

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

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INTRODUCTION

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

OBJECTIVE

To explore the tolerability, safety, and treatment responses of flexible doses of paliperidone ER in adult patients with non-acute schizophrenia, who had previously been unsuccessfully treated with oral quetiapine.

Table 1. Baseline characteristics (N = 173)

Characteristic	n (%)
Sex, n (%)	
Male	102 (59.0)
Female	71 (41.0)
Age, years, mean ± SD	39.0 ± 12.8
Duration since diagnosis of schizophrenia, years, mean ± SD	8.4 ± 8.3
Diagnosis of paranoid schizophrenia, n (%)	132 (76.3)
Last used total daily dose of previous treatment with quetiapine, mg/day	
Mean ± SD	485.3 ± 279.0
Median	500
Main reason for switching from quetiapine, n (%)	
Lack of efficacy	123 (71.1)
Lack of tolerability	3 (1.9)
Lack of compliance	9 (5.2)
Other	8 (4.6)

SD, standard deviation.

Table 2. Patient disposition (N = 173)

Patient disposition	n (%)
Completed 6 months of treatment	110 (63.6)
Reasons for early discontinuation of quetiapine	
Withdrew consent	14 (8.1)
Adverse event	14 (8.1)
Adverse event plus lack of efficacy	12 (6.9)
Lack of efficacy	9 (5.2)
Lost to follow-up	8 (4.6)
Other	4 (2.3)
Study medication non-compliance	2 (1.2)

METHODS

Patients

Inclusion criteria for analyses

- Adult in- or out-patients aged ≥ 18 years, with a DSM-IV diagnosis of schizophrenia.
- Definition of non-acute schizophrenia: patient treated with oral quetiapine 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 oral quetiapine 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 or self-harm; substance dependence over the past 6 months; or known hypersensitivity to paliperidone ER or quetiapine.

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

- The primary efficacy outcome was based on the main reason for transitioning to paliperidone ER.
 - Patients switching for the main reason of lack of efficacy: response defined as ≥ 20% improvement in Positive and Negative Syndrome Scale (PANSS) total score from baseline to endpoint
 - Patients switching for main reason other than lack of efficacy: change in PANSS total score from baseline to endpoint
- 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: (1) very poor; (2) poor; (3) moderate; (4) good; or (5) very good.

Safety and tolerability

- Treatment-emergent adverse events (TEAEs).
- Extrapyramidal Symptom Rating Scale (ESRS) total scores and body weight.

Data analysis

- For responses, 95% confidence intervals (CIs) were estimated. Non-inferiority, i.e. absence of clinical worsening of PANSS score after baseline defined as a difference of ≤ 5 points in change versus baseline on the PANSS total score, was 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 patients who received paliperidone ER at least once were included in the analysis (intent-to-treat [ITT] analysis set). Post-baseline efficacy and safety data were available for 163 patients (ITT analysis set for efficacy) and 173 patients (ITT analysis set for safety), respectively.

RESULTS

Table 3. Paliperidone ER treatment (N = 173)

Paliperidone ER dosing	n (%)
Initial dose, mg/day, mean ± SD	5.4 ± 2.0
Mode dose, mg/day	
Mean mode dose ± SD	6.8 ± 3.0
Median mode dose	6.0
Duration of exposure, days, mean ± SD	137.6 ± 65.7
Patients with a change in dosing, n (%)	
Increase	99 (57.2)
Decrease	54 (31.2)

