

A Flexible-dose Study of Paliperidone ER in Non-acute Patients With Schizophrenia Previously Unsuccessfully Treated With Other Oral Antipsychotics

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INTRODUCTION

- Extended-release paliperidone (paliperidone ER) uses an innovative osmotic controlled-release oral delivery system (OROS[®]) in order to achieve minimal peak-to-trough fluctuations over 24 hours with once-daily dosing.¹
- Paliperidone ER is approved for the treatment of schizophrenia, with efficacy, tolerability, and safety demonstrated in randomized controlled clinical trials.^{2,3}

OBJECTIVE

To explore tolerability, safety, and treatment response of flexible doses of paliperidone ER in adult patients with non-acute schizophrenia, previously unsuccessfully treated with other oral antipsychotics.

Table 1. Baseline characteristics (N = 1,812).

Characteristic	n (%)
Sex, n (%)	
Male	1,086 (59.9)
Female	726 (40.1)
Age, mean years ± SD	40.1 ± 12.6
Duration since diagnosis of schizophrenia, mean years ± SD	10.1 ± 9.7
Diagnosis of paranoid schizophrenia, n (%)	1,373 (75.8)
Main reason for switching from previous antipsychotic, n (%)	
Lack of efficacy	1,025 (56.6)
Lack of tolerability	490 (27.0)
Lack of compliance	165 (9.1)
Other	132 (7.3)

SD, standard deviation.

Table 2. Patient disposition (N = 1,812).

Patient disposition	n (%)
Completed 6 months of treatment	1,281 (70.7)
Reasons for early discontinuation of paliperidone ER	
Withdrew consent	160 (8.8)
AE	91 (5.0)
Lack of efficacy	91 (5.0)
AE plus lack of efficacy	73 (4.0)
Non-compliance	35 (1.9)
Lost to follow-up	33 (1.8)
Death*	3 (0.2)
Other	45 (2.5)

* Causes of death were acute cardiac insufficiency (n = 1, considered to be unrelated to paliperidone ER) and unknown (n = 2; no autopsy or other information available). One case was identified as unrelated to paliperidone ER and causal relationship data were missing for the other.

METHODS

Patients

Inclusion criteria for analyses

- Adult inpatients or outpatients aged ≥ 18 years, with a DSM-IV diagnosis of schizophrenia.
- Schizophrenia considered to be non-acute: patient treated with any other oral antipsychotic with a change in Clinical Global Impression – Severity (CGI-S) score of ≤ 1 during the 4 weeks before enrolment.
- Patient previously received an adequate dose of any other oral antipsychotic for an adequate period of time prior to enrolment, per investigator judgment.

Exclusion criteria

- Patients were excluded if they had: been treated with clozapine or a long-acting injectable antipsychotic during the preceding 3 months; significant medical illness; tardive dyskinesia; neuroleptic malignant syndrome; high risk for adverse events (AEs) or self-harm; substance dependence over the past 6 months; or known hypersensitivity to paliperidone ER or risperidone.

Treatment

- Flexibly dosed paliperidone ER (3–12 mg/day).
 - Recommended dose 6 mg once daily
 - Transitioned to effective dose without titration
 - Treated for up to 6 months

Outcome measures

Efficacy assessments

- Primary efficacy outcome was based on main reason for transitioning to paliperidone ER.
 - Patients switching for the main reason of lack of efficacy: response defined by ≥ 20% improvement in Positive and Negative Syndrome Scale (PANSS) total score from baseline to endpoint
 - Patients switching for main reasons other than lack of efficacy: change in PANSS total score from baseline to endpoint
 - Non-inferiority was defined by a difference of 5 points in change versus baseline on the PANSS total score
- Additional efficacy measures: PANSS total, subscale, and Marder factor scores, CGI-S score, Personal and Social Performance (PSP) scale score, and patient satisfaction with previous treatment measured at baseline and with paliperidone ER at week 26 (or endpoint). Satisfaction was rated as: very poor (1); poor (2); moderate (3); good (4); or very good (5).

Safety and tolerability

- Treatment-emergent AEs.
- Extrapyramidal Symptom Rating Scale (ESRS) score and body weight.

