

Predictors for Treatment Response in Patients With Acute Schizophrenia

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BACKGROUND

- Paliperidone ER is formulated for once-daily, extended-release treatment using an innovative osmotic-release technology that allows patients to achieve therapeutically effective dosing starting from the initial dose.¹
- The formulation predicts early-onset efficacy with low peak-to-trough fluctuations over 24 hours, allowing for once-daily treatment.^{2,3}
- Paliperidone ER is approved for the treatment of schizophrenia, with efficacy and safety demonstrated in randomized controlled clinical trials⁴
- Demographic and baseline characteristics have been shown to predict treatment response in patients with schizophrenia or related disorders treated with oral risperidone or haloperidol.^{5,6}
- Antipsychotic polypharmacy predicts in-patient treatment with high doses of antipsychotics.⁷

OBJECTIVE

- To explore predictors of treatment response and dosing in patients with schizophrenia suffering from an acute episode and treated with paliperidone ER.

METHODS

Study design

- Multicentre, phase IIIb, open-label, single-arm, 6-week study using flexible doses of paliperidone ER (3–12 mg once daily) in patients with an acute exacerbation of schizophrenia.
- The current poster presents a stepwise logistic regression analysis seeking to identify predictors of treatment outcome and dosing

Patients

- Adults aged ≥ 18 years.
- DSM-IV diagnosis of schizophrenia admitted for acute exacerbation (baseline Positive and Negative Syndrome Scale [PANSS] total score of ≥ 70).
- All patients were hospitalized for at least the first 7 days of treatment
- Exclusion criteria included: first antipsychotic treatment ever; treated with clozapine or long-acting injectable antipsychotic during the preceding 3 months; significant medical illness; high risk for 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 once daily.
- Generally, 6 mg once daily was the recommended dose
- Switched to effective dose without titration
 - Dose selected based on the treating clinician's preference, due to expected high variability of patient baseline clinical characteristics
- A total of 6 weeks of treatment.

Outcome measures

- The primary efficacy outcome was treatment response.
 - Response defined as $\geq 30\%$ decrease in PANSS total score from baseline to end-point
 - High response defined as a reduction in PANSS total score from baseline to end-point of $\geq 50\%$
- The secondary efficacy measures were:
 - PANSS total scores obtained at baseline and treatment days 2, 3, 4, 5, 7, 14, 28, and 42
 - Clinical Global Impression-Severity (CGI-S) categories were recorded at baseline and treatment days 7, 14, 28, and 42, with comparison between baseline and treatment day 42 or end-point (last observation carried forward)
 - Personal and Social Performance (PSP) scale obtained at baseline for predictive analyses
- Predictive models were evaluated for the following conditions:
 - Dose increase to above 6 mg/day paliperidone ER
 - Evaluated in patients for whom initial paliperidone ER dose was 6 mg
 - Mode dose 9 mg/day
 - Evaluated in patients who had a daily mode dose of 6 or 9 mg/day
 - High response status
 - Defined by a $\geq 50\%$ reduction in PANSS total score at end-point, evaluated in all patients
 - Concomitant treatment with any benzodiazepines
 - Evaluated in all patients
- Safety and tolerability measures were:
 - Treatment-emergent adverse events (TEAEs)
 - Weight at baseline and end-point
 - Baseline body mass index (BMI) was calculated at baseline using weight and height for predictive analyses

Data analysis

- Intent-to-treat analysis set used for efficacy and safety.
- Patient demographics were assessed with descriptive statistics.
- Efficacy changes versus baseline were evaluated using 2-tailed Wilcoxon signed-rank test.
- For the analysis of explanatory variables, a stepwise logistic regression was used, taking into account participating countries, age, sex, BMI, diagnosis and duration of schizophrenia, prior hospitalizations, psychotic symptoms (PANSS), disease severity (CGI-S), and patient functioning (PSP) recorded at baseline.
- In country analyses, Romania was used as the anchor because it was the last country listed alphabetically

RESULTS

Patients

- 294 patients participated in this study (Table 1).
- The study was completed by 234 patients (79.6%).
 - Reasons for discontinuation:
 - Patient choice, n = 26 (8.8%)
 - Lack of efficacy, n = 18 (6.1%)
 - Adverse events, n = 9 (3.1%)
 - Lost to follow-up, n = 4 (1.4%)
 - Other, n = 3 (1.0%)
- Paliperidone ER dosing is shown in Table 2.
- Mean compliance, as measured by pill counts, was $99.7 \pm 3.4\%$ at treatment day 14; $99.6 \pm 2.6\%$ at day 28; $99.0 \pm 7.2\%$ at day 42; and $99.1 \pm 6.5\%$ at end-point.

Table 1. Baseline demographics and disease characteristics (N = 294).

