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Comparison of long-acting and oral antipsychotic treatment effects in patients with schizophrenia, comorbid substance abuse, and a history of recent incarceration: An exploratory analysis of the PRIDE study

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ABSTRACT

Introduction: Comorbid substance abuse is known to blunt response to treatment for underlying psychiatric disorders, but it has not been investigated in schizophrenia when comparing the effects of long-acting injectable antipsychotics with those of oral antipsychotics.
Methods: This exploratory analysis compared once-monthly paliperidone palmitate (PP1M) with daily oral antipsychotics on time to treatment failure in patients with schizophrenia and a history of incarceration. Subjects were stratified into substance abuse (reported substance or alcohol misuse in the past 30 days on the baseline Addiction Severity Index–Lite Version and/or met criteria for a current MINI diagnosis of a substance abuse disorder) and nonabuse cohorts.
Results: In the substance abuse cohort, treatment failure was observed in 56.2% (73/130) and 64.2% (86/134) of subjects in the PP1M and oral antipsychotic groups, respectively. For the nonabuse cohort, treatment failure was observed in 36.5% (35/96) and 53.6% (45/84) of subjects in the PP1M and oral antipsychotic groups, respectively. Median (95% confidence interval [CI]) time to first treatment failure was 291 (179–428) days and 186 (94–296) days in the PP1M and oral antipsychotic groups, respectively. Median (95% CI) time to first treatment failure was >450 and 284 (147 to >450) days in the respective treatment groups.
Conclusion: Greater treatment effects were evident with PP1M compared with oral antipsychotics in both cohorts. The observed beneficial effect of PP1M was attenuated in the substance-abuse cohort, further reinforcing both the need for and value of continued research to optimize patient care in these complex patient populations.

1. Introduction

Schizophrenia is a chronic, serious mental illness affecting approximately 1.1% of US adults annually, whose disease course is frequently complicated by cognitive dysfunction, comorbid substance abuse, poor and unstable living conditions, multiple hospitalizations, and arrests/incarcerations (Regier et al., 1993; National Institute of Mental Health, 2016; Hoge, 2007; Folsom and Jeste, 2002; Ascher-Svanum et al., 2010). As a consequence of these comorbidities and resulting psychosocial instabilities, many patients exhibit nonadherence to essential antipsychotic medications, thus increasing their risk for relapses and hospitalizations (Lang et al., 2010; Novick et al., 2010; Higashi et al., 2013). Long-acting injectable (LAI) antipsychotic medications provide therapeutic plasma concentrations that are sustained over several weeks and with some, such as once-monthly paliperidone palmitate (PP1M), achieved within days of administration, thereby eliminating the need for adherence to daily oral antipsychotics (Pandina et al., 2010; Pandina et al., 2011). LAIs can also improve the consistency of antipsychotic medication delivery over a period of weeks to months, increasing the duration of effective symptom control and reducing the risk of relapse (Berwaerts et al., 2015).

Substance abuse is a common comorbidity in individuals with schizophrenia. It contributes to suboptimal adherence to treatment, poor symptom control, loss of function, increased suicidality, hospitalization, and a disproportionate increase in contact with the criminal justice system (CJS) (Gut-Fayand et al., 2001; Greenberg et al., 2011; Picci et al., 2013; Dumais et al., 2011; Lang et al., 2010; Novick et al., 2010; Higashi et al., 2013). As such, this subpopulation is difficult to treat and represents an important public health problem (Ascher-Svanum et al., 2010; Greenberg et al., 2011; National GAINS Center, 2001).

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Numerous prior studies document lower adherence to treatment plans and poorer treatment responses among substance-abusing patients (Picci et al., 2013; Lang et al., 2010; Ascher-Svanum et al., 2006; Greenberg et al., 2011; Novick et al., 2010; Hoge, 2007). Substance abuse, and consequent nonadherence to treatment, has been linked to an increased risk of psychosis and symptom exacerbation (Fenton et al., 1997; Lacro et al., 2002; Ascher-Svanum et al., 2010; Olivares et al., 2013; San et al., 2013) as well as increased CJS contact, incarceration, and risk of hospitalization (Olivares et al., 2013; San et al., 2013). The present study explores the negative impact of substance abuse and whether it is completely mitigated in this population despite the assured adherence associated with injectable drugs.