Data analysis

- For response, 95% confidence intervals (CIs) are estimated.
- Non-inferiority, defined by a difference of 5 points in change versus baseline on the PANSS total score, is evaluated using the Schuirmann 1-sided test ($\alpha = 0.025$).
- Within-group changes versus baseline were evaluated using the 2-tailed Wilcoxon signed-rank test ($\alpha = 0.05$).
- All data were assessed using intent-to-treat populations, with actual numbers available noted within each assessment below.

RESULTS

Table 3. Paliperidone ER treatment* (N=1,812).

Paliperidone ER dosing	n (%)
Initial dose, mean mg/day ± SD	5.3 ± 2.0
Mode dose, mg/day	
Mean mode dose ± SD	7.1 ± 2.9
Median mode dose	6.0
Duration of exposure, mean days ± SD	149.6 ± 58.6
Patients with a change in dosing, n (%)	
Increase	1,041 (57.5)
Decrease	324 (17.9)

* Paliperidone ER dosing was comparable for patients switching for reasons other than lack of efficacy but slightly higher for patients switching for the reason of lack of efficacy.

Table 4. Primary efficacy measure for patients switching for reasons other than lack of efficacy was change in PANSS total score from baseline to endpoint.

Main reason for switching to paliperidone ER	Mean change in PANSS total score (SD)
Lack of tolerability (n = 475)	–8.4 (19.2)***
Lack of compliance (n = 155)	–18.4 (21.2)***
Other (n = 128)	–9.5 (17.3)***

***Schuirmann's 1-sided test confirmed that equivalence to within the specified equivalence bounds can be claimed: $P < 0.0001$.

Table 5. Mean PANSS scores at baseline and endpoint (all patients, N = 1,756).

PANSS score ± SD	Baseline	Endpoint	P value
Total	79.4 ± 20.4	66.1 ± 21.5	< 0.0001
Subscale			
Positive	17.1 ± 6.1	14.0 ± 6.1	< 0.0001
Negative	22.3 ± 6.6	18.5 ± 6.6	< 0.0001
General psychopathology	40.0 ± 11.0	33.6 ± 11.2	< 0.0001
Marder factors			
Positive	21.5 ± 7.0	17.7 ± 7.0	< 0.0001
Negative	21.6 ± 6.6	17.7 ± 6.4	< 0.0001
Disorganized thoughts	18.0 ± 5.5	15.3 ± 5.4	< 0.0001
Uncontrolled hostility/excitement	7.7 ± 3.4	6.9 ± 3.3	< 0.0001
Anxiety/depression	10.5 ± 3.8	8.5 ± 3.6	< 0.0001

Figure 3. PSP categories at baseline and endpoint.