Characteristic	
Mean age, years \pm SD	40.3 \pm 12.4
Sex, n (%)	
Male	156 (53.1)
Female	138 (46.9)
Type of schizophrenia, n (%)	
Paranoid	260 (88.4)
Disorganized	7 (2.4)
Undifferentiated	15 (5.1)
Residual	12 (4.1)
Schizophrenia course, n (%)	
Episodic with inter-episode residual symptoms	177 (60.2)
Episodic without inter-episode residual symptoms	49 (16.7)
Continuous	47 (16.0)
Single episode in partial remission	5 (1.7)
Other or unknown	16 (5.4)
Mean duration since first diagnosis, years \pm SD	10.9 \pm 9.3
Previous hospitalizations	
Median number of previous hospitalizations	5
Mean number during the preceding 12 months \pm SD	0.8 \pm 1.3
Mean baseline PANSS total score \pm SD	100.2 \pm 17.2

Figure 1. Percentage of patients with an improvement of PANSS total score of at least 30% versus baseline.

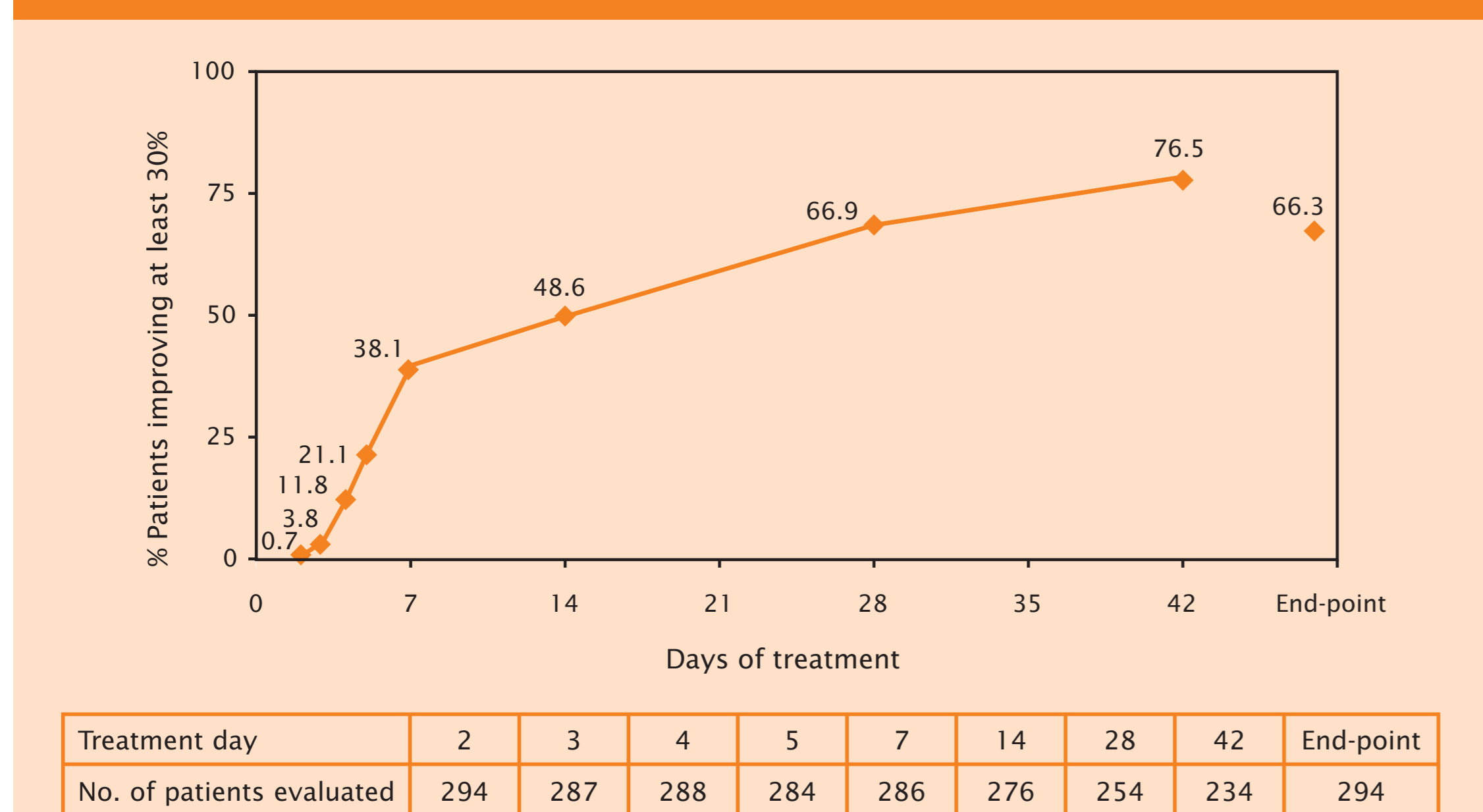


Table 2. Paliperidone ER dosing and exposure.

