**Journal of Health, Wellness and Community Research**
**ISSN: 3007, 0570**

OPEN ACCESS

**JHWCR**

**Type:** Narrative Review
**Published:** 07 October 2025
**Volume:** III, **Issue:** XIV
**DOI: https://doi.org/10.61919/70a0mc76**

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**Received** 04, 08, 25
**Accepted** 26, 09, 2025

**Authors' Contributions**
Concept: SA; Design: MNN; Data Collection: MK; Analysis: TH; Drafting: SA



**Declarations**
No funding was received for this study. The authors declare no conflict of interest. The study received ethical approval. All participants provided informed consent.

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# Efficacy of Paliperidone in Patients Who Are Encountering Their First Episode of Schizophrenia

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## ABSTRACT

*Background: Early, effective treatment during the first episode of schizophrenia can reduce symptomatic burden and improve trajectories, yet real-world evidence using the Brief Psychiatric Rating Scale (BPRS) for oral paliperidone extended-release (ER) in routine settings remains limited. Objective: To determine the 12-week symptomatic efficacy of oral paliperidone ER in first-episode schizophrenia. Methods: This prospective, single-arm before–after study enrolled consecutive outpatients aged 18–60 years with first-episode schizophrenia at two public hospitals in Pakistan (1 February–30 December 2024). Participants initiated paliperidone ER 3 mg once daily, titrated to a maximum of 12 mg once daily as clinically indicated. BPRS was assessed at baseline and 12 weeks; the primary outcome was changed in BPRS. The predefined responder endpoint was ≥40% BPRS reduction at 12 weeks. Analyses (SPSS v26) included paired t-tests, Wilson 95% CIs for responder proportion, chi-square tests and effect sizes across age, sex, education, and socioeconomic strata, with exploratory logistic regression. Results: Among 160 participants, mean BPRS decreased from 52.63±6.54 to 33.15±12.46 (mean change −19.48; ≈37% relative; $p<0.001$). The responder rate was 58.1% (93/160; 95% CI 50.4–65.5). Responder proportions did not differ by age, sex, education, or socioeconomic status (all $p>0.05$; effect sizes near null). Conclusion: Oral paliperidone ER produced clinically meaningful 12-week symptom reductions in first-episode schizophrenia with consistent efficacy across demographic subgroups, supporting its use as a dependable first-line option in routine early-intervention care and motivating longer-term, controlled studies with systematic safety and functional outcomes.*

***Keywords***
*Schizophrenia; First-Episode Psychosis; Paliperidone; Extended-Release; BPRS; Real-World Evidence; Pakistan.*

## INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by disturbances in thought, perception, affect, and behavior that lead to substantial functional impairment and excess morbidity and mortality. Early illness course is clinically pivotal: timely, effective treatment during the first episode of psychosis can shorten the duration of untreated psychosis, reduce symptomatic burden, and improve longer-term functional trajectories (1,6,16). Socio-environmental and familial factors—including lower socioeconomic status and family history of psychiatric disorders—have been associated with elevated risk, highlighting the need for accessible, tolerable first-line therapies that can be implemented early in care pathways (14,15).

Second-generation antipsychotics are the cornerstone of acute and maintenance treatment. Paliperidone—the primary active metabolite of risperidone—exerts antagonism at dopamine D2 and serotonin 5-HT2A receptors with relatively lower affinity for histaminergic and adrenergic receptors and negligible muscarinic activity, a profile that underpins antipsychotic efficacy with a generally manageable tolerability spectrum (9). Both oral extended-release paliperidone and long-acting injectable paliperidone palmitate have demonstrated antipsychotic effects across acute and maintenance settings, with evidence of relapse prevention benefits during longer-term follow-up (6,7,16,17).

Evidence specific to first-episode psychosis suggests that patients can experience robust symptomatic improvements with paliperidone while tolerability remains acceptable. An open-label multicenter trial of first-episode psychosis reported clinically meaningful reductions in symptom scales over eight weeks with oral paliperidone extended-release (1). In a head-to-head randomized study enrolling first-episode schizophrenia, paliperidone palmitate yielded antipsychotic efficacy comparable to an established comparator while enabling practical initiation in early care (2). Pooled analyses from placebo-controlled and open-label programs further indicate substantial response rates and maintenance of gains with continued treatment, although estimates vary by scale (PANSS vs BPRS), population, and follow-up duration (18,20).

Despite this body of work, important gaps remain in routine, real-world care of first-episode schizophrenia, particularly in resource-constrained settings where diagnostic delays, socioeconomic barriers, and medication discontinuation can undermine outcomes (14–16). Moreover, much of the paliperidone literature reports outcomes using the PANSS; data using the Brief Psychiatric Rating Scale (BPRS)—a widely used transdiagnostic measure sensitive to change in acute psychosis—are comparatively limited (1,18). Pragmatic, single-arm evaluations that quantify the magnitude

of symptomatic change and responder proportions on the BPRS over the first 12 weeks of treatment can therefore add practical value for clinicians initiating therapy in early illness.

Against this background, the present prospective, single-arm study assessed the efficacy of oral paliperidone extended-release over 12 weeks in first-episode schizophrenia, using the BPRS to quantify change from baseline and a predefined responder threshold. By focusing on an early-episode cohort in two public sector Pakistani medical colleges and reporting standardized response metrics, this study aims to complement randomized and pooled evidence and to inform early-intervention prescribing in comparable clinical contexts (1,2,6,16–18,20).

