Heterogeneity of Treatment Effects of Long-Acting Injectable Antipsychotic Medications

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ABSTRACT

Objective: To investigate subgroup responses to long-acting injectable (LAI) medications haloperidol decanoate (HD) and paliperidone palmitate (PP) in a randomized controlled trial that found no difference between the treatments on the primary outcome of efficacy failure.

Methods: A Comparison of Long-Acting Injectable Medications for Schizophrenia (ACLAIMS) enrolled 311 participants from March 2011 to July 2013 meeting *DSM-IV-TR* criteria for diagnoses of schizophrenia or schizoaffective disorder at risk of relapse due to medication nonadherence or substance abuse. Participants were randomly assigned to double-blinded treatment with HD or PP and followed for up to 2 years. A committee blinded to treatment assignment adjudicated efficacy failure on the basis of participants' meeting at least 1 of these criteria: psychiatric hospitalization, crisis stabilization, increased outpatient visits, could not discontinue oral antipsychotic, discontinued assigned LAI due to inadequate therapeutic benefit, or ongoing or repeated need for adjunctive oral antipsychotic medication. Survival analyses examined modification of treatment effects on efficacy failure by age, sex, race, substance abuse, baseline symptom severity, and baseline adherence. Mixed-effect linear models and analysis of covariance examined this modification on safety outcomes.

Results: An interaction between age and treatment ($P = .009$) revealed younger participants assigned HD had longer time to efficacy failure than those assigned PP. Interactions were not significant between treatment group and sex, race, substance use disorder, baseline symptom severity, or baseline adherence. An interaction of treatment and age on akathisia ($P = .047$) found an advantage for PP that was larger among younger persons. An advantage for HD on serum prolactin levels was larger among younger women ($P = .033$).

Conclusions: Among younger persons, HD was associated with lower rates of efficacy failure than PP. Age effects on adverse effects were mixed. Age-related heterogeneity of antipsychotic treatment effects warrants further investigation and consideration in clinical practice.

Trial Registration: ClinicalTrials.gov identifier: NCT01136772

J Clin Psychiatry 2019;80(1):18m12109

To cite: Stroup TS, Bareis NA, Rosenheck RA, et al. Heterogeneity of treatment effects of long-acting injectable antipsychotic medications. *J Clin Psychiatry.* 2019;80(1):18m12109.

To share: https://doi.org/10.4088/JCP.18m12109

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Long-acting injectable (LAI) antipsychotic medications are an important treatment option for individuals diagnosed with schizophrenia because they ensure medication delivery and allow for accurate assessment of medication adherence. This mode of medication delivery is widely believed to improve outcomes by improving medication adherence and thereby reducing symptoms and rates of relapse and rehospitalization.[1] Treatment guidelines[2] recommend LAI antipsychotics for patients who are at risk of nonadherence and for those who prefer biweekly or monthly injections to daily pills. There are increasingly frequent expert recommendations to use LAI antipsychotics among young people who are experiencing a first episode of schizophrenia because of high rates of nonadherence in this population and some evidence of improved outcomes with LAIs over oral antipsychotics.[3–5]

A Comparison of Long-acting Injectable Medications for Schizophrenia (ACLAIMS) is a National Institute of Mental Health–sponsored randomized controlled trial (NCT01136772)[6] that compared the effectiveness of paliperidone palmitate (PP), a newer LAI, to LAI haloperidol decanoate (HD), which has been available for several decades. The study found no difference in rates of efficacy failure among study participants, all of whom had a history of relapse due to medication nonadherence or substance abuse.

In this investigation, we explored whether different subgroups previously found to have differential responses to antipsychotics, defined by age, sex, race, the presence of a substance use disorder, Positive and Negative Syndrome Scale (PANSS)[7] score at baseline, and baseline adherence, responded differently to HD and PP. We investigated heterogeneity of effects in the primary outcome of efficacy failure, which was no different between the 2 medications in ACLAIMS, and secondary safety outcomes that were different in the overall analyses.