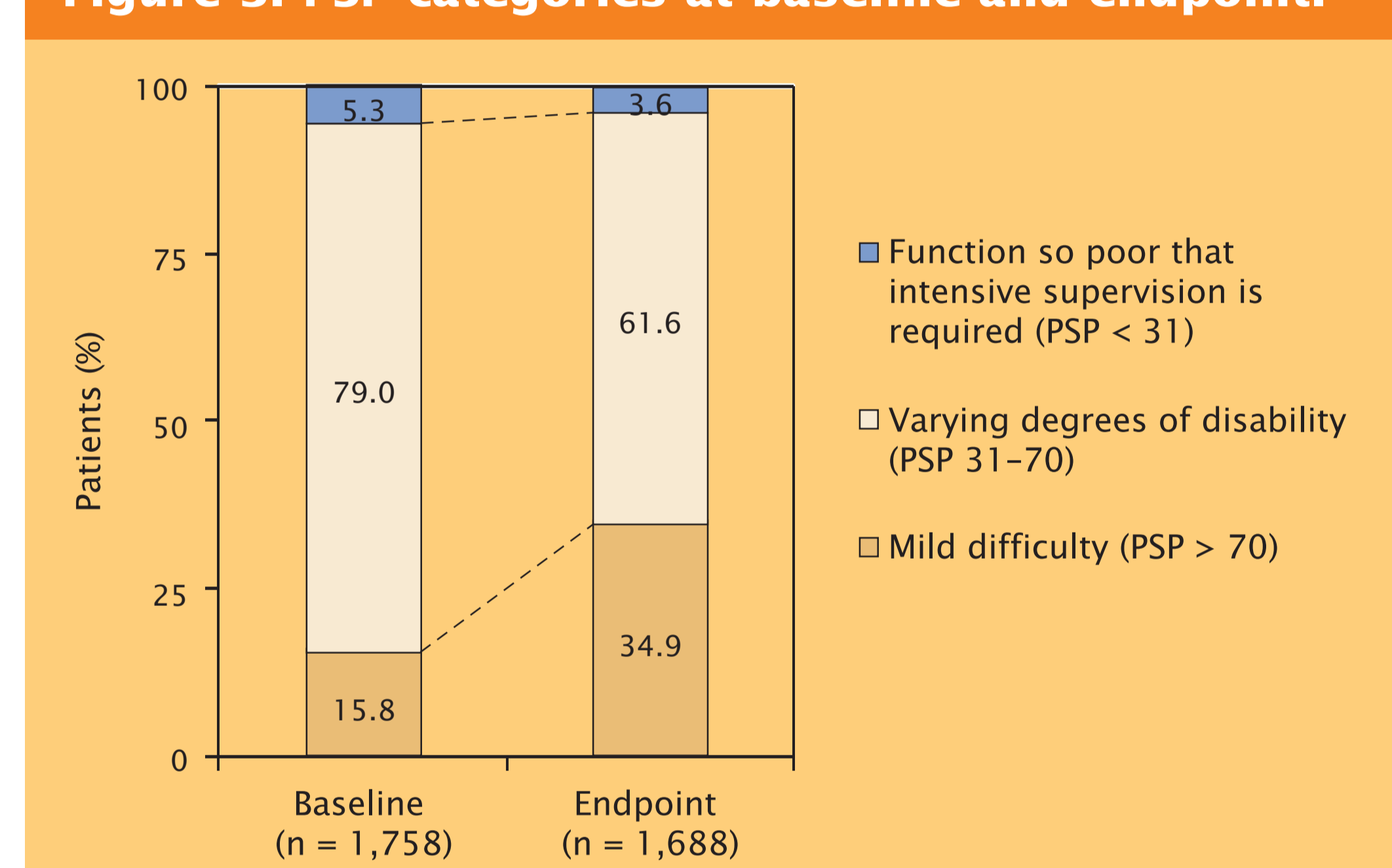


Figure 4. Patient satisfaction with previous antipsychotic treatment at baseline and with paliperidone ER at endpoint.

