

A Prospective Randomized Controlled Trial of Paliperidone ER Versus Oral Olanzapine in Patients With Schizophrenia

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INTRODUCTION

- Metabolic effects are generally more pronounced with second-generation compared with first-generation antipsychotics.¹
 - Weight gain is greatest with olanzapine versus other atypicals^{2,3}
 - Diabetes risk is increased with olanzapine and clozapine^{2,4}
 - Risk of dyslipidemia greater with olanzapine and clozapine⁵
 - Metabolic syndrome has not been consistently linked to individual antipsychotic drugs⁶
- The atypical antipsychotic paliperidone ER has proven to be effective, well tolerated, and associated with significant improvement in patient functioning, as well as having a beneficial weight and metabolic profile.⁷⁻¹²

OBJECTIVE

To compare the longer-term metabolic effects and efficacy of paliperidone ER with oral olanzapine in patients with schizophrenia.

Table 1. Baseline patient characteristics (N = 459).

	Paliperidone ER (n = 239)	Olanzapine (n = 220)	P value*
Sex, %			
Male	55.6	60.5	0.30
Female	44.4	39.5	0.30
Age, mean years ± SD	38.8 ± 11.1	37.5 ± 11.4	0.22
Duration since diagnosis, mean years ± SD	10.1 ± 9.2	11.2 ± 9.9	0.23
Diagnosis of paranoid schizophrenia, %	68.2	71.4	0.60 [†]
Baseline weight, mean kg ± SD	76.0 ± 17.0	78.0 ± 16.4	0.11
Baseline BMI, mean kg/m ² ± SD	26.9 ± 6.3	27.0 ± 5.7	0.45
Comorbid medical illness, %	58.2	61.8	0.45
	(n = 222)	(n = 203)	
Met criteria for metabolic syndrome (NCEP/ATP III) at baseline, %	22.1	19.7	0.05
Reason for switching from previous antipsychotic (> 1 reason allowed), %			0.19
Lack of efficacy	57.7	64.5	
Lack of tolerability	17.6	12.7	
Lack of compliance	14.6	10.5	
Other	10.0	12.3	

* Between-group differences were evaluated using Fisher's exact test, 2-tailed for categorical data, and Wilcoxon's signed-rank test, 2-tailed for ordinal or continuous data.

[†] P value refers to between-treatment difference in proportion within different diagnostic categories; paranoid schizophrenia alone was not evaluated separately. BMI, body mass index; NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III; SD, standard deviation.

METHODS

Study design

- Multicenter, 6-month prospective, randomized controlled, open-label, parallel-group study of adult patients with schizophrenia treated with paliperidone ER (6–9 mg/day) or oral olanzapine (10–15 mg/day).
- Patients were stratified to a treatment arm according to the metabolic effects of their previous antipsychotic medication (weight-neutral versus non-weight-neutral).
 - Weight-neutral antipsychotics: high-potent conventional antipsychotics and the atypical antipsychotics amisulpride, aripiprazole, and ziprasidone
 - Non-weight-neutral antipsychotics: olanzapine, risperidone, and quetiapine

Patients

Inclusion criteria for analyses

- Adults aged 18–65 years with a DSM-IV diagnosis of schizophrenia and baseline Positive and Negative Syndrome Scale (PANSS) total scores between 60 and 100.

Exclusion criteria

- Treatment-naïve to antipsychotics; treated within the previous 6 months with paliperidone ER, olanzapine, or clozapine; treated within the last 3 months with a depot antipsychotic; treatment with a mood stabilizer or antidepressant; history of diabetes or abnormal fasting plasma glucose (> 126 mg/dL) or fasting triglyceride (TG) level (> 400 mg/dL) at screening.

Outcome measures

Primary outcome

- Mean change in the ratio of serum TG level to high-density lipoprotein level (TG:HDL) at endpoint versus baseline.