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

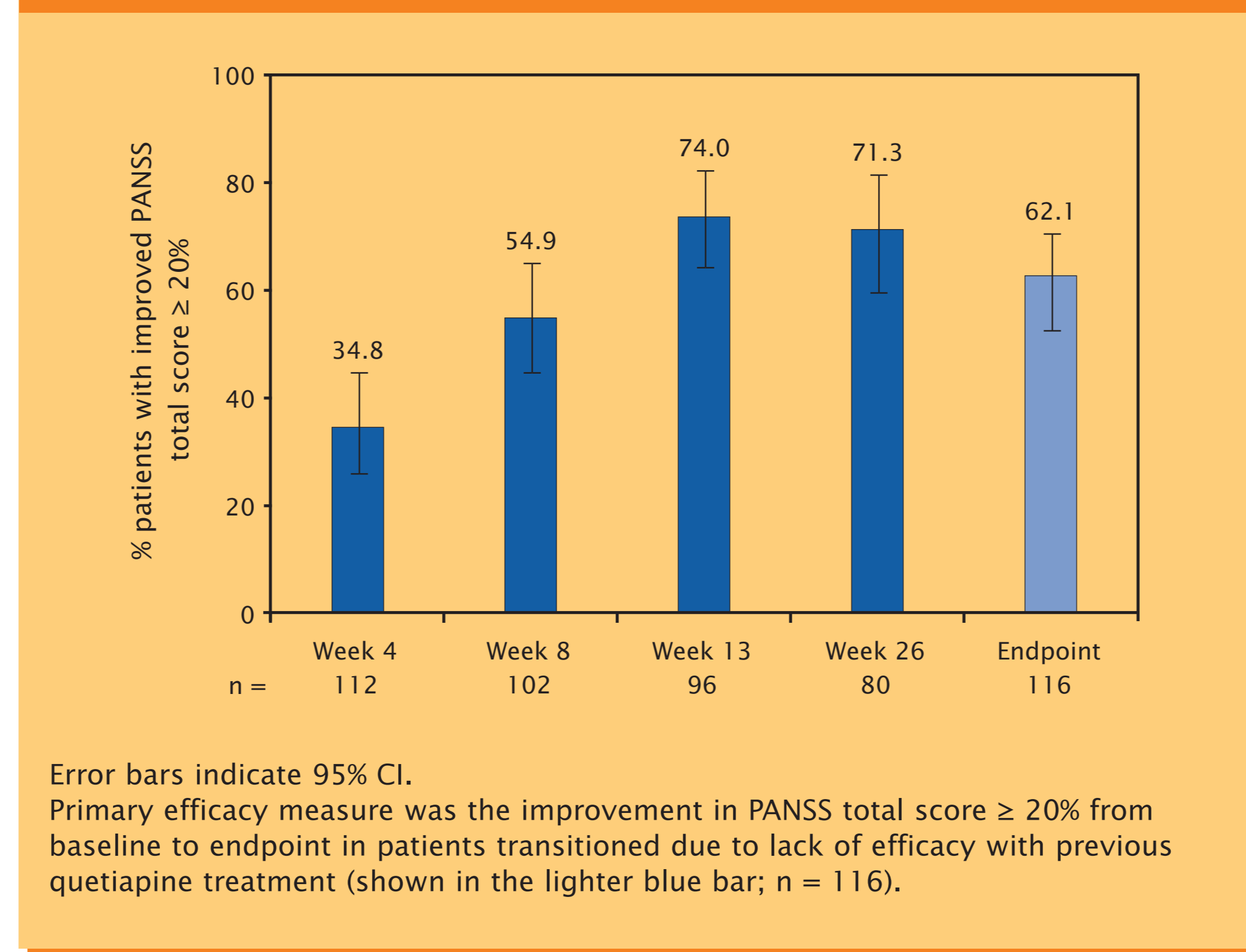


Table 4. Primary efficacy outcome in patients switching for reasons other than lack of efficacy was change in PANSS total score from baseline to endpoint

Main reason for switching to paliperidone ER	Baseline mean PANSS total score ± SD	Mean change in PANSS total score ± SD
Lack of tolerability (n = 29)	65.4 ± 18.1	-6.2 ± 19.7*
Lack of compliance (n = 9)	80.9 ± 21.1	-29.1 ± 22.4*
Other (n = 8)	71.0 ± 8.5	-10.6 ± 10.9*

*Schuirmann 1-sided test confirmed that equivalence to within the specified equivalence bounds could be claimed ($P < 0.0025$).