METHODS

Participants

Analyses were conducted using data from ACLAIMS, which took place from March 2011 to July 2013. Participants were eligible to join the

Clinical Points

- Identification of heterogeneous treatment response in clinical subgroups may lead to improved medication selection.
- Long-acting injectable antipsychotic medications are important options ensuring medication delivery in schizophrenia.
- Although a large NIMH-sponsored study found no difference in effectiveness between paliperidone palmitate and haloperidol decanoate (HD), this analysis found HD to be more effective among younger patients, warranting further research into age effects.

study if they were between the ages of 18 and 65 years, met criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[8] for diagnoses of schizophrenia or schizoaffective disorder, and had the capacity to provide informed consent.[9] Of the 353 individuals assessed for eligibility, 311 were randomized to either PP or HD. The final intent-to-treat sample consisted of 294 participants (147 participants in the PP group and 147 participants in the HD group) who received at least 1 injection, with 4 participants who had no visit after their first injection removed from the sample. The resulting modified intent-to-treat sample consisted of 290 participants (145 in each group). The study was conducted at 22 US clinical sites, and each site obtained institutional review board approval to conduct the study. Further details on the design of ACLAIMS can be found in McEvoy et al.[6]

Outcome Measures

Primary outcome. The primary outcome of interest in this analysis was efficacy failure, which was defined as meeting at least 1 of the following criteria: a psychiatric hospitalization, a need for crisis stabilization, a clinically meaningful increase in the frequency of outpatient visits, clinicians' decisions that oral antipsychotic medication could not be discontinued within 8 weeks after starting the LAI, clinicians' decisions to discontinue assigned LAI treatment due to inadequate therapeutic benefit, and ongoing or repeated need for adjunctive oral antipsychotic medication.[6] A committee blinded to treatment assignment adjudicated efficacy failure on the basis of these predetermined criteria.

Secondary outcomes. Tolerability failure was based on clinicians' decisions and classified according to common antipsychotic adverse effects including weight gain, lipid changes, glucose changes, extrapyramidal symptoms, tardive dyskinesia, akathisia, sexual dysfunction, gynecomastia/galactorrhea, menstrual irregularities, and hypersensitivity during the oral antipsychotic trial.[6]

Other secondary outcomes were those examined by McEvoy et al,[6] which are common adverse effects variably associated with different antipsychotics.[10–14] These included weight change over the course of the study and incidence of gaining 15 pounds or more. Worst change from baseline of 6 laboratory measures was also examined. Worst change from baseline over the course of the study and incidence of clinically significant scores of 3 neurologic effect measures were determined. These included the Abnormal Involuntary Movement Scale (AIMS)[15] global severity score and incidence of scores ≥ 2, the Barnes Akathisia Rating Scale (BAS)[16] global score and incidence of scores ≥ 3, and the Simpson-Angus Extrapyramidal Side Effects Scale Abbreviated Form (SAS)[17] mean score and incidence of scores ≥ 1. In addition, highest levels of prolactin and worst Arizona Sexual Experience Scale (ASEX)[18] score and incidence of scores ≥ 19 were determined grouped by sex.

Statistical Analyses

Primary analysis. The primary analysis included the modified intent-to-treat population (N = 290). Specific groups previously found to have heterogeneous responses to antipsychotic treatments were tested for modification of the effects of participants' assigned treatments on efficacy failure.[19–27] The Kaplan-Meier method[28] was used for the survivor analysis to estimate survival probabilities of the population that did not experience efficacy failure in days from first injection. Modification of this association was then tested by age (continuous in years), sex (female or male), race (white or African American), substance use disorder (meeting criteria of at least 3 of 5 on the Drug Use and/or Alcohol Use Scales),[29] baseline PANSS score (median split), and baseline adherence (Brief Adherence Rating Scale; BARS)[30] percentage (median split) taken in the last month. Following the methods in McEvoy et al,[6] participants were censored 90 days after their last injection. Analyses were adjusted for baseline PANSS score and study site.