Assessments

- PANSS total and subscale scores.
- Clinical Global Impression – Severity (CGI-S).
- Metabolic evaluations
 - Lipid markers: fasting TG and HDL
 - Homeostasis model assessments (HOMA): insulin resistance (HOMA-IR) and beta-cell function (HOMA-%B)
 - Body weight
 - Waist circumference

Safety and tolerability

- Treatment-emergent adverse events (TEAEs).

Data analysis

- Between-treatment differences in change in TG:HDL ratio from baseline to endpoint were assessed using the Wilcoxon 2-sample test.
- Within-treatment changes from baseline to each visit and endpoint for secondary efficacy and safety measures were evaluated using the Wilcoxon signed-rank test for ordinal/continuous data, and sign test for nominal data.
- Between-treatment group differences were tested using the Wilcoxon 2-sample test for ordinal/continuous data and the Fisher exact test for nominal data.
- Non-inferiority in efficacy of paliperidone ER versus olanzapine was measured by change in PANSS total scores and tested using the Schuirmann test.

RESULTS

Table 2. Study drug dosing.

	Paliperidone ER (n = 239)	Olanzapine (n = 220)
Initial dose, mean mg/day ± SD	6.4 ± 1.2	10.6 ± 2.0
Average dose, mean mg/day ± SD	6.9 ± 1.3	11.6 ± 2.3
Median mode dose, mg/day	6.0	10.0
Duration of exposure, mean days ± SD	151.0 ± 52.1	159.8 ± 46.8

Figure 2. Change in PANSS total scores.