Figure 2. Mean changes in outcome measures

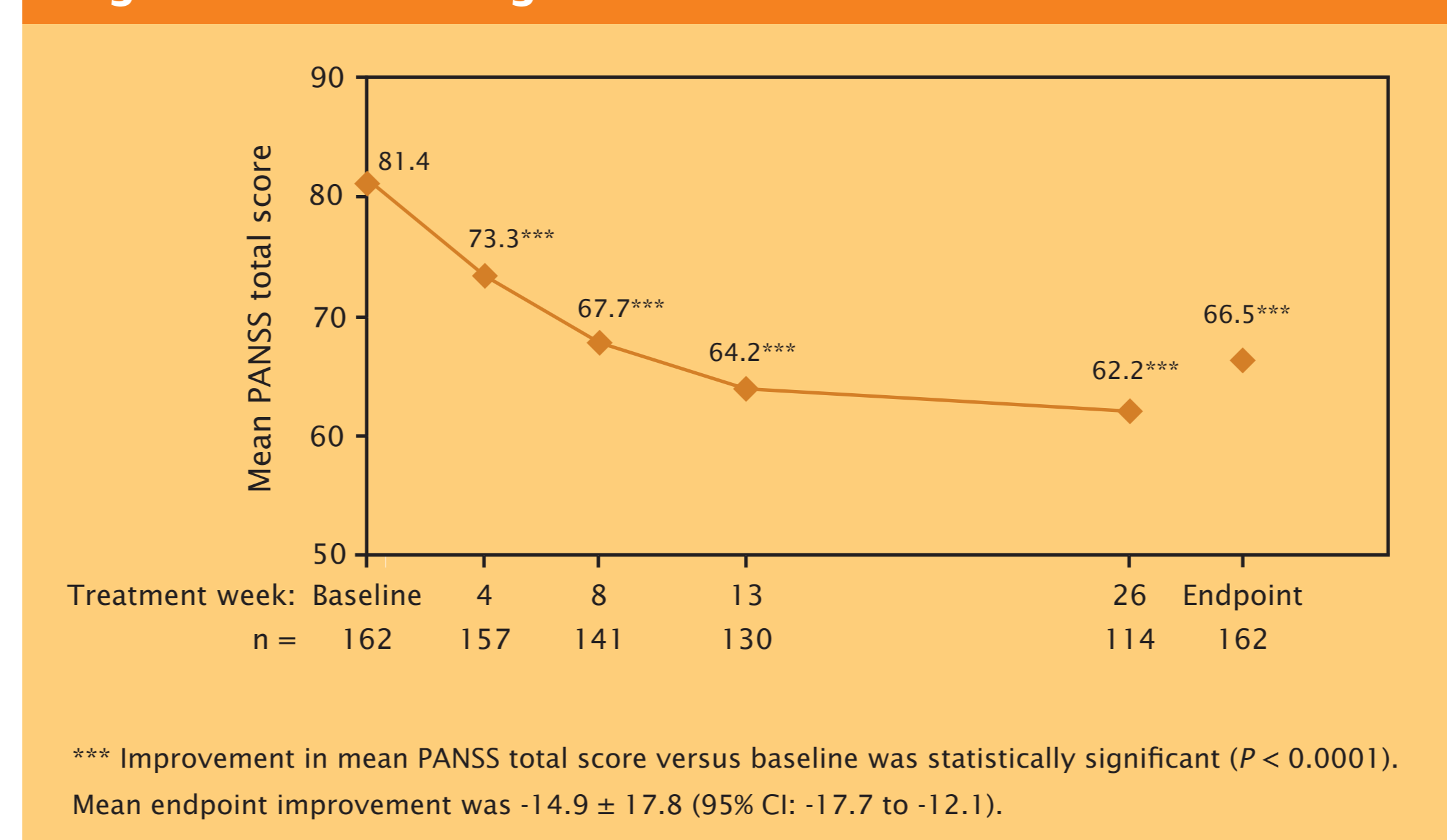


Table 5. Mean PANSS scores at baseline and endpoint (N = 162)

Paliperidone ER dosing	Baseline	Endpoint	P value
PANSS score ± SD			
Total	81.4 ± 20.7	66.5 ± 21.7	< 0.0001
Subscale			
Positive	18.2 ± 6.1	14.2 ± 5.9	< 0.0001
Negative	21.8 ± 7.2	18.1 ± 7.0	< 0.0001
General psychopathology	41.4 ± 11.6	34.2 ± 11.4	< 0.0001
Marder factors			
Positive	22.6 ± 6.9	18.1 ± 7.2	< 0.0001
Negative	21.0 ± 7.1	17.1 ± 6.6	< 0.0001
Disorganized thoughts	18.5 ± 6.2	15.5 ± 5.8	< 0.0001
Uncontrolled hostility/excitement	8.2 ± 3.5	6.8 ± 3.0	< 0.0001
Anxiety/depression	11.1 ± 4.1	8.9 ± 3.8	< 0.0001