PRIDE (Paliperidone Palmitate Research in Demonstrating Effectiveness) was a prospective, randomized study that compared the effects of PP1M with daily oral antipsychotics on time to treatment failure. PRIDE incorporated both explanatory (efficacy) and pragmatic (effectiveness) design elements to better reflect real-world schizophrenia patients, treatments, and outcomes (Alphs et al., 2014). This was achieved by including subjects with a history of incarceration and comorbid substance abuse, allowing considerable flexibility in treatment and management decisions, and including a range of real-world outcomes as endpoints (i.e., arrest/incarceration, hospitalization, or treatment discontinuation for reasons of poor tolerability or inadequate efficacy) (Alphs et al., 2014). The time to first treatment failure (the primary endpoint for the PRIDE study), was significantly delayed by PP1M compared with daily oral antipsychotics, with a difference in median time to treatment failure of 190 days that favored the PP1M arm ($P = 0.011$) (Alphs et al., 2015). The time to first psychiatric hospitalization or arrest/incarceration was also significantly delayed by PP1M compared with daily oral antipsychotics ($P = 0.019$). Median time to first psychiatric arrest/incarceration was not reached with PP1M (>450 days) and was 274 days in the oral antipsychotic group (Alphs et al., 2015). Given the unusual inclusion of patients who met criteria for comorbid substance abuse in a long-term prospective interventional study in schizophrenia, the objective of the current post hoc analysis is to explore whether the greater effect of PP1M on treatment response compared with daily oral antipsychotics persisted in a subpopulation of schizophrenia patients with comorbid substance abuse and a history of recent incarceration.

2. Materials and methods

2.1. Study design

PRIDE was a prospective, randomized, open-label, event-monitoring board-blinded, active-controlled, multicenter US study (NCT01157351) (Alphs et al., 2014; Alphs et al., 2015). The study included a screening phase of up to 2 weeks, followed by a 15-month randomized treatment phase. All subjects were encouraged to continue in the study for the full 15-month study period, regardless of early discontinuation from randomized treatment or whether they experienced a primary study endpoint. The current exploratory post hoc analysis was based on the pragmatic intent-to-treat (pITT) analysis set. In contrast to an explanatory approach, which tends to limit evaluation of treatment response to the period when subjects receive their randomly assigned medication, this pragmatic approach examined treatment effects until the 15-month endpoint (or final recorded observation), regardless of whether subjects were maintained on their initial randomized treatment (Alphs et al., 2014), and therefore more closely reflects real-world outcomes.

2.2. Study population

The PRIDE study population has been previously described (Alphs et al., 2014; Alphs et al., 2015). In brief, the key inclusion criteria were adults aged 18 to 65 years with a current diagnosis of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV], criteria) (American Psychiatric Association, 2000) as confirmed by the M.I.N.I. International Neuropsychiatric Interview (MINI), version 6.0 (Cacciola et al., 2007); contact with the CJS (i.e., taken into custody) with ≥1 instance of custody leading to incarceration in the previous 2 years; and release from most recent CJS custody within 90 days of screening. Subjects were excluded if they had been actively abusing intravenous drugs within the past 3 months or had an opiate dependence disorder. Otherwise, substance abuse was not an exclusionary factor.

In the current analysis, subjects were included in the substance abuse cohort if they reported substance or alcohol misuse in the past 30 days on the baseline Addiction Severity Index–Lite Version (ASI-Lite) (Cacciola et al., 2007) and/or met the criteria for a current MINI diagnosis of a substance abuse disorder (Cacciola et al., 2007). This definition was consistent with DSM-IV criteria, which was used at the time of study execution (Sheehan et al., 1998). Nicotine was not included in the list of substances of abuse.

2.3. Treatments

Treatment details for subjects enrolled in the PRIDE study have been previously reported (Alphs et al., 2014; Alphs et al., 2015). In brief, antipsychotic treatment for individual subjects was randomly assigned (1:1) to flexibly dosed PP1M (78–234 mg) or daily oral antipsychotic therapy using an equipoise-stratified randomization scheme. The equipoised stratum was defined by the set of suitable oral antipsychotic treatments selected by the principal investigator and patients prior to randomization.

2.4. Assessments

The primary endpoint was defined as the time from subject randomization to occurrence of their first treatment failure. A treatment failure included any of the following events: arrest or incarceration, psychiatric hospitalization, suicide, discontinuation of treatment due to inadequate efficacy, treatment supplementation with another antipsychotic due to inadequate efficacy, discontinuation of treatment due to safety or tolerability, or increase in psychiatric services to prevent imminent psychiatric hospitalization. Safety assessments included monitoring of treatment-emergent adverse events (TEAEs).

2.5. Statistical analysis

The primary objectives of this exploratory analysis were to determine if the treatment effect of PP1M differed from the treatment effect with oral antipsychotics in (1) the nonabuse cohort and (2) the substance abuse cohort. Exploratory analyses included data from all subjects who received at least one dose of their randomly assigned study drug during the entire 15-month follow-up period regardless of whether they were still taking their randomized study medication (pITT analysis set). Demographic, baseline clinical characteristics, and TEAEs were summarized using descriptive statistics. Time to first treatment failure was estimated using the Kaplan-Meier method. Hazard ratio and treatment differences were estimated using the Cox proportional hazards regression model with treatment group (PP1M vs oral antipsychotics) and covariates for multiple prior incarcerations (yes/no), and whether subjects were randomized to the same medications they were taking before study entry (yes/no). No adjustments were made for multiplicity.

3. Results

3.1. Subjects and disposition

A total of 450 subjects were randomized. Of these, 269 subjects (60% of total population) were included in the comorbid substance abuse cohort and 181 (40%) were included in the nonabuse cohort. The pITT

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