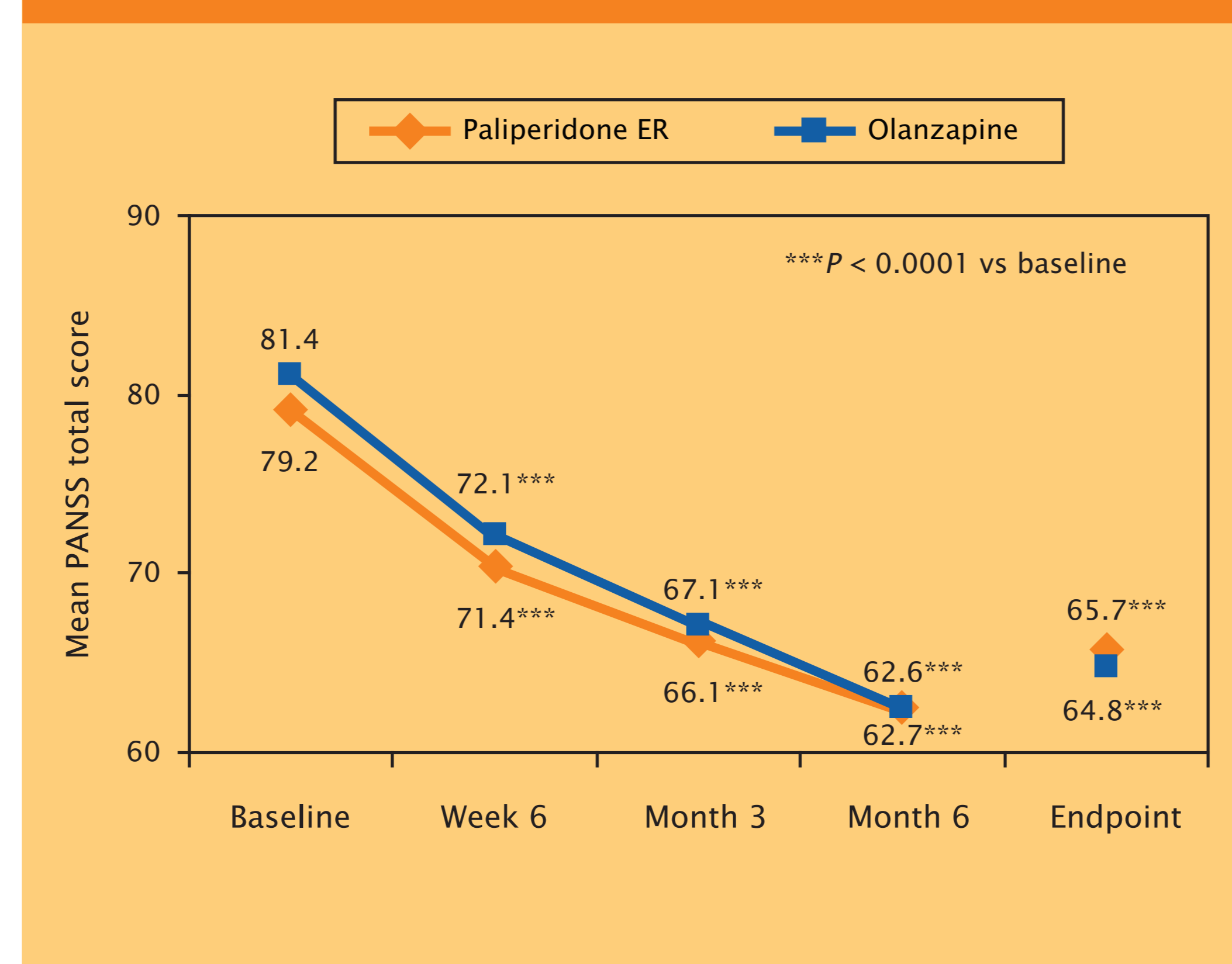


Figure 3. Homeostasis model assessment (HOMA).