Secondary analyses. Exploratory analyses were conducted to determine whether there was significant modification by our groups of interest on the relationship between the assigned treatment and our outcome measures. Modification of the association between assigned treatment and tolerability failure was tested for each of the groups using a Wald χ^2 test that adjusted for treatment site.

For the analysis of weight change over time, mixed-effect linear models with spatial power covariance structure were used to determine weight change (kg) in least squares means (LSMean) from baseline at 4 timepoints: 6 months from baseline, 12 months from baseline, 18 months from baseline, and 24 months from baseline. Type III tests of fixed effects were used to determine the significance of the modification of the assigned treatment by our groups of interest, adjusting for treatment site and baseline weight.

A modified sample limited to those who had at least 1 laboratory assessment after their first injection (n = 126 for HD, n = 129 for PP) was used to determine the worst change from baseline of 6 laboratory measures including hemoglobin A_{1c} (HbA_{1c}), blood glucose, total cholesterol, low-density lipoprotein cholesterol (LDL), triglycerides, and high-density lipoprotein cholesterol (HDL). An analysis of covariance (ANCOVA) tested the significance of the interaction between our groups of interest and assigned treatment on the worst LSMean of these 6 laboratory assessments, using a Type III sum of squares (Type III SS)

Table 1. Baseline Characteristics of the Modified Intent-to-Treat Sample

Characteristic	Total Sample	Haloperidol	Paliperidone
N (%)	290	145 (50.0)	145 (50.0)
Age, mean (SD), y	44 (12.5)	45 (12.3)	43 (12.6)
18–45 years, n (%)	141 (48.6)	66 (45.5)	75 (51.7)
46–65 years, n (%)	149 (51.4)	79 (54.5)	70 (48.3)
Female, n (%)	74 (25.5)	35 (24.1)	39 (26.9)
Race, n (%)			
African American	166 (57.2)	83 (57.2)	83 (57.2)
White	110 (37.9)	54 (37.2)	56 (38.6)
Other[a]	14 (4.8)	8 (5.5)	6 (4.1)
Hispanic, n (%)	14 (4.8)	8 (5.5)	6 (4.1)
Substance use disorder, n (%)	72 (24.8)	36 (24.8)	36 (24.8)
Clinical, mean (SD)			
Weight	89.94 (22.1)	90 (22.5)	90 (21.7)
HbA_{1c} score	5.8 (1.0)	5.6 (0.6)	5.9 (1.3)
Blood glucose, mg/dL	99.3 (25.2)	94.6 (17.6)	104.0 (31.5)
Total cholesterol, mg/dL	180.6 (40.3)	181.5 (41.9)	179.7 (38.5)
LDL cholesterol, mg/dL	106.3 (34.2)	108.1 (33.00)	104.6 (35.1)
Triglycerides, mg/dL	122.3 (83.5)	119.9 (80.5)	123.2 (86.4)
HDL cholesterol, mg/dL	49.7 (14.7)	48.7 (13.0)	50.6 (16.1)
Prolactin, µg/L			
Female	33.1 (36.8)	32.2 (38.5)	35.9 (35.2)
Male	17.8 (17.6)	17.8 (13.5)	17.4 (20.8)
PANSS total score, median (range)	71.0 (36.0–116.0)	70.0 (36.0–116.0)	73.0 (37.0–116.0)
BARS proportion taken, median (range)	93.0 (0–100.0)	93.5 (0–100.0)	90.0 (0–100.0)
Time to efficacy failure, d, mean (SD)			
Age 18–45 years		336.0 (209.6)	313.7 (216.3)
Age 46–65 years		287.3 (217.1)	304.0 (186.2)
AIMS global severity score, median (range)	0 (0–2.0)	0 (0–2.0)	0 (0–2.0)
BAS global score, median (range)	0 (0–3.0)	0 (0–3.0)	0 (0–3.0)
SAS mean score, median (range)	0 (0–1.5)	1.0 (0–1.5)	0 (0–1.5)
ASEX score, median (range)			
Female	19.0 (7.0–30.0)	19.0 (7.0–30.0)	18.0 (10.0–30.0)
Male	14.0 (5.0–30.0)	14.0 (5.0–30.0)	14.0 (5.0–30.0)