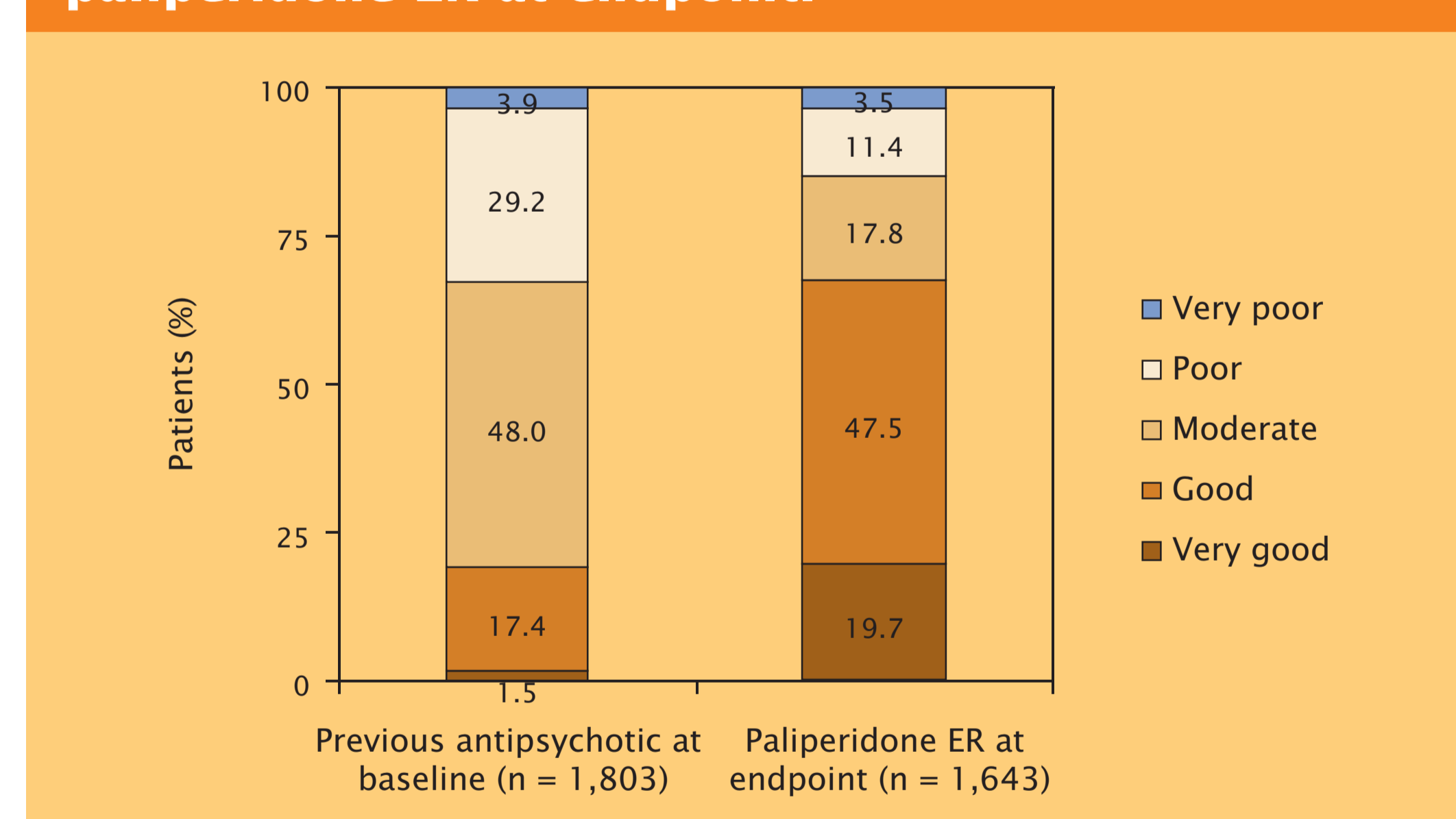