Figure 3. CGI-S categories at baseline and endpoint

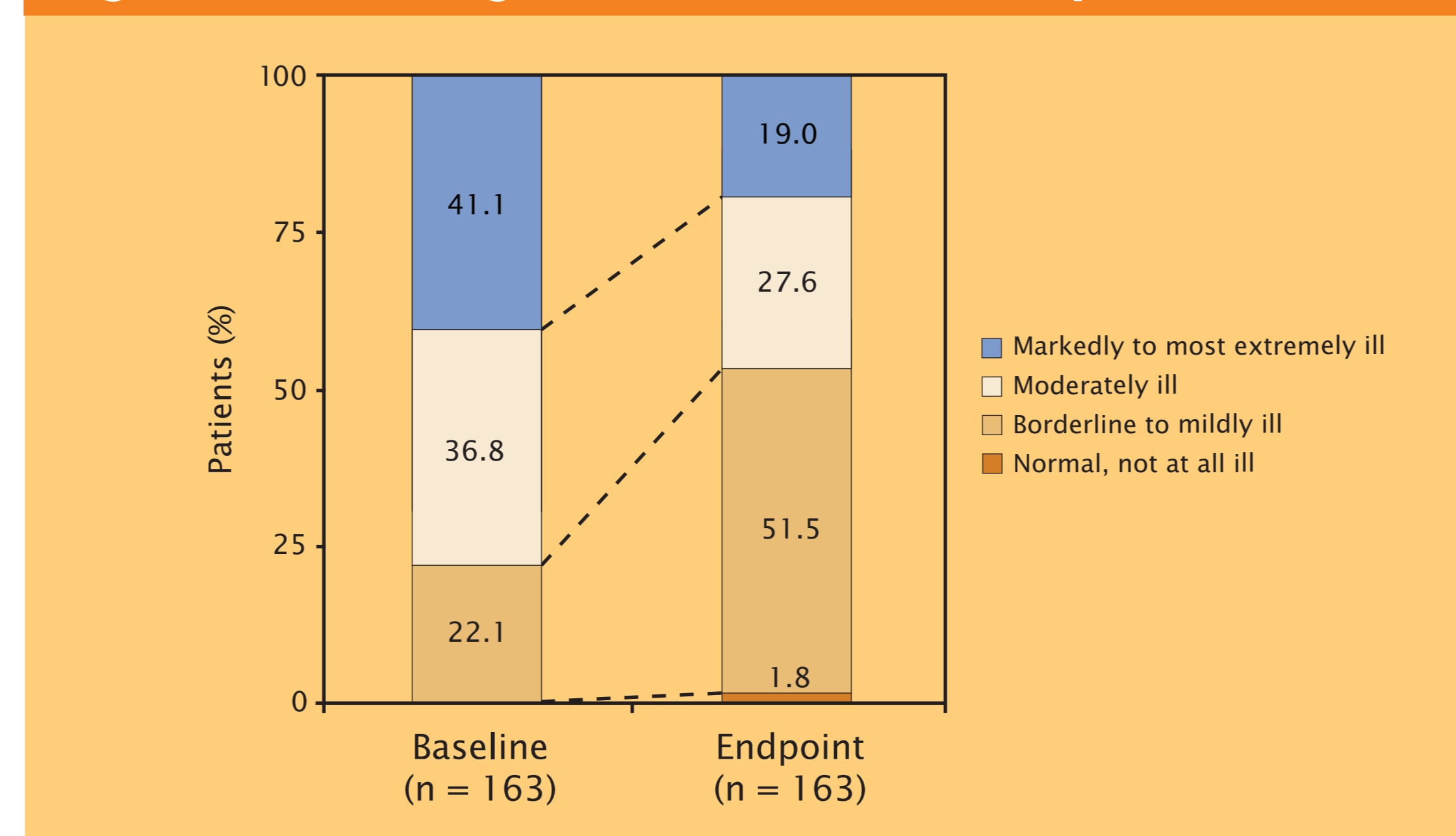


Figure 4. PSP categories at baseline and endpoint

