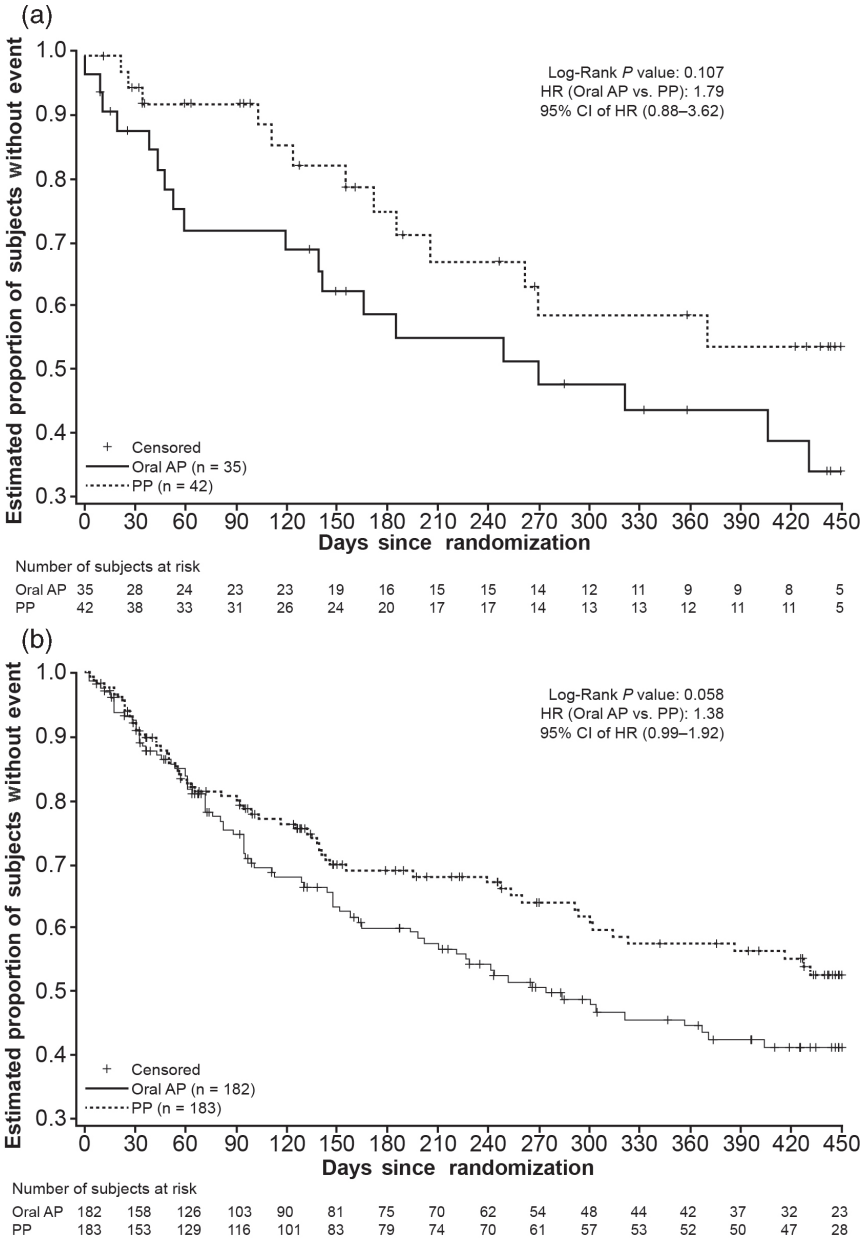
DISCUSSION

The use of LAIs for schizophrenia is usually reserved for those with a history of chronic illness and a history of multiple treatment failures using oral AP regimens. However, this practice is not evidence based and there are anecdotal reports that LAIs may be of particular value when used early in the course of illness.[16,23,26–30] Recently, a few randomized studies have demonstrated the value of using APs early in the course of schizophrenia.[31,32] In particular, a study by Subotnik *et al*. provides evidence that LAI risperidone may reduce psychotic exacerbations and relapse rates compared with oral risperidone in patients with schizophrenia early in the disease course.[32] In this study, LAI risperidone compared to oral risperidone better controlled mean levels of hallucinations and delusions throughout follow-up ($t_{68} = -2.6$; $P = 0.01$), despite failure to identify differences in cognitive remediation and training in healthy behaviours.[32] In addition, adherence to oral risperidone did not appear to differ between the oral and LAI risperidone groups before randomization, but adherence was better in the LAI risperidone group than in the oral risperidone group postrandomization ($t_{80} = 5.3$; $P < 0.001$).[32]

Nonadherence to treatment is particularly prominent in recent-onset schizophrenia and likely contributes to this group's increased risk for relapse and rehospitalization. Indeed, there is a growing body of evidence suggesting that early nonadherence is associated with persistent psychotic symptoms, worsening disease course and greater functional disability.[33,34]

This post hoc analysis of a pragmatically oriented trial of subjects with schizophrenia and a recent history of CJS custody found a 73% risk reduction for first treatment failure in those with recent-onset schizophrenia (≤5 years since psychiatric diagnosis) compared with a 37% risk reduction in a subpopulation with more chronic illness. This

FIGURE 3. Kaplan–Meier estimate of time to first psychiatric hospitalization or arrest/incarceration for subjects with (a) recent-onset (≤5 years) and (b) chronic illness (>5 years). AP, antipsychotic; CI, confidence interval; HR, hazard ratio; PP, paliperidone palmitate.



suggests that the benefit of PP compared with oral AP medication is greater in subjects early in the course of illness than in those who have more chronic illness. This difference is likely not accounted for by other differences in the patient population characteristics because demographic characteristics of the two populations appeared to be generally similar (Table 2). Although the risk for treatment failure for PP compared with oral APs did not reach statistical significance for the recent-onset subpopulation, this is likely driven by the low power of this post hoc comparison and the sample size ($n = 77$). A sample of 246 subjects (123 per group) would have been needed to provide approximately 80% power to detect the observed treatment group difference (HR of 1.73).