[a]Other includes American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale (higher is worse), ASEX = Arizona Sexual Experience Scale (higher is worse), BARS = Brief Adherence Rating Scale (higher is better), BAS = Barnes Akathisia Rating Scale (higher is worse), HbA_{1c} = hemoglobin A_{1c}, HDL = high-density lipoprotein, LDL = low-density lipoprotein, PANSS = Positive and Negative Syndrome Scale (higher is worse), SAS = Simpson-Angus Extrapyramidal Side Effects Scale Abbreviated Form (higher is worse).

F-test with a significance of α = .05, adjusting for treatment site and baseline levels.

The same ANCOVA method was also used to determine the worst change from baseline in LSMean as the outcome for the AIMS, BAS, and SAS scores and adjusted for treatment site and baseline scores. Modification of the relationship between these outcomes and assigned treatment by our groups of interest were tested for significance using the Type III SS *F*-test with a significance of α = .05. Finally, using the same ANCOVA method, we determined the highest levels of prolactin after baseline (LSMean), worst ASEX score (LSMean) after baseline, and incidence of an ASEX score ≥ 19 grouped by sex. The interaction between the assigned treatment and our groups of interest was tested for significance using the Type III SS *F*-test with a significance of α = .05.

For all secondary analyses, data collected more than 6 weeks after each participant's last injection were excluded. Individuals with baseline values equal to or greater than the clinically significant scores for the AIMS, BAS, SAS, and ASEX were excluded from the individual analyses that examined incidence of the clinically significant score. SAS 9.4 software[31] was used to conduct these statistical analyses.

Table 2. Modification of Assigned Treatment by Groups of Interest on Efficacy Failure for Modified Intent-to-Treat Sample (N = 290)