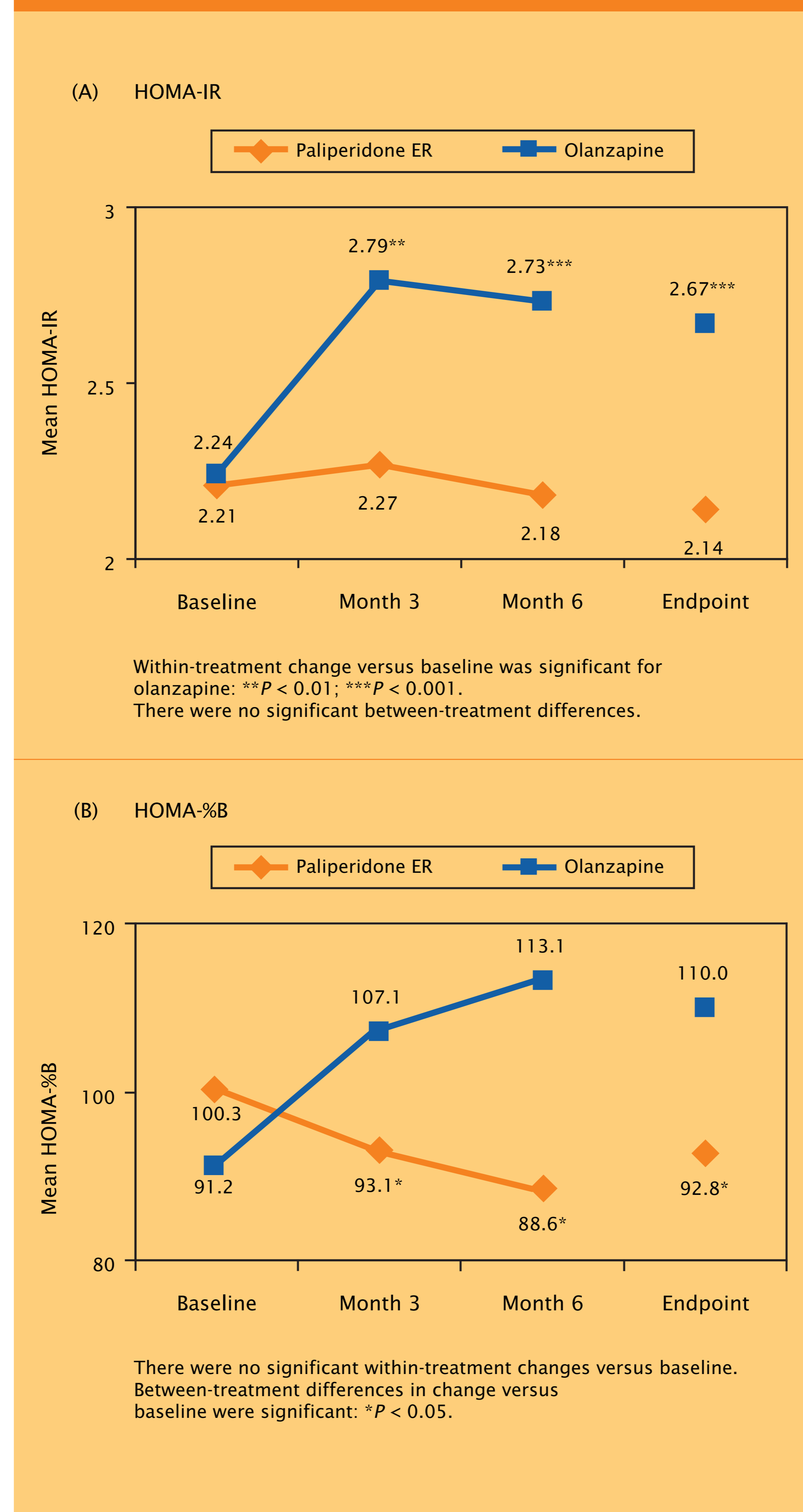


Table 4. Treatment-emergent adverse events (TEAEs).

TEAE, %	Paliperidone ER (n = 239)	Olanzapine (n = 220)
Any TEAE	54.4	51.8
TEAE causally related to study drug*	32.2	38.2
TEAE resulted in treatment discontinuation	4.6	2.3
Serious TEAE	8.8	5.5
TEAEs occurring in ≥ 5% in any treatment arm		
Weight increase	9.6	18.2
Somnolence	3.3	9.5
Insomnia	9.6	1.4
Schizophrenia	5.0	1.8
Severity of TEAEs [†]		
Mild	54.7	61.7
Moderate	39.7	31.0
Severe	5.7	7.3

* Causally related is defined as: possibly, probably, or very likely related. [†] Based on number of TEAEs (n = 300 for paliperidone ER and n = 248 for olanzapine) rather than number of patients.

Figure 1. Mean TG:HDL ratio at each visit and endpoint.