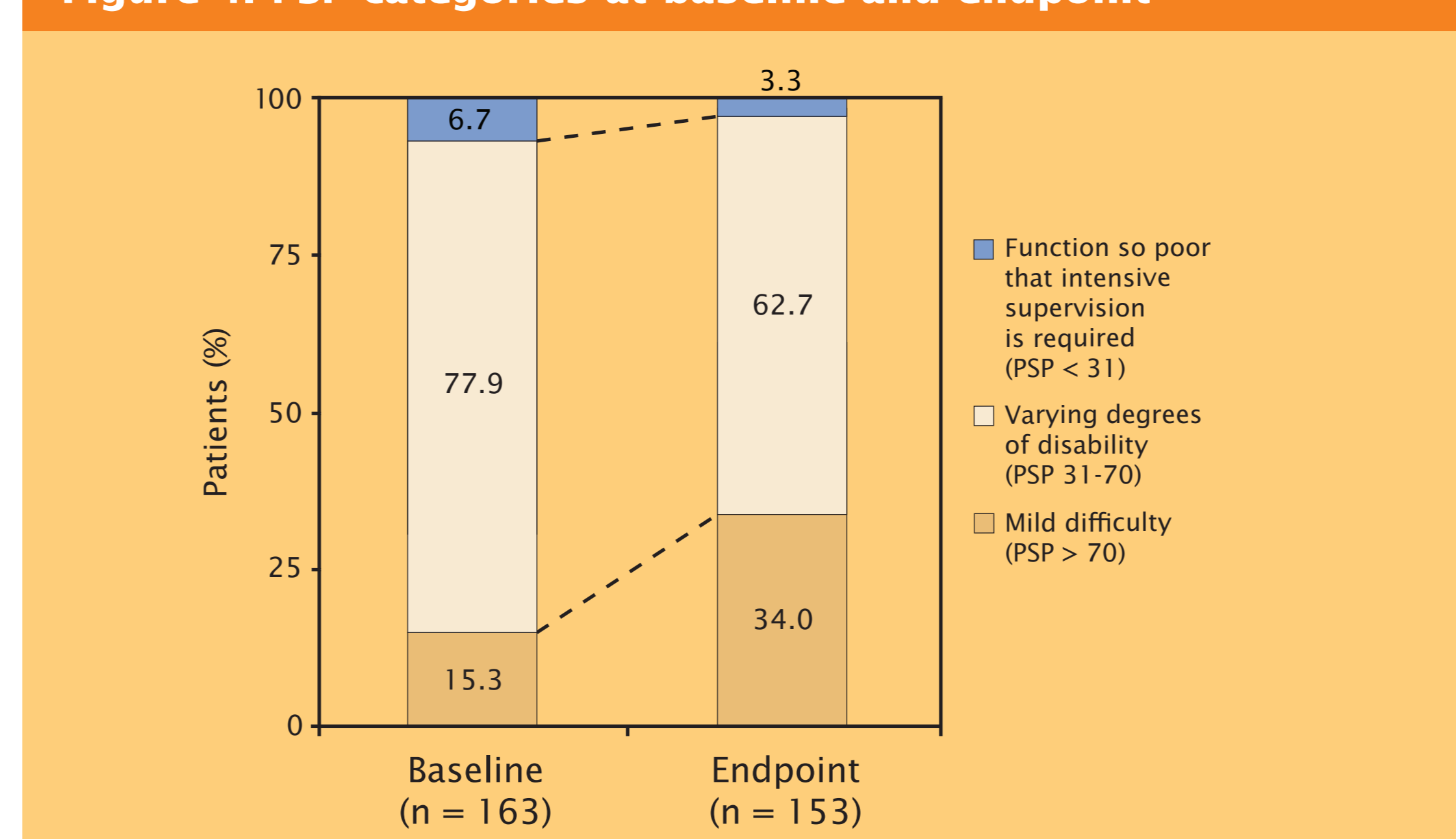


Figure 5. Patient satisfaction with oral quetiapine at baseline and with paliperidone ER at endpoint