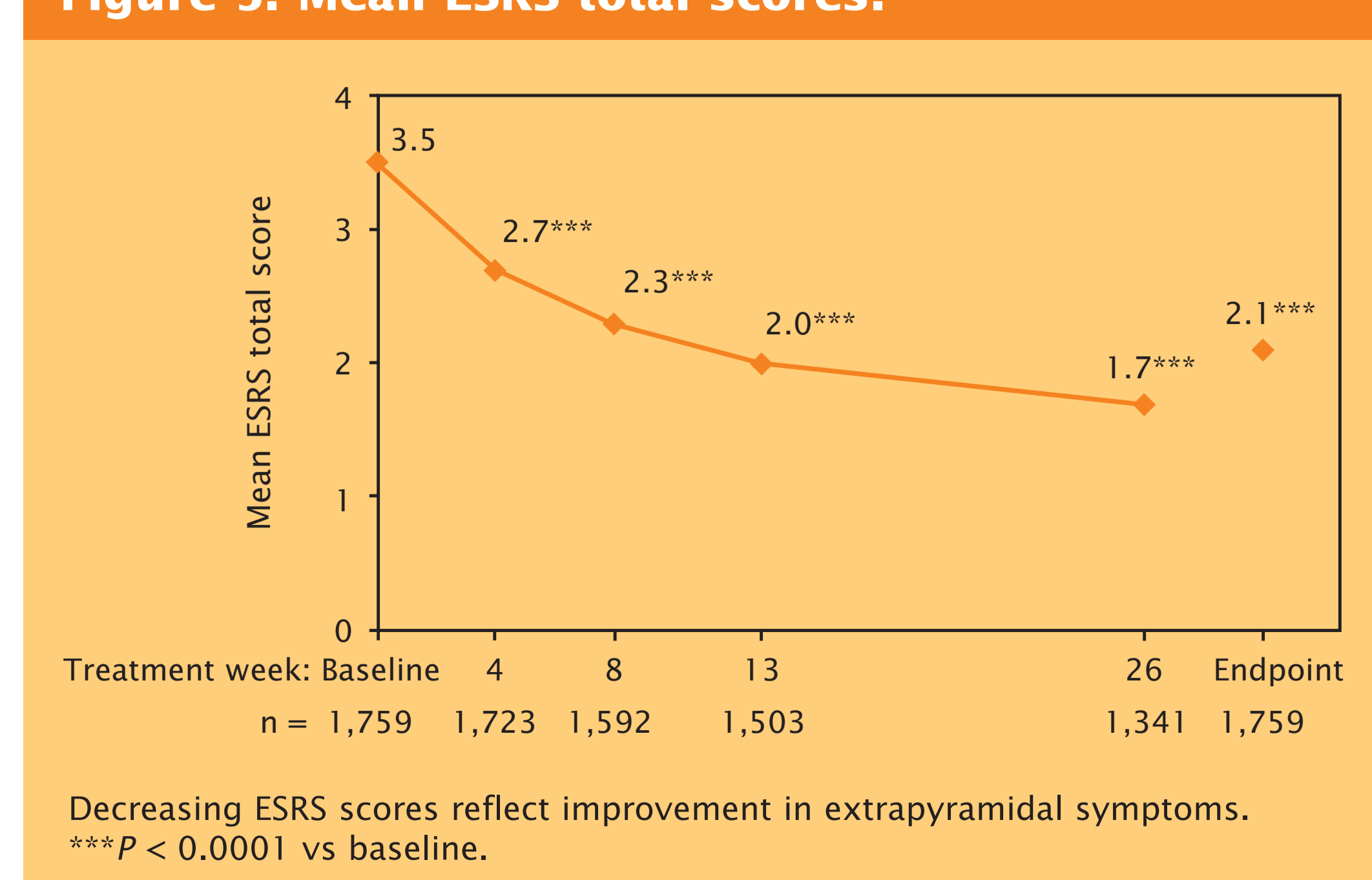