Characteristic	
Mean duration of exposure, days \pm SD	37.3 \pm 11.0
Mean initiation dose, mg \pm SD	5.8 \pm 1.7
Average dose, mg \pm SD	
Mean dose	7.5 \pm 2.1
Mode dose	7.7 \pm 2.6
Change in dose, % of patients	
Dose increased	60.9
Dose decreased	10.9

Efficacy

- 2 of every 3 patients showed an improvement of at least 30% in PANSS total score at end-point versus baseline (Figure 1).
- 66.3% of patients showed an improvement in PANSS total score of at least 30% (95% confidence interval [CI] 60.6–71.7).
- A high treatment response ($\geq 50\%$ reduction in PANSS total score) occurred in 34.7% of patients at end-point
- Decreases in PANSS total scores compared to baseline were significant and began on the first post-baseline assessment (day 2) and continued throughout the remaining 6 weeks of treatment ($P < 0.0001$) (Figure 2).
- PANSS total scores decreased by a mean of 27.5 ± 20.1 at end-point (95% CI –29.8 to –25.2; $P < 0.0001$)
- Based on CGI-S categories, 74.1% of patients were markedly to most extremely ill at baseline. At end-point, 20.0% were markedly to most extremely ill (Figure 3).

Figure 2. Changes in mean PANSS total score throughout treatment.