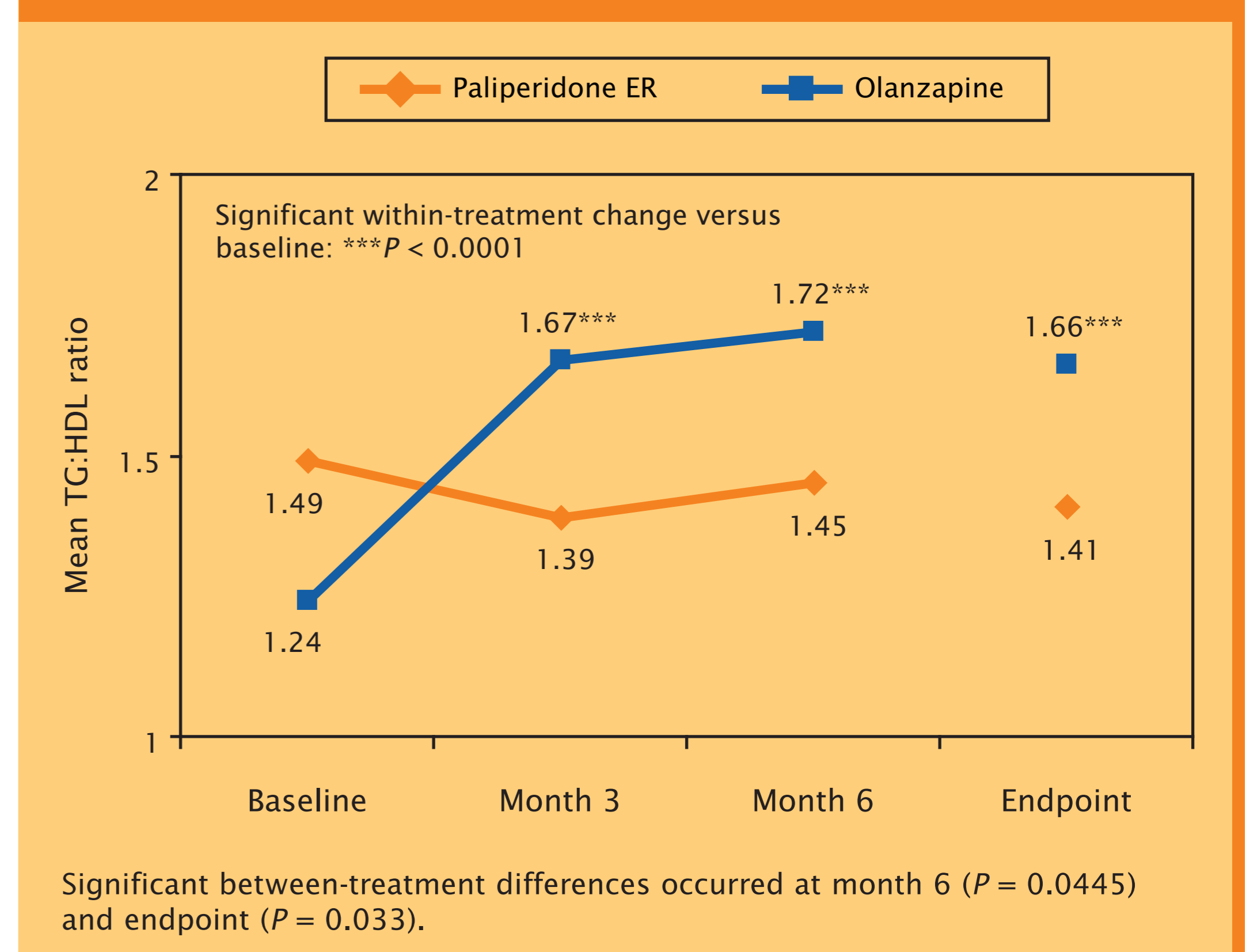


Table 3. Effects on lipid profiles and metabolic syndrome.