Table 6. Treatment-emergent adverse events (TEAEs) (N = 1,811).

TEAE	n (%)
Any TEAE*	999 (55.2)
TEAE causally related to paliperidone ER	636 (35.1)
Serious TEAEs†	155 (8.6)
TEAEs occurring in ≥ 5% of patients	
Insomnia	166 (9.2)
Anxiety	129 (7.1)
Action taken due to TEAE‡	
None	1,918 (75.1)
Dose adjustment	378 (14.8)
Temporary stop	14 (0.5)
Permanent discontinuation	244 (9.6)

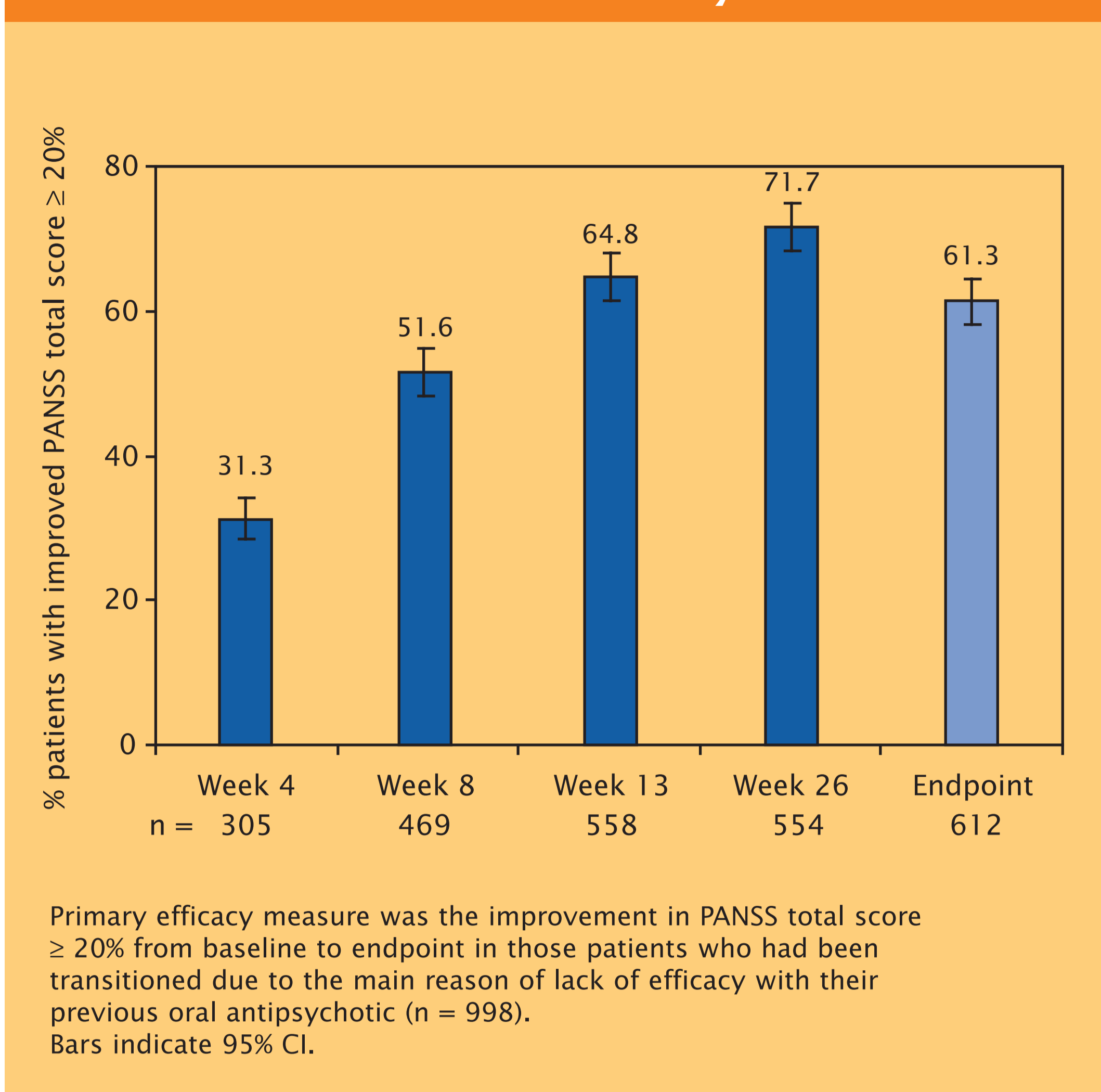
* Most TEAEs (90.7%) were mild to moderate in intensity.
 † Most commonly psychotic disorder (2.4%) and schizophrenia (1.5%).
 ‡ Based on number of TEAEs (n = 2,554) rather than number of patients.

Figure 5. Mean ESRS total scores.