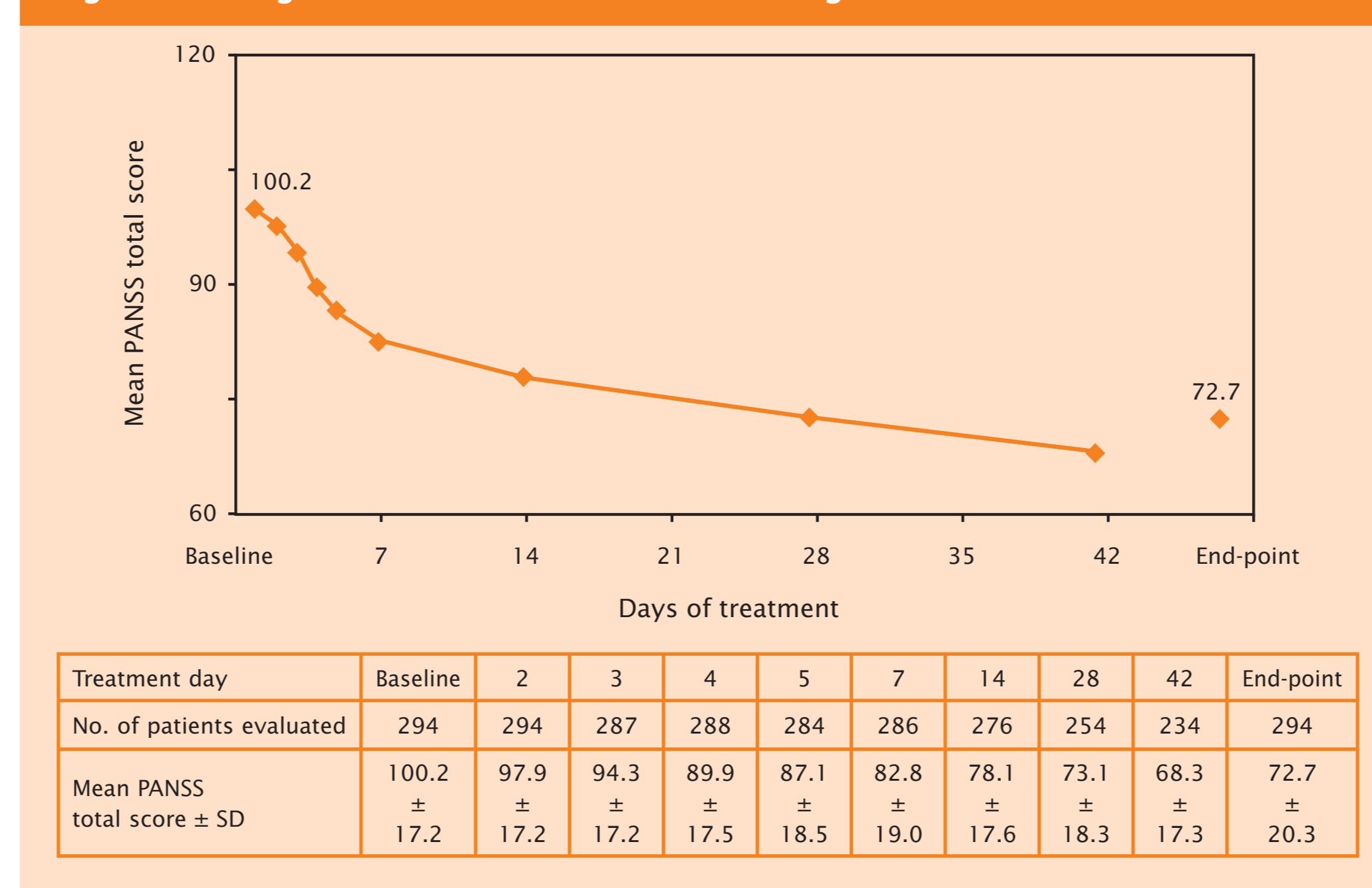
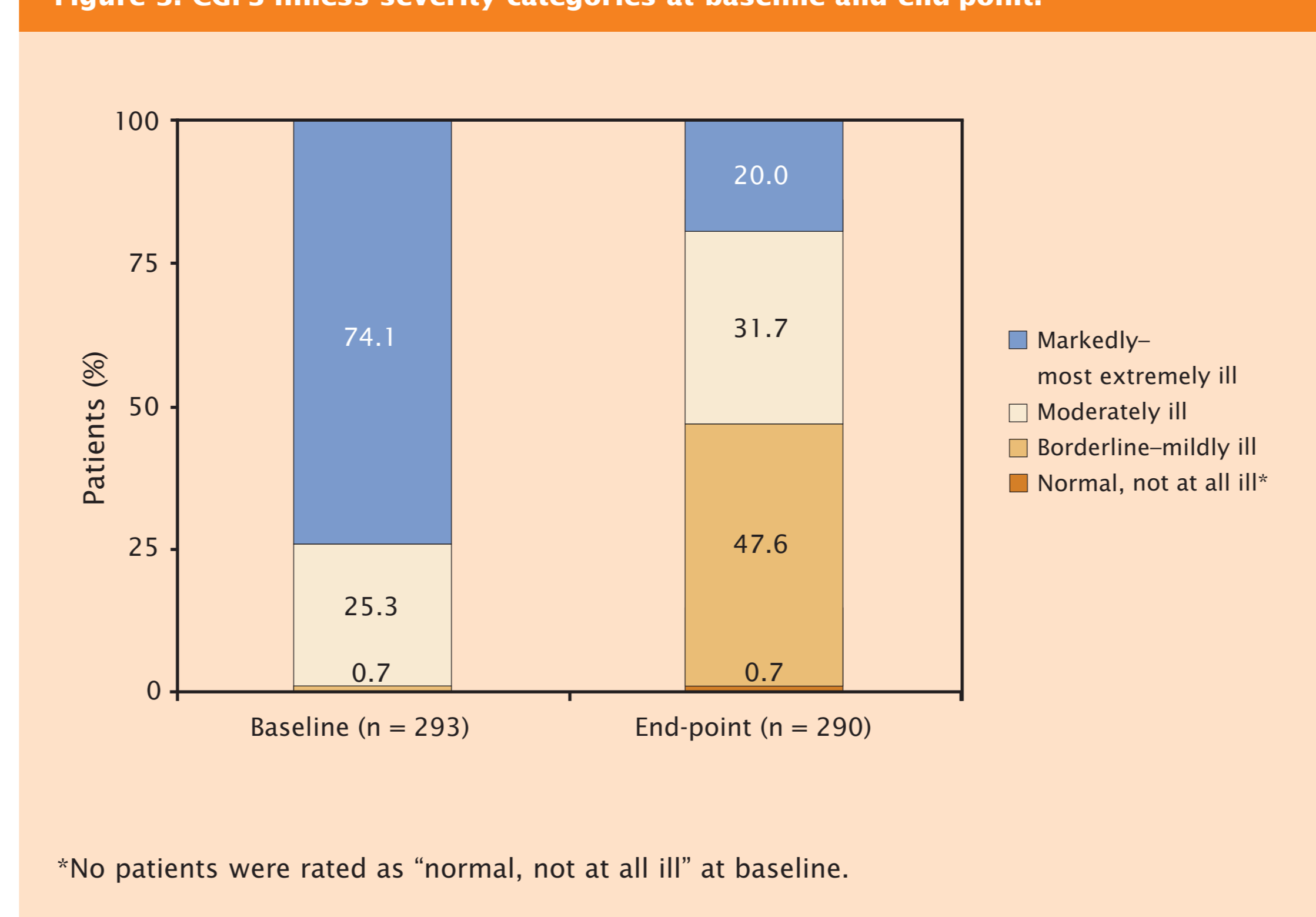


Figure 3. CGI-S illness severity categories at baseline and end-point.