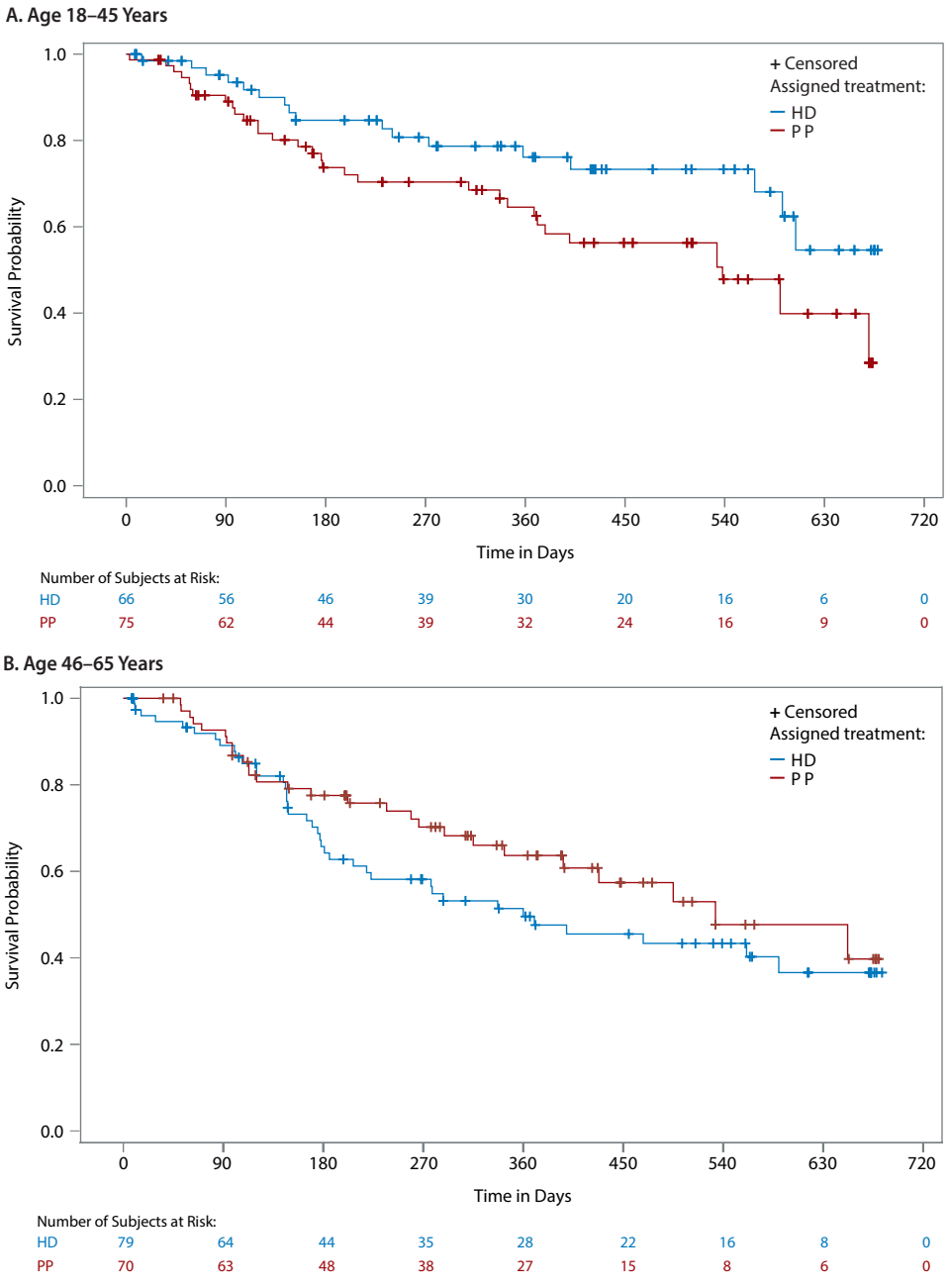
	Efficacy Failure	
Predicting	χ^2	*P* Value[a]
Age (continuous years)	7.260	**.009**
Sex	0.129	.720
Substance use disorder	0.139	.710
Race	2.267	.132
PANSS (median split)	0.828	.363
BARS (median split)	0.510	.475

[a]Adjusted for baseline PANSS score and site. Boldface type indicates significance.
Abbreviations: BARS = Brief Adherence Rating Scale, PANSS = Positive and Negative Syndrome Scale.

RESULTS

The analytic sample was the modified intent-to-treat population, which included 290 participants who received at least 1 injection and returned for at least 1 follow-up visit. Table 1 shows the distribution of the subgroups among the treatments and the baseline characteristics of the study population. The survival analysis revealed a significant interaction between age and treatment assignment in the

Figure 1. Primary Outcome: Product-Limit Survival Estimates of LAI Paliperidone Palmitate (PP) vs LAI Haloperidol Decanoate (HD) Stratified by Age Group[a]



[a]Age 18–45 years, log rank $P = .03$; age 46–65 years, log rank $P = .21$.
Abbreviation: LAI = long-acting injectable.

primary outcome of efficacy failure ($P = .009$). There was no significant interaction between treatment assignment and sex, race, presence of a substance use disorder, baseline PANSS score, or baseline BARS score on efficacy failure (Table 2).

To further investigate the modification of assigned treatment efficacy failure by age, we split the population at the median age as seen in Figure 1. We found that among the younger group (age 18–45 years; n = 141), HD was associated with a significantly longer time to efficacy failure ($P = .029$) than PP. Among the older group (age 46–65 years; n = 149), there was a trend for longer time to efficacy failure among the PP group ($P = .196$). In addition, among the criteria for efficacy failure (Table 3), psychiatric hospitalization and the need for crisis stabilization were significantly different between the assigned treatments in the younger age group (ie, $P = .016$ and $P = .025$, respectively). All the other, rarer criteria defining efficacy failure trended in the same direction, with participants assigned to PP having more events than those assigned to HD. No differences between assigned treatment and efficacy failure criteria were seen in the older age group.