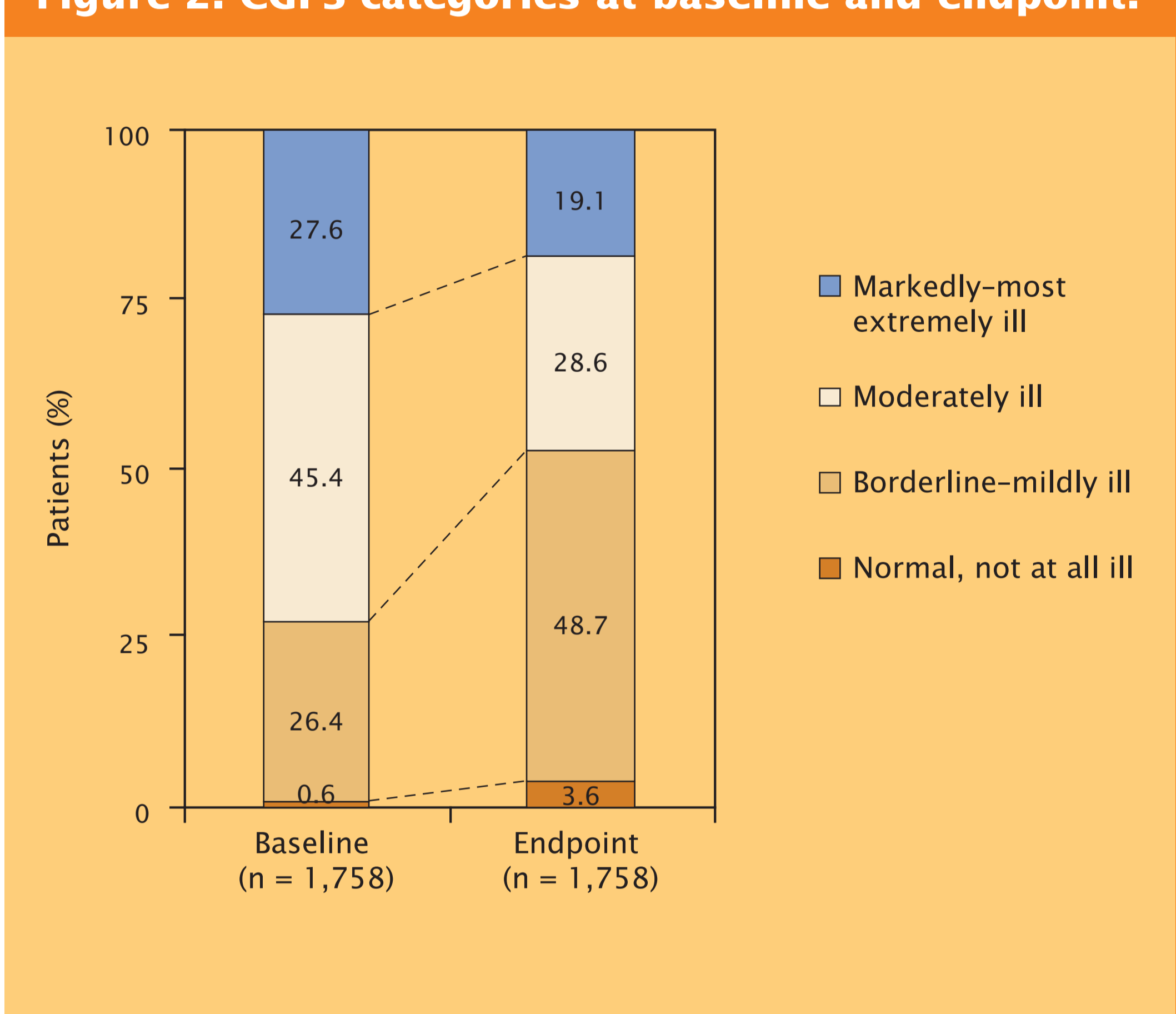
Decreasing ESRS scores reflect improvement in extrapyramidal symptoms. *** $P < 0.0001$ vs baseline.

Figure 1. Primary efficacy outcome for patients transitioned due to lack of efficacy.



Primary efficacy measure was the improvement in PANSS total score ≥ 20% from baseline to endpoint in those patients who had been transitioned due to the main reason of lack of efficacy with their previous oral antipsychotic (n = 998). Bars indicate 95% CI.