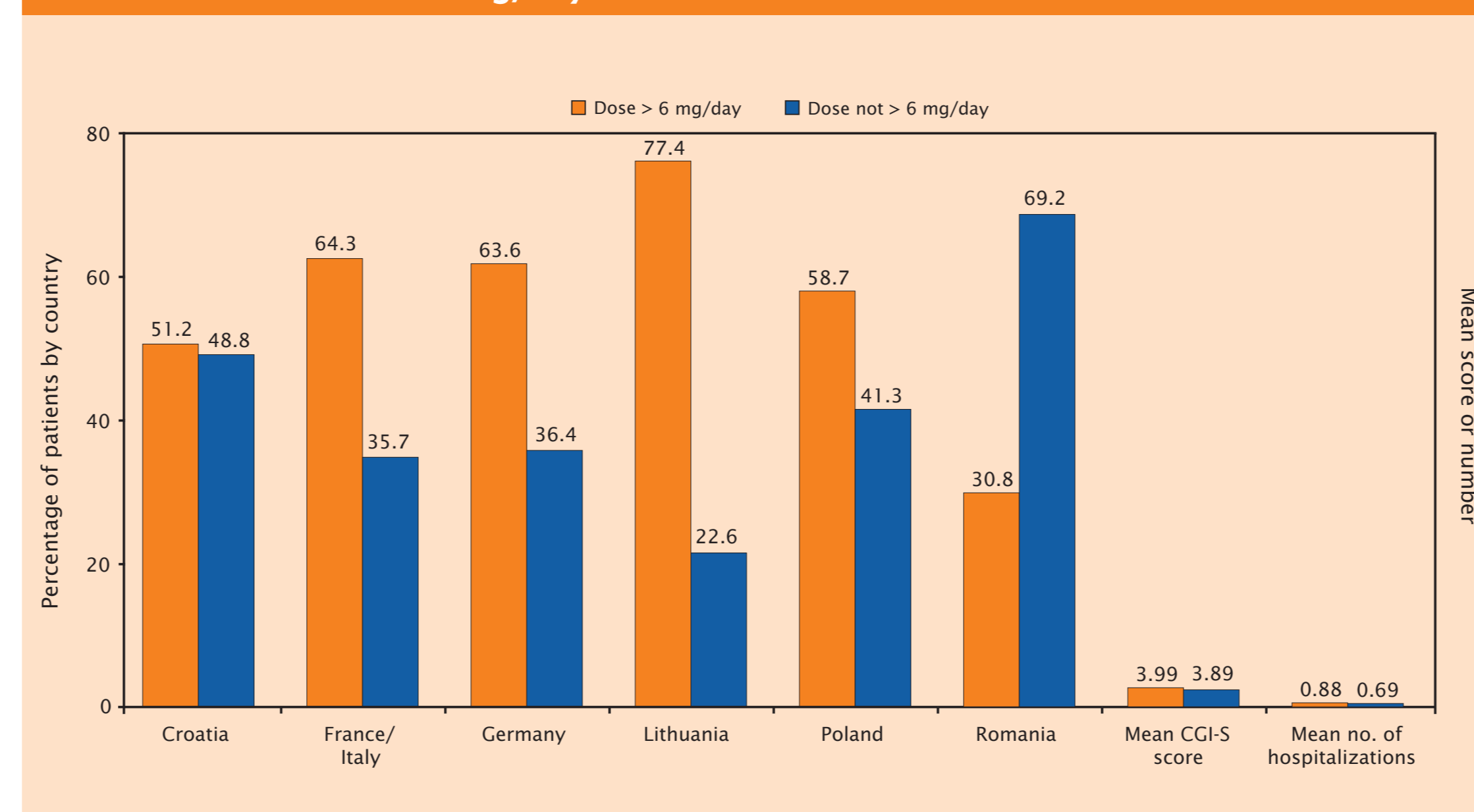
*No patients were rated as "normal, not at all ill" at baseline.

Table 3. Important predictors identified through stepwise logistic regression.