A valuable aspect of the design of the PRIDE trial was its broad inclusion criteria and treatment flexibility reflecting real-world treatment practice. The patient population was representative of persons with schizophrenia who are frequently encountered in US real-world clinical practice. Despite their

TABLE 4. Summary of TEAEs and proportion of subjects with weight increase (intent-to-treat population)

TEAE, *n* (%)	Recent-Onset Illness (≤5 years)		Chronic Illness (>5 years)	
	PP (*n* = 42)	Oral APs (*n* = 35)	PP (*n* = 183)	Oral APs (*n* = 182)
≥1 TEAE	38 (90.5)	27 (77.1)	155 (84.7)	146 (80.2)
Serious	5 (11.9)	7 (20.0)	34 (18.6)	40 (22.0)
TEAEs occurring in ≥ 10% of subjects by preferred term				
Injection site pain	11 (26.2)	0	31 (16.9)	0
Weight increased	6 (14.3)	2 (5.7)	21 (11.5)	11 (6.0)
Akathisia	6 (14.3)	3 (8.6)	19 (10.4)	12 (6.6)
Insomnia	5 (11.9)	6 (17.1)	33 (18.0)	19 (10.4)
Anxiety	5 (11.9)	2 (5.7)	19 (10.4)	14 (7.7)
Sedation	5 (11.9)	1 (2.9)	10 (5.5)	15 (8.2)
Back pain	5 (11.9)	1 (2.9)	8 (4.4)	7 (3.8)
Headache	2 (4.8)	4 (11.4)	12 (6.6)	14 (7.7)
TEAEs of special interest				
Prolactin related	12 (28.6)	1 (2.9)	41 (22.4)	8 (4.4)
EPS related	9 (21.4)	7 (20.0)	45 (24.6)	34 (18.7)
Weight increase of ≥ 7%†‡	16 (38.1)	6 (18.2)	54 (30.7)	24 (13.7)

†Measured at 15 months last observation carried forward. ‡Patient numbers: recent-onset illness (PP: *n* = 42; oral APs: *n* = 33), chronic illness (PP: *n* = 176; oral APs: *n* = 175). AP, antipsychotic; EPS, extrapyramidal symptom; TEAE, treatment-emergent adverse event.

prevalence within the broader population, patients with schizophrenia and a history of recent CJS contact and/or comorbid substance abuse are normally excluded from clinical trials. Similarly, expansion of the primary end-point to include events such as time to arrest (i.e. the most common treatment failure outcome for this study) extended observations to include events that are of broad public health interest and that can be highly informative.[21] However, to our knowledge, this outcome has not been previously assessed in this type of trial. Although these results come from a post-hoc analysis and cannot be generalized beyond the population included in this trial, they suggest that this effect is most pronounced in persons early in the course of illness. Although incarceration has an impact at any time, the burden of schizophrenia and a history of incarceration are likely to enhance recidivism and increase the difficulty of moving patients into circumstances that can facilitate optimal treatment and outcomes. This might be particularly detrimental to persons early in illness because of enhanced stigma and, particularly, lack of disease awareness.

Early in their illness, patients with schizophrenia are thought to be more sensitive to AP-associated adverse events (AEs), such as sedation, EPSs, weight gain and prolactin-related AEs.[35,36] However, in this analysis, with a few exceptions, no broad differences in AE rates were identified between the recent-onset and chronic illness subpopulations. Similarly, discontinuation of oral APs for safety or tolerability as a first treatment failure event appeared to be similar for both groups (Table 3). Overall, the AE profile of PP was consistent with that reported previously; the most notable events were well-established risks for injection site pain, akathisia, weight gain and elevated prolactin levels.[37–39] Because individual oral APs included as potential comparators in this study could be deselected and because the documented reasons for deselection were usually related to a history of AEs, relative rates for these events were likely underrepresented in this study. In addition, the oral AP group represents pooled effects of seven different oral medications with different side effect profiles. Together, these factors limit the interpretation of safety comparison of AEs between oral APs and the PP group.

Several additional considerations should be noted when interpreting the findings from these exploratory analyses. First, the study was not designed to address differences in treatment effect between patients with recent-onset illness and those with chronic illness. The selection criteria for this study and the nonrandom selection of both patients and sites limit the generalizability of the results of this analysis. For example, duration of illness (recent-onset and chronic) was not a randomization or stratification factor; consequently, meaningful baseline differences between treatment groups in each subpopulation may have affected the results observed in this analysis. Two patient subpopulations were excluded from or underrepresented in the study: those aged <18 years and >65 years. Therefore, the results of this study cannot be readily generalized to these patient

populations. Furthermore, the study was not powered to detect differences between treatment groups (PP vs. oral APs) in any subpopulations. This is especially important for the recent-onset group because its sample size was particularly small and results must be considered exploratory. Supporting the limitations in sample representativeness is the finding that persons with recent-onset schizophrenia in this study sample were older at first psychiatric diagnosis than those with chronic illness. In addition, the completion rates in this study were relatively low, further limiting the interpretation of results.

Although this exploratory analysis was neither pre-planned nor adequately powered, the results suggest that the relative advantage of PP over oral APs for reducing the risk for treatment failure may be greater in patients with recent-onset schizophrenia than those with more chronic illness.

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