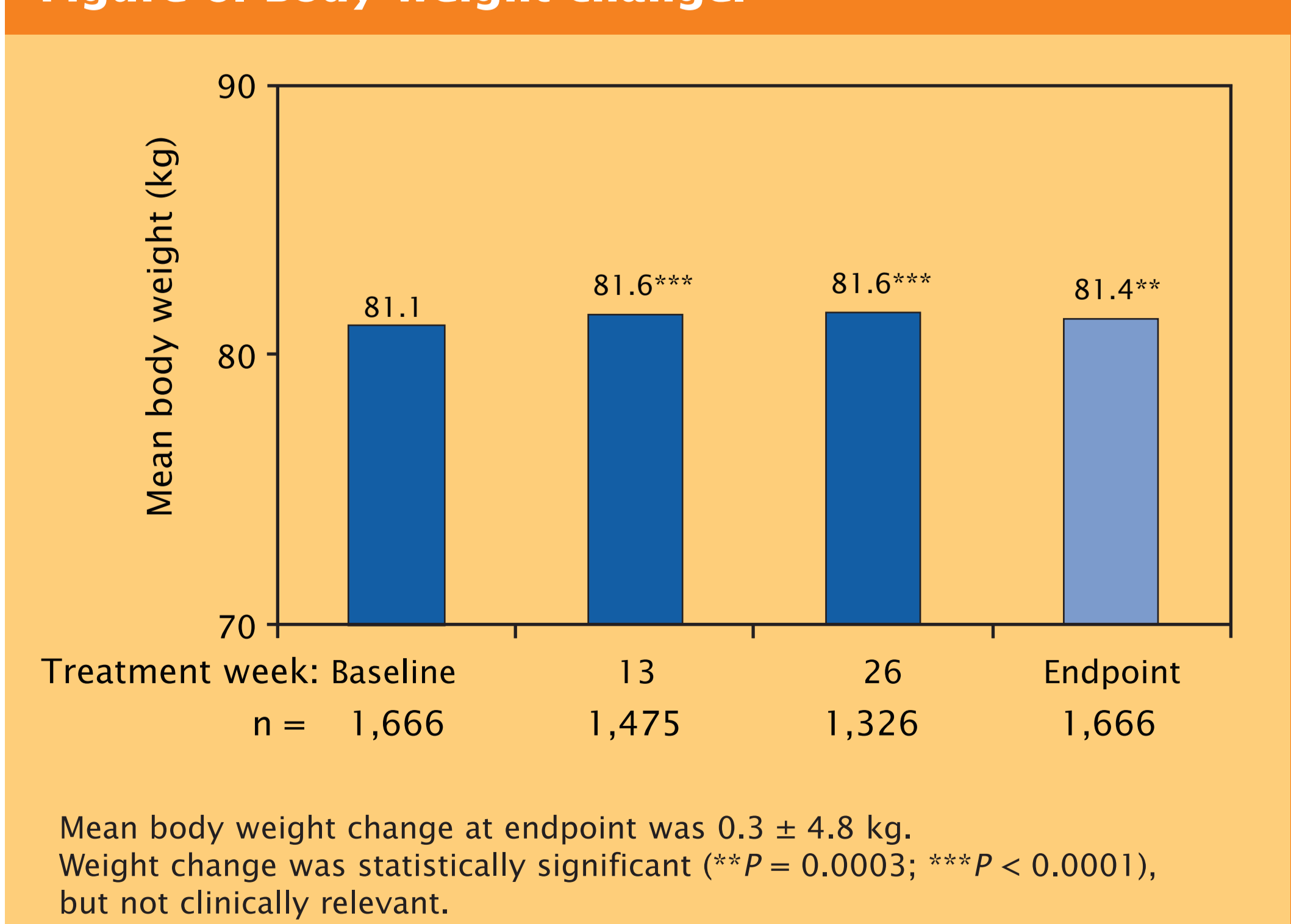
Figure 2. CGI-S categories at baseline and endpoint.



SUMMARY and CONCLUSION

- Among patients transitioned to paliperidone ER for the main reason of lack of efficacy with their previous oral antipsychotic, 61% had an improvement in PANSS total scores of ≥ 20% from baseline to endpoint.
- Among patients switching to paliperidone ER for main reasons other than lack of efficacy, PANSS total score at endpoint was not inferior to PANSS total score at baseline. Even more, PANSS total score from baseline to endpoint improved significantly ($P < 0.0001$).
- Clinically relevant and statistically significant improvements were observed for PANSS total, PANSS subscale, and Marder factor scores ($P < 0.0001$).
- The percentage of patients in CGI-S categories mildly ill or less increased from 27% at baseline to 52% at endpoint.
- The percentage of patients with PSP-defined mild functional impairment increased from 16% to 35% from baseline to endpoint.
- AEs occurring in ≥ 5% of patients were insomnia (9.2%) and anxiety (7.1%).
- ESRS scores decreased (i.e., improved) statistically significantly from 3.5 ± 5.8 to 2.1 ± 4.6 ($P < 0.0001$).
- Mean body weight change from baseline to endpoint was 0.3 ± 4.8 kg.
- Flexibly dosed paliperidone ER treatment over 6 months was safe, well tolerated, and associated with meaningful clinical response in patients previously unsuccessfully treated with oral antipsychotics, supporting recent randomized controlled studies.^{2,3}

Figure 6. Body weight change.



Mean body weight change at endpoint was 0.3 ± 4.8 kg. Weight change was statistically significant (** $P = 0.0003$; *** $P < 0.0001$), but not clinically relevant.

REFERENCES

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- Meltzer HY, et al. *J Clin Psychiatry.* 2008;69:817-29.
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