Variable	Odds ratio	95% CI	χ^2	P value
Dose > 6 mg/day paliperidone ER, for patients with an initial dose of 6 mg/day				
Country vs Romania				
Croatia	4.26	1.55–11.73	7.86	< 0.01
France/Italy*	5.98	1.48–24.14	6.31	< 0.05
Germany	7.40	2.18–25.15	10.29	< 0.01
Israel	2.31	0.52–10.22	1.22	0.27
Lithuania	16.45	4.82–56.09	20.02	< 0.001
Poland	8.28	2.67–25.67	13.43	< 0.001
Baseline CGI-S score vs the lowest value of 2	2.08	1.22–3.55	7.26	< 0.01
No. of hospitalizations in the previous 12 months vs no hospitalizations	1.30	0.96–1.76	2.92	0.0874
Mean mode dose of 6 mg/day vs 9 mg/day				
Country vs Romania				
Croatia	1.07	0.41–2.77	0.02	0.89
France	0.74	0.13–4.25	0.11	0.74
Germany	0.78	0.24–2.57	0.16	0.69
Israel	0.93	0.27–3.18	0.01	0.90
Italy	0.96	0.08–11.91	0.00	0.98
Lithuania	3.12	1.12–8.72	4.74	< 0.05
Poland	0.48	0.17–1.34	1.94	0.16
BMI vs the lowest BMI of 17.7 kg/m ²	1.08	1.01–1.14	5.37	< 0.05
No. of hospitalizations in the previous 12 months vs no hospitalizations	1.33	1.01–1.76	4.02	< 0.05
High response status (reduction in PANSS total score of $\geq 50\%$)				
Country vs Romania				
Croatia	0.69	0.29–1.67	0.68	0.41
France	3.24	0.78–13.49	2.61	0.11
Germany	1.23	0.50–2.98	0.20	0.65
Israel	1.00	0.38–2.67	0.00	0.99
Italy	0.59	0.15–2.28	0.59	0.44
Lithuania	1.29	0.55–3.01	0.35	0.56
Poland	0.11	0.04–0.35	14.10	< 0.001
Baseline PANSS total score vs the lowest value of 70	0.98	0.96–1.00	4.66	< 0.05
Any concomitant benzodiazepine treatment				
Baseline CGI-S score vs the lowest value of 2	2.40	1.60–3.60	17.89	< 0.001

*France and Italy were combined because all 5 patients from Italy were treated with a paliperidone ER dose > 6 mg/day.

Figure 4. Predictors of paliperidone ER dose increase above 6 mg/day for patients with an initial dose of 6 mg/day.



Predictive analyses

- Explanatory analyses identified the following variables as significant predictors:
 - For dose increases to above 6 mg/day in patients initiated on 6 mg paliperidone ER daily: country and BMI
 - For mode dose of 9 mg/day: country, BMI, and hospitalizations within the previous 12 months
 - For high response status ($\geq 50\%$ reduction in PANSS total score at end-point): country
 - For any concomitant benzodiazepine use: country, CGI-S category, and PSP scale
- Important predictors after stepwise logistic regression analysis are shown in Table 3.
- Significant predictors of dose increase above 6 mg/day were country and higher baseline CGI-S score. More hospitalizations during the previous 12 months showed a trend towards predicting paliperidone ER dose > 6 mg/day (Figure 4)
- Significant predictors of mode dose of 9 mg/day were country, higher BMI, and more hospitalizations during the previous 12 months (Figure 5)
- A lesser likelihood of high response status was predicted by country (Poland versus Romania) and a higher baseline PANSS total score (Figure 6)
- A higher baseline CGI-S score predicted concomitant treatment with any benzodiazepines
 - Mean baseline CGI-S score was 4.04 ± 0.68 (95% CI 3.95–4.13) for patients treated with any benzodiazepines and 3.65 ± 0.61 (95% CI 3.52–3.78) for patients who were not treated with benzodiazepines

Safety and tolerability

- TEAEs are summarized in Table 4.
- There were no deaths
- Potentially prolactin-related TEAEs occurred in 7 patients (2.4%): hyperprolactinaemia in 2 patients; and blood prolactin increased, breast swelling, galactorrhoea, menstruation disorder, and sexual dysfunction each in 1 patient.
- Glucose-related TEAEs occurred in 2 patients (0.7%): diabetes mellitus and hyperglycaemia.
- Body weight showed a small but statistically significant increase versus baseline at day 42 (0.78 ± 2.94) and end-point (0.63 ± 2.86) ($P < 0.0001$).
- Although statistically significant, these small changes were not considered to be clinically relevant
- Weight increased by $\geq 7\%$ from baseline in 7.2% of patients at end-point

Figure 5. Significant predictors of paliperidone ER mode dose 9 mg/day.