Table 3. Criteria for Efficacy Failure Within Age Groups by Medication for Modified Intent-to-Treat Sample (N = 290)[a]

	Age 18–45 Years (n = 141)			Age 46–65 Years (n = 149)		
Category	HD	PP	*P* Value[b]	HD	PP	*P* Value
N (%)	66 (45.5)	75 (51.7)		79 (54.5)	70 (48.3)	
Efficacy failure, n (%)	17 (25.8)	34 (45.3)	**.02**	39 (49.4)	27 (38.6)	.19
Criteria for efficacy failure, n (%)						
Psychiatric hospitalization	9 (13.6)	23 (30.7)	**.02**	29 (36.7)	23 (32.9)	.62
Need for crisis stabilization	4 (6.1)	14 (18.7)	**.03**	17 (21.5)	7 (10.0)	.06
Increased frequency of outpatient visits	0	2 (2.7)	.18	4 (5.1)	3 (4.3)	.82
Oral antipsychotic medication could not be discontinued	1 (1.5)	5 (6.7)	.13	10 (12.7)	6 (8.6)	.42
Discontinued the assigned LAI due to inadequate therapeutic benefit	6 (9.1)	12 (16.0)	.22	20 (25.3)	16 (22.9)	.73
Ongoing need for adjunctive oral antipsychotic medication	3 (4.5)	7 (9.3)	.27	11 (13.9)	9 (12.9)	.85

[a]Not mutually exclusive categories. [b]Boldface type indicates significance.
Abbreviations: HD = haloperidol decanoate, LAI = long-acting injectable, PP = paliperidone palmitate.

Table 4. Worst Change From Baseline and Incidence of Clinically Significant Scores for Neurologic Effects and Prolactin Levels Among Age Groups

	Age 18–45 Years		Age 46–65 Years		
Score	HD	PP	HD	PP	*P* Value[a]
AIMS global severity score					
Incidence of AIMS ≥ 2, n (%)	8 (12.1)	9 (12.0)	24 (30.4)	22 (31.4)	.98
Worst change from baseline, mean[b] (95% CI)	0.4 (0.2–0.6)	0.3 (0.1–0.4)	0.7 (0.5–0.9)	0.6 (0.5–0.8)	.82
BAS global score					
Incidence of BAS ≥ 3, n (%)	10 (15.2)	4 (5.3)	4 (5.1)	2 (2.9)	.22
Worst change from baseline, mean[b] (95% CI)	0.9 (0.7–1.1)	0.4 (0.2–0.6)	0.5 (0.3–0.7)	0.4 (0.2–0.6)	**.047**
SAS mean score					
Incidence of SAS ≥ 1, n (%)	11 (16.7)	8 (10.7)	15 (19.0)	9 (12.9)	.75
Worst change from baseline, mean[b] (95% CI)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.3 (0.3–0.4)	0.3 (0.2–0.4)	.57
Among women only					
Highest serum prolactin level after baseline, µg/L, mean[b] (95% CI)	21.9 (0.8–43.1)	89.1 (69.4–108.7)	26.6 (6.5–46.7)	55.5 (39.0–72.2)	**.033**
Worst ASEX after baseline, mean[b] (95% CI)	22.0 (17.4–26.4)	22.4 (18.2–26.6)	24.8 (20.5–29.1)	25.1 (21.5–28.6)	.95
ASEX score ≥ 19, n (%)	2 (13.3)	6 (30.0)	2 (10.0)	3 (15.8)	.47
Among men only					
Highest serum prolactin level after baseline, µg/L, mean[b] (95% CI)	14.8 (7.6–22.0)	35.3 (28.4–42.3)	15.9 (9.2–22.6)	33.2 (26.2–40.3)	.64
Worst ASEX after baseline, mean[b] (95% CI)	18.7 (16.7–20.7)	16.3 (14.4–18.2)	17.3 (15.5–19.1)	19.4 (17.5–21.3)	**.018**
ASEX score ≥ 19, n (%)	7 (13.7)	7 (12.7)	7 (11.9)	12 (23.5)	.15