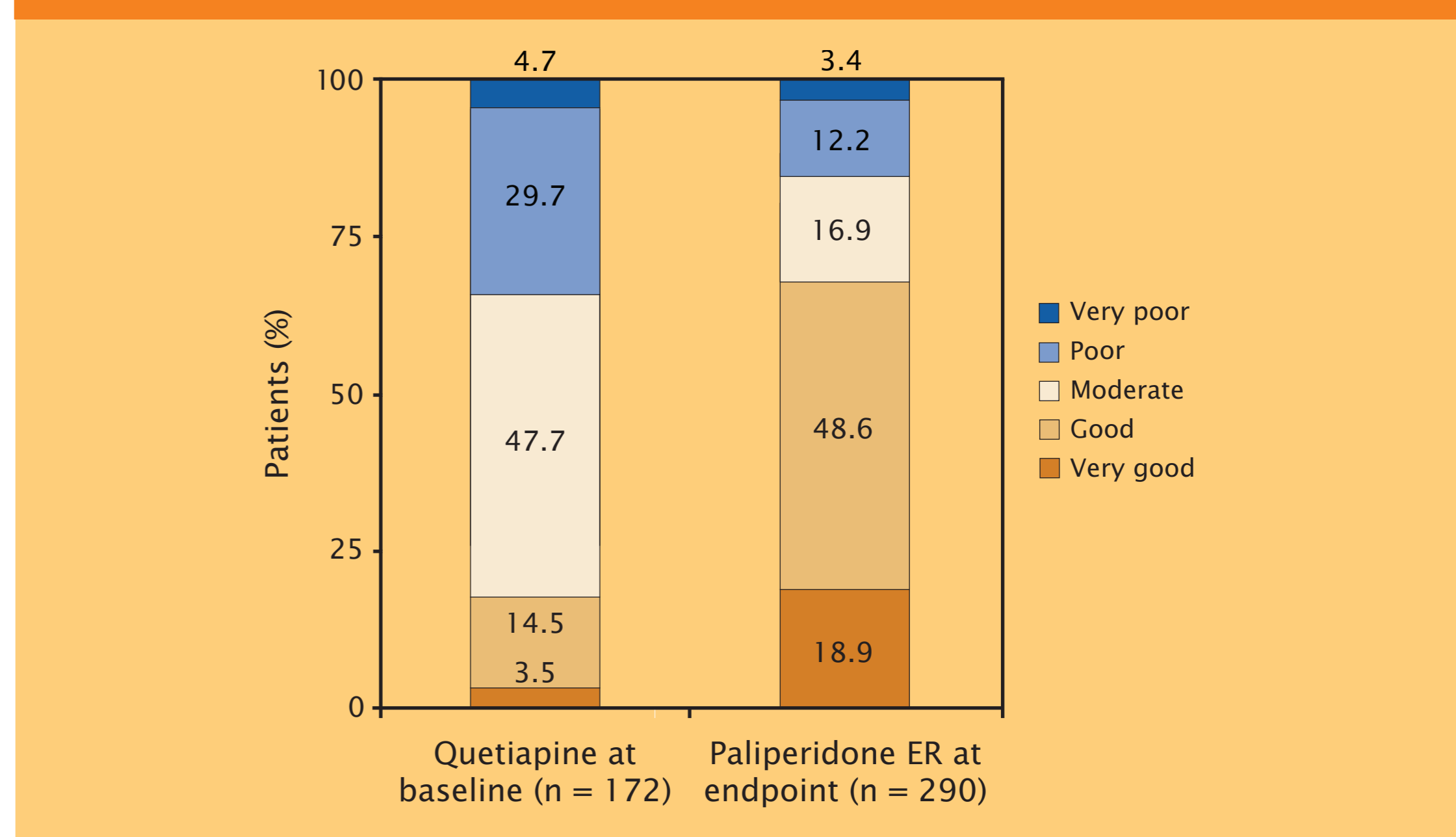


Table 6. TEAEs (N = 173)

TEAE	n (%)
Any TEAE*	111 (64.2)
TEAE causally related to paliperidone ER	80 (46.2)
Serious TEAEs†	16 (9.2)
TEAEs occurring in ≥ 5% of patients	
Insomnia	19 (11.0)
Anxiety	17 (9.8)
Extrapyramidal disorder	13 (7.5)
Nausea	12 (6.9)
Headache	11 (6.4)
Depression	10 (5.8)
Sleep disorder	10 (5.8)
Somnolence	10 (5.8)
Akathisia	9 (5.2)
Action taken due to TEAE‡	
None	239 (70.3)
Dose adjustment	56 (16.5)
Temporary stop	3 (0.9)
Permanent discontinuation	42 (12.4)

*Most TEAEs (92.3%) were mild to moderate in intensity.

†Most commonly schizophrenia (2.3%) and anxiety (1.2%).

‡Based on total number of TEAEs (n = 340) rather than number of patients.