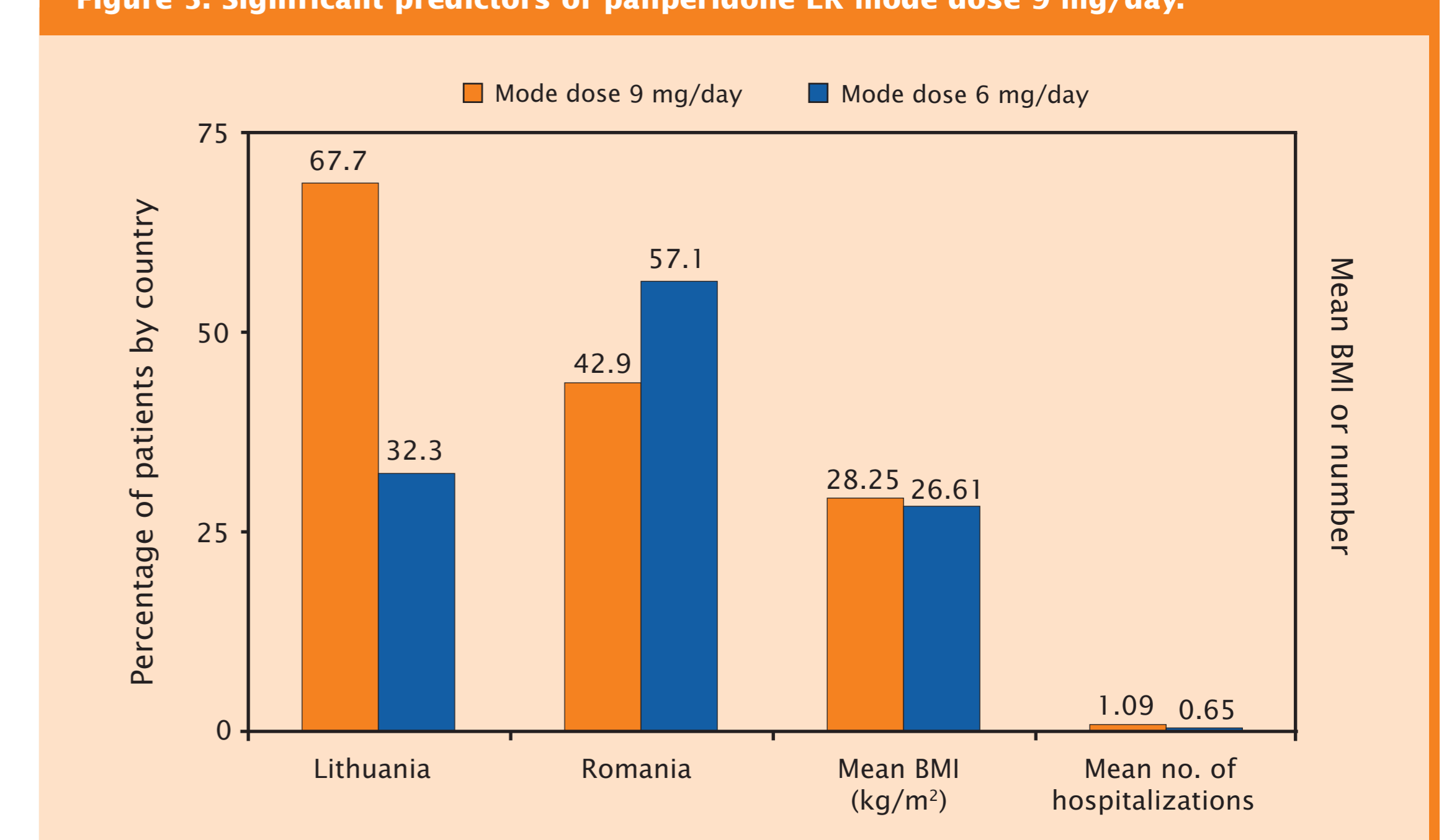


Figure 6. Significant predictors of high response status.