[a]Significance of interaction (modification) of treatment by age group. Boldface type indicates statistical significance.
[b]Least squares means from analysis of covariance model.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale (higher is worse); ASEX = Arizona Sexual Experience Scale (higher is worse); BAS = Barnes Akathisia Rating Scale (higher is worse); HD = haloperidol decanoate; PP = paliperidone palmitate; SAS = Simpson-Angus Extrapyramidal Side Effects Scale Abbreviated Form (higher is worse).

Other assigned treatment outcomes modified by age included akathisia measured by the BAS and increases in serum prolactin levels (Table 4). The greater mean increase in the BAS score associated with HD was larger in the 18–45 age group ($P = .047$). All prolactin analyses were conducted by sex; the greater increase associated with PP was of larger magnitude among younger women ($P = .033$).

PP was associated with more weight gain than HD; there was no modification by age (weight change by assigned treatment modified by age group at 6 months, $P = .82$; at 12 months, $P = .28$; at 18 months, $P = .34$; and at 24 months, $P = .95$; ever gained 15 pounds or more by assigned treatment modified by age group, $P = .44$). No effects on laboratory measures were modified by age (HbA_{1c}, $P = .39$; blood glucose, $P = .90$; total cholesterol, $P = .12$; LDL, $P = .29$; triglycerides, $P = .76$; HDL, $P = .69$). Thirty people in each treatment group discontinued the study medication because of poor tolerability; we found no significant interaction between age ($P = .29$), sex ($P = .41$), race ($P = .41$), presence of a substance use disorder ($P = .81$), baseline PANSS score ($P = .60$), or baseline BARS score ($P = .66$) and treatment assignment on this outcome.

We conducted several post hoc analyses to further investigate the modification of assigned treatment on efficacy failure by age. To examine the possibility that differential adherence between the 2 medications might explain the significant findings, we determined whether there was an association between nonadherence to assigned LAI among those assigned to that LAI and whether that association was modified by age. The association was not significant ($\chi^2 = 0.45$, $P = .50$). There was no difference between the assigned treatments and duration and dose equivalents[32] of the oral supplementation phase, with the oral supplementation discontinued by week 8 for the vast

Table 5. Sensitivity Analysis of Differences Between Assigned Treatments Within Each Subgroup

Subgroup	Haloperidol	Paliperidone	*P* Value[a]
Age, mean (SD), y	45.0 (12.3)	43.0 (12.6)	.21
Female, n (%)	35 (24.1)	39 (26.9)	.85
Race, n (%)			.93
African American	83 (57.2)	83 (67.2)	
White	54 (37.2)	56 (38.6)	
Substance use disorder, n (%)	36 (24.8)	36 (24.8)	1.00
PANSS, median split, n (%)			.73
Lower	78 (53.8)	65 (44.8)	
Upper	67 (46.2)	80 (55.2)	
BARS, median split, n (%)			.87
Lower	92 (63.4)	95 (65.5)	
Upper	53 (36.6)	50 (34.5)	

[a]Differences between prevalence of assigned LAI for each subgroup.
Abbreviations: BARS = Brief Adherence Rating Scale, LAI = long-acting injectable, PANSS = Positive and Negative Syndrome Scale.

majority of participants. Because antipsychotics may not be as effective at treating affective symptoms as treating psychosis, we tested whether there was an interaction between assigned treatment and age on the likelihood that ending treatment was due to affective symptomatology. Age did not modify this association ($\chi^2 = 1.79$, $P = .18$). The effect of anticholinergic load on memory and cognition was tested by first identifying participants who started anticholinergic medications after entering the study to determine if the initiation of anticholinergics by assigned treatment was modified by age. Second, we calculated whether the association between mean change from baseline of the Verbal Memory Response (measured from the Brief Assessment of Cognition in Schizophrenia, BAC[33]) and assigned LAI was modified by age. Age did not modify either of these associations (ie, $\chi^2 = 0.49$, $P = .48$ for anticholinergic-naïve participants and $\chi^2 = 1.4$, $P = .24$ for the BAC).