SUMMARY AND CONCLUSION

- Among non-acute patients transitioned from previous oral quetiapine treatment to paliperidone ER for the main reason of lack of efficacy, 62% of patients had an improvement in PANSS total scores of ≥ 20% from baseline to endpoint.
- Among patients switching to paliperidone ER from oral quetiapine for main reasons other than lack of efficacy, PANSS total score at endpoint was not inferior to total PANSS score at baseline.
- Numerical improvement was greatest among patients switching for the main reason of lack of compliance. However, baseline PANSS total was also most impaired in this group and previous data has shown improvement after switching antipsychotic therapy may be greater among patients with greater baseline impairment.⁴
- Furthermore, PANSS total score from baseline to endpoint, showing improvement, was statistically significant ($P < 0.05$).
- Clinically relevant and statistically significant improvements were observed in PANSS total, subscale, and Marder factor scores ($P < 0.0001$), with significant improvements in PANSS total scores noted at the first post-baseline assessment (4 weeks after initiating paliperidone ER).
- The percentage of patients with mild functional impairment increased from 15% at baseline to 34% at endpoint.
- Flexibly dosed paliperidone ER over 6 months was safe, well tolerated, and associated with meaningful treatment response in patients previously unsuccessfully treated with oral quetiapine.

Figure 6. Mean ESRS total scores

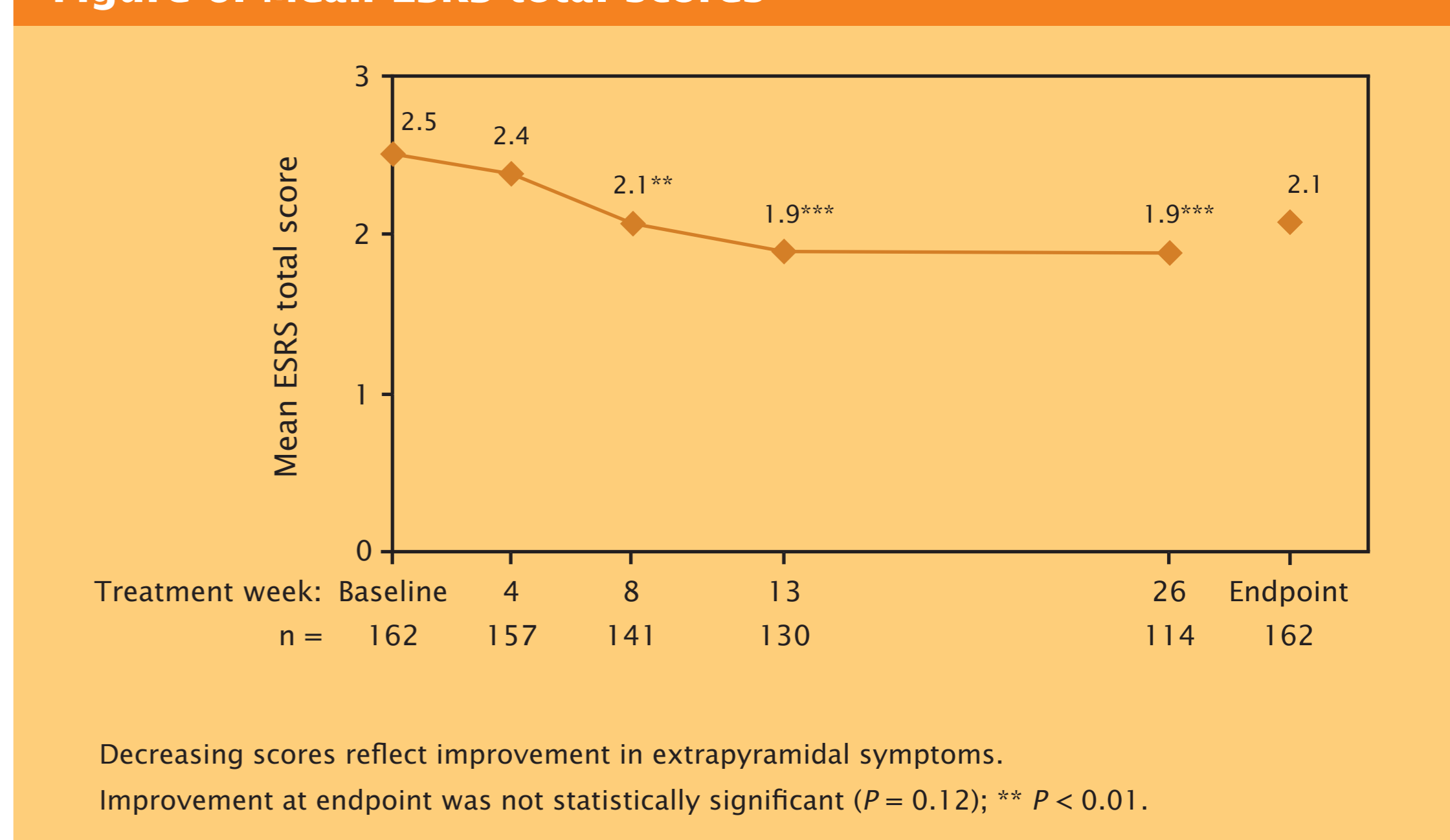
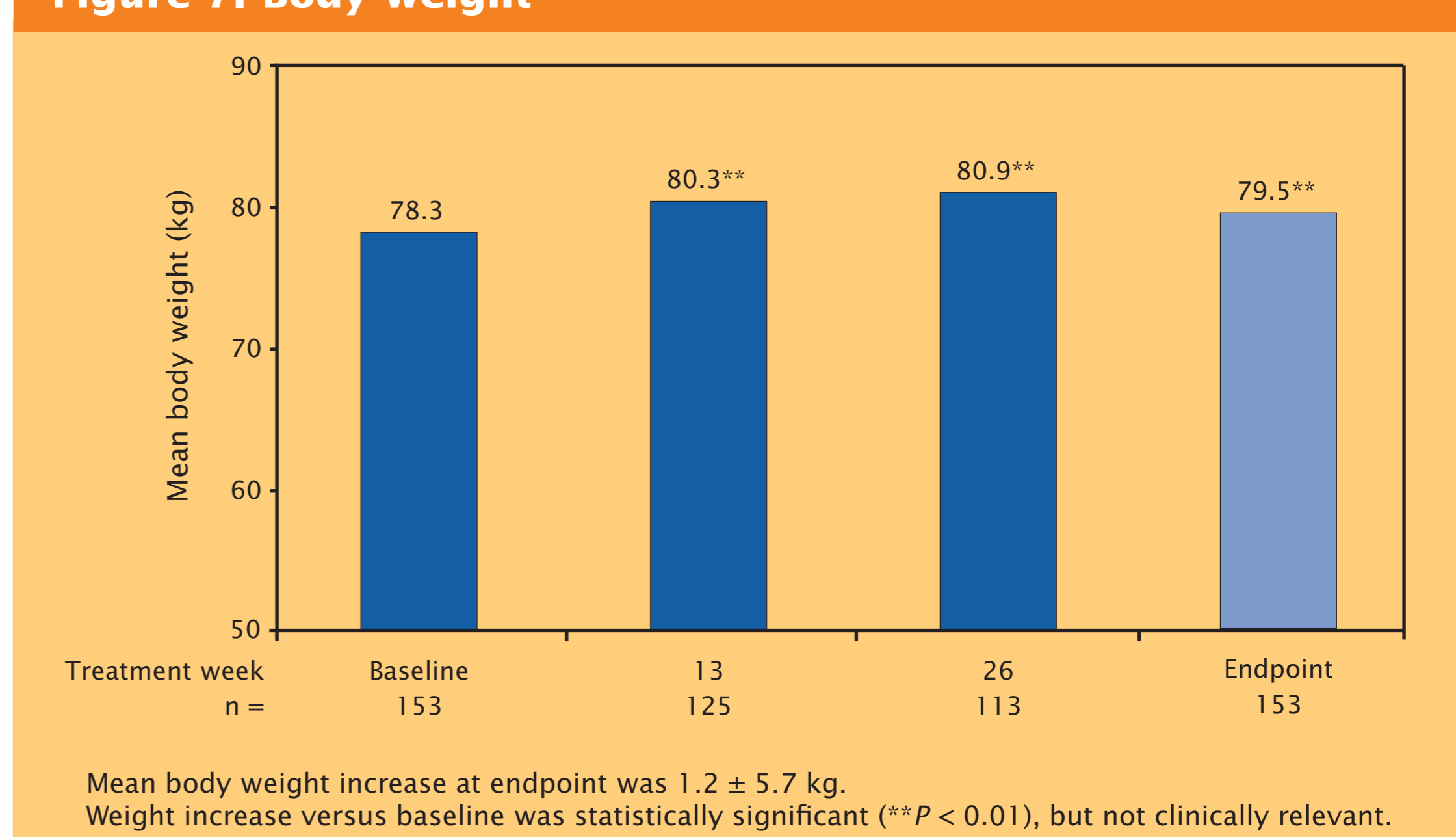


Figure 7. Body weight



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