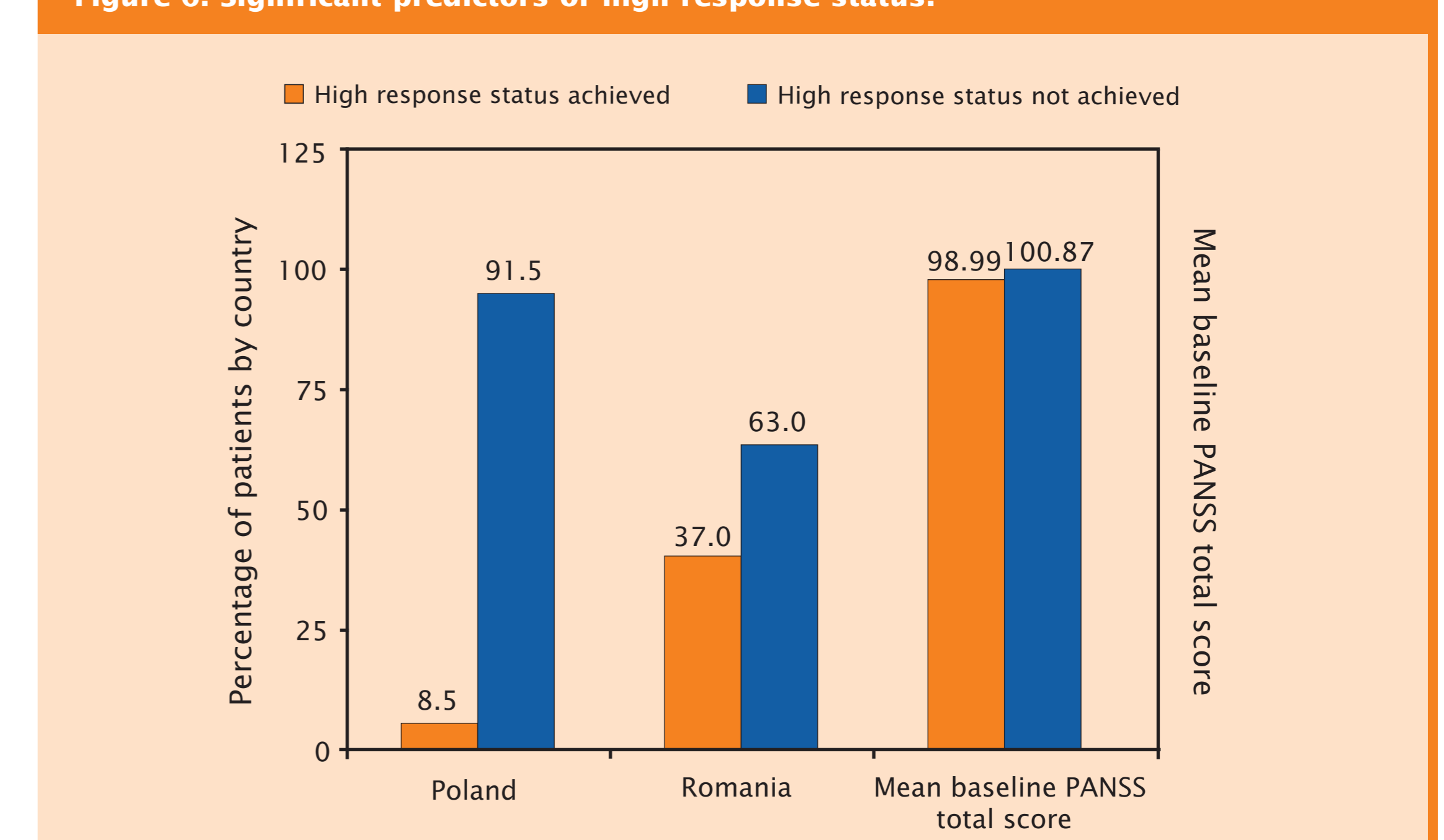


Table 4. Treatment-emergent adverse events.

TEAE, n (%)	
Any TEAE	199 (67.7)
Serious TEAE	23 (7.8)
Common* TEAEs	
Insomnia [†]	69 (23.5)
Tachycardia	26 (8.8)
Headache	22 (7.5)
Extrapyramidal disorder	20 (6.8)
Anxiety	16 (5.4)
TEAE causally related to paliperidone ER	91 (31.0)
Severity [†] of TEAEs	
Mild	334 (63.5)
Moderate	167 (31.8)
Severe	25 (4.8)

*Occurring in $\geq 5\%$ of patients.
[†]Only 15 patients (5.1%) had insomnia that was considered to be causally related to paliperidone ER.
[‡]Based on the number of events.

CONCLUSIONS

- Flexibly dosed paliperidone ER (3–12 mg once daily) was effective for the treatment of acutely exacerbated patients with schizophrenia.
- 66.3% of patients showed an improvement in PANSS total score of at least 30% at end-point versus baseline
- 34.7% of patients achieved high response status ($\geq 50\%$ improvement in PANSS total score at end-point)
- Rapid onset of action: significant improvement in psychotic symptoms began on treatment day 2, i.e. after one single treatment
- For most explanatory analyses, differences between participating countries affected antipsychotic dosing, with less of an effect on treatment response.
- Stepwise regression identified predictors for paliperidone ER dosing, treatment response, and concomitant use of benzodiazepines.
 - Significant predictors of dose increase above 6 mg/day included country and higher baseline CGI-S scores, with a trend for number of previous hospitalizations
 - Significant predictors of mode dose of 9 mg/day were country, higher BMI, and more hospitalizations during the previous 12 months
 - Country was a significant predictor of high response status, with significantly fewer patients achieving high response status in Poland (8.5%). Higher baseline PANSS total score also predicted a lesser likelihood of achieving high response status
 - Higher baseline CGI-S score predicted concomitant treatment with any benzodiazepines
- Paliperidone ER was well tolerated.
 - Most TEAEs were mild to moderate in severity, with few patients discontinuing due to TEAEs
 - Weight change was small and not clinically relevant

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