DISCUSSION

This randomized trial compared HD to PP in participants considered likely to benefit from LAI medications and did not find an advantage for PP on the main outcome of efficacy failure. This result is consistent with a long history of research that finds that standard antipsychotics (ie, other than clozapine) are generally similarly effective and are most distinct in their side effect profiles.[34,35]

The desire to personalize treatments has led to numerous calls to investigate heterogeneity of treatment effects in patient subgroups. A prior investigation[22] of antipsychotics found ethnic differences in metabolic complications from antipsychotic therapy. Sernyak et al[11] found an increased risk of diabetes in younger adults (< 40 years of age) taking atypical antipsychotics. A reduction in the risk of hospitalization was associated with older age in individuals with schizophrenia who were compliant with their medication regimens.[36] Sex differences have been found in the incidence and progression of schizophrenia.[37] Another investigation[38] found that clusters of individuals with differing levels of cognitive impairment had differential responses to treatments. Those with schizophrenia who are less adherent in taking their medications as prescribed are more likely to experience relapse than those who are highly adherent.[39]

The analyses presented here evaluated whether some subgroups of clinical interest responded differently to HD and PP. The effect of age was strongly significant, but there was no modification by sex, race, presence of a substance use disorder, baseline symptoms (PANSS score), or baseline adherence (BARS score). Age also modified the effects of the treatments on akathisia and serum prolactin levels. In both cases, younger participants had an exaggerated adverse effect compared to older participants. To illustrate the possible clinical significance of our preliminary findings, we found that the number needed to treat (NNT) for those aged 18–45 taking HD versus PP was 5.26, while the NNT for PP versus HD for those aged 46–65 was 10. An NNT of 5 or lower is considered effective, while higher values indicate less effectiveness.[40]

Limitations

A limitation of our study is that the analyses do not explain why HD is associated with lower rates of efficacy failure than PP in younger participants. The expectation that PP might be better tolerated among young persons who are more sensitive to side effects was not confirmed.[41] One possible explanation is use of different dosages of medications in younger and older patients.[42] However, analysis of the maximum dosage prescribed after baseline of assigned treatments found no difference by age ($P = .56$ for the HD group and $P = .69$ for the PP group).

In addition, subgroup analyses may affect the balance achieved through the initial randomization. We tested for differences between assigned LAIs for each of our subgroups and none was significant (see Table 5). However, unmeasured differences between assigned LAIs for our subgroups may still exist, which could affect our results.

We investigated 6 possible treatment modifiers, which increases the chance that the significant finding is due to chance. If we were to control for multiple comparisons using a Bonferroni correction (0.05/6 = 0.008), then the interaction of age with assigned treatment would still closely approximate the usual standard for statistical significance.[43]

Our post hoc analyses of treatment heterogeneity must be considered preliminary. Further efforts to examine heterogeneity of treatment response of antipsychotic medications by age are needed. If differential effects of medications by age are confirmed, this may lead to improved selection of treatments, shorter time to treatment response, and better outcomes.

Submitted: January 3, 2018; accepted June 1, 2018.
Published online: November 27, 2018.
Potential conflicts of interest: **Dr Stroup** received a research grant from Auspex Pharmaceuticals. **Dr McEvoy** has received consulting fees, honoraria, or grants from Alkermes, Avanir, Boehringer Ingelheim, Neurocrine, Teva, and Otsuka. **Drs Bareis, Swartz**, and **Rosenheck** have no conflicts of interest to disclose.
Funding/support: This study was funded by National Institute of Mental Health (NIMH) grant R01MH081107. Dr Bareis was funded by NIMH grant 5T32MH020004-18.

Role of the sponsor: The funders had no role in the conduct and publication of this study.

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