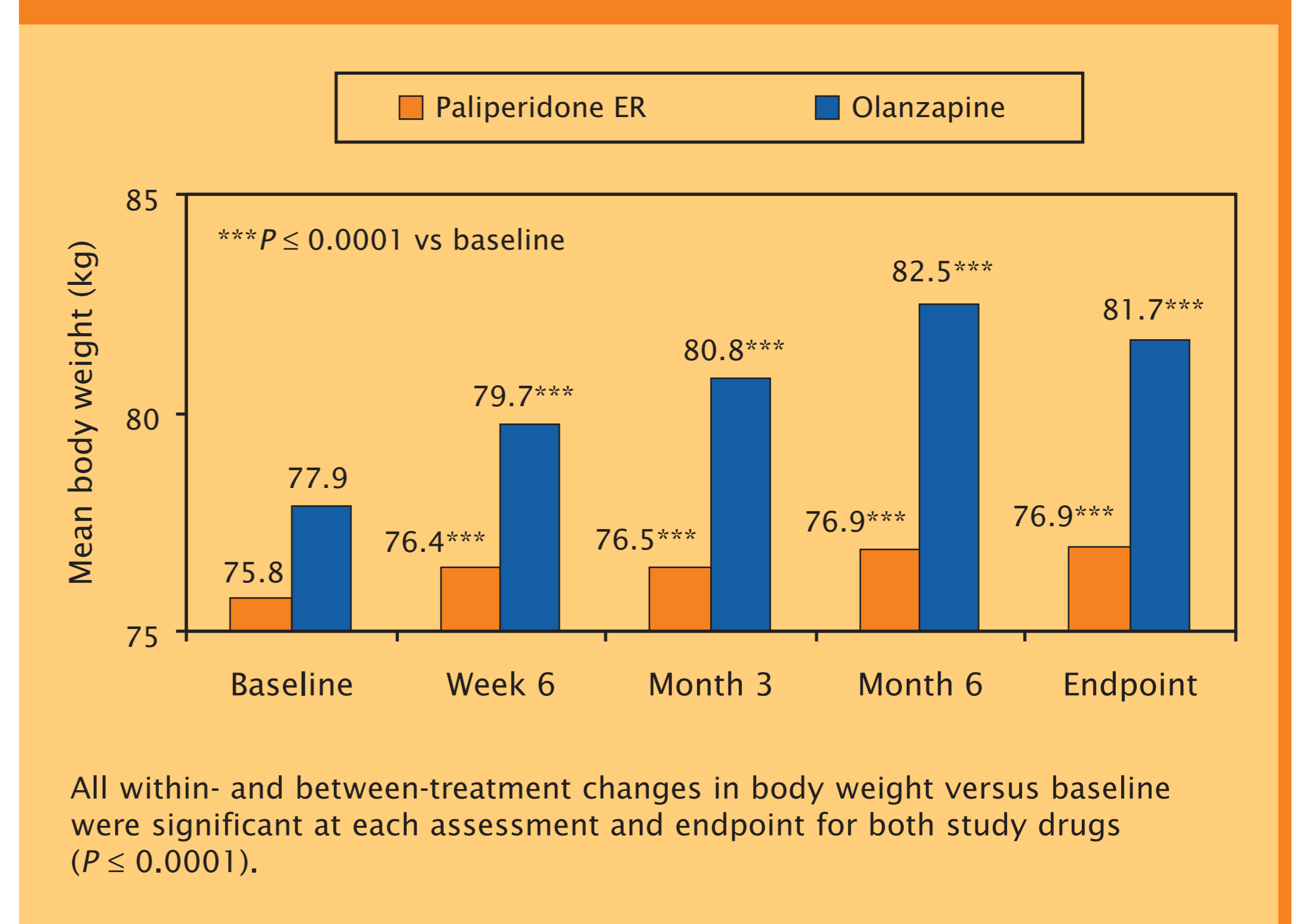
First onset of lipid dysfunction during scheduled follow-up, %	Paliperidone ER (n = 111)	Olanzapine (n = 130)
Impaired HDL < 40 mg/dL	19.8	23.8
Impaired TG ≥ 150 mg/dL	27.0	39.8*
Metabolic syndrome (NCEP/ATP III criteria)	13.2	23.3*

* P < 0.05 (Fisher's exact test, 2-tailed).

SUMMARY and CONCLUSION

- Efficacy and overall safety and tolerability were similar with paliperidone ER and olanzapine, and significant improvements in psychotic symptoms were observed with both treatments (P < 0.0001 versus baseline).
- Insulin resistance, as measured by changes in TG:HDL ratio versus baseline, was significantly higher at endpoint with olanzapine compared with paliperidone ER.
- Newly diagnosed impairment in TG and metabolic syndrome was more common with olanzapine than paliperidone ER (P < 0.05).
- Endpoint increase in body weight was significantly higher with olanzapine than paliperidone ER (3.8 versus 1.2 kg, P = 0.0013).
- Endpoint increase in waist circumference was significantly higher with olanzapine than paliperidone ER (3.4 versus 0.70 cm, P < 0.0001).
- This 6-month, randomized, comparative study confirms significant advantages in the metabolic profile of flexible doses of the newer atypical antipsychotic paliperidone ER compared with oral olanzapine. Olanzapine showed significantly more weight gain, lipid changes, insulin resistance, and new-onset metabolic syndrome, whereas efficacy of paliperidone ER was demonstrated to be non-inferior compared with oral olanzapine treatment.

Figure 4. Body weight change.



All within- and between-treatment changes in body weight versus baseline were significant at each assessment and endpoint for both study drugs (P ≤ 0.0001).

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