## MATERIAL AND METHODS

This was a prospective, single-arm before–after study undertaken to estimate the symptomatic efficacy of oral paliperidone extended-release (ER) over 12 weeks in patients presenting with a first episode of schizophrenia. A single-arm design was chosen to provide pragmatic effectiveness data from routine clinical services in early illness, complementing randomized and pooled evidence while enabling standardized dosing and uniform outcome assessment within the constraints of two public-sector centers (1,2,18,20). The study was conducted in the Psychiatry Departments of Loralai Medical College, Loralai, and Jhalawan Medical College, Khuzdar, Pakistan. Screening and enrollment occurred consecutively during usual outpatient hours from 1 February 2024 through 30 December 2024, with each participant followed for 12 weeks from baseline.

Eligible participants were adults aged 18–60 years with a clinician's diagnosis of first-episode schizophrenia according to standard diagnostic practice, with symptom onset within the last 24 months and no prior adequate antipsychotic trial. Patients were required to be antipsychotic-naïve or to have had ≤14 cumulative days of antipsychotic exposure for the index episode. Exclusion criteria were schizoaffective or substance-induced psychotic disorders; current moderate-to-severe substance use disorder; clinically significant neurological or unstable medical illness; known hypersensitivity to risperidone/paliperidone; pregnancy or lactation; and any condition judged to preclude reliable assessment or safe participation. Consecutive patients meeting criteria were approached by a study clinician who explained procedures in the local language; written informed consent was obtained prior to any study-specific activity. For patients with limited literacy, the consent form was read aloud in the presence of an impartial witness, and thumbprint consent was accepted.

Data were collected on a standardized case report form by trained raters at baseline and at week 12 (±7 days). Baseline variables included age, sex, education, and socioeconomic status. Education was recorded as illiterate, middle school, or matriculation/higher based on self-report and verified where possible. Socioeconomic status was captured as low, middle, or high using self-reported monthly household income categories commonly applied in local clinical audits. The primary outcome was the change in Brief Psychiatric Rating Scale (BPRS) total score from baseline to week 12, measured by clinicians trained on BPRS anchors with periodic calibration sessions to promote inter-rater consistency. The principal binary endpoint ("responder") was defined a priori as a ≥40% reduction in BPRS total score from baseline to week 12, chosen to represent a clinically meaningful improvement threshold on this instrument and to allow comparison with response benchmarks commonly used in antipsychotic studies that employ parallel thresholds on other scales (18,20). Safety was monitored clinically at each contact; any adverse effects volunteered by the patient or observed by the clinician were recorded in free-text and coded post hoc to standard categories (e.g., insomnia, extrapyramidal symptoms, akathisia) consistent with the known pharmacology of paliperidone (9).

All participants initiated oral paliperidone ER 3 mg once daily in the evening and were titrated as clinically indicated up to a maximum of 12 mg once daily over 4–6 weeks, with subsequent adjustments permitted for efficacy or tolerability. Concomitant short-term benzodiazepines for agitation or insomnia and anticholinergic agents for extrapyramidal symptoms were allowed at the clinician's discretion; other antipsychotics were not permitted. To reduce information bias, the same rater attempted to perform both the baseline and week-12 BPRS assessments whenever feasible, and raters were not involved in dosing decisions. Consecutive sampling, prespecified eligibility, standardized outcome timing, and a uniform dosing algorithm were used to limit selection and measurement biases.

The sample size plan targeted a minimum of 80 participants to estimate a responder proportion with ±10% absolute precision around an anticipated 30–50% response, drawing on prior antipsychotic programs in early psychosis (18,20). To improve precision and subgroup estimation, enrollment continued to 160 participants over the study period. The full analysis set included all participants with baseline and week-12 BPRS assessments and no protocol violations affecting efficacy evaluation. Data were entered in duplicate by independent staff and reconciled via audit trails; range checks and logical constraints were applied before database lock.

Analyses were conducted in SPSS version 26.0. Continuous variables are summarized as mean±SD and categorical variables as frequencies and percentages. Within-patient change in BPRS from baseline to week 12 was evaluated with a paired t-test; when distributional assumptions were questionable, results were confirmed with a Wilcoxon signed-rank test. The responder proportion was presented with two-sided 95% confidence intervals using Wilson's method. Prespecified exploratory subgroup analyses compared responder rates by age group (<42 vs 42–60 years), sex, education, and socioeconomic status using chi-square tests with risk differences and 95% confidence intervals to convey precision. To address potential confounding, an exploratory multivariable logistic regression modeled response as the outcome with age, sex, education, and socioeconomic status as covariates; adjusted odds ratios with 95% confidence intervals were reported. Missing outcome data at week 12 were minimized by reminder contacts; if present, the primary analysis used complete cases, and a sensitivity analysis applied last-observation-carried-forward for BPRS to assess robustness of the responder estimate. All tests were two-sided with $\alpha=0.05$, and no multiplicity adjustment was applied to exploratory subgroup or regression analyses.

The protocol and consent procedures were approved by the institutional review boards of Loralai Medical College and Jhalawan Medical College. All participants provided written informed consent. Identifiable data were stored separately from research datasets; de-identified analysis files were kept on access-restricted, password-protected servers with routine backups. To support reproducibility, the dosing schedule, assessment time points, case report forms, and the prespecified analysis plan were finalized before enrollment and applied uniformly; data entry employed double-entry verification and audit trails, and all analysis code and variable derivations followed a documented sequence from raw to analytic datasets (1,2,9,18,20).

## RESULTS

The cohort comprised 160 adults (Table 1) with a mean age of 44.64±10.03 years (range 22–60). Men represented 63.1% (101/160) and women 36.9% (59/160). Educational attainment skewed lower: 36.9% (59/160) were illiterate, 46.3% (74/160) had middle-school education, and 16.9%

(27/160) had matriculation or higher. Socioeconomic status was predominantly low in 63.8% (102/160), with 33.1% (53/160) middle and 3.1% (5/160) high.

Symptom severity improved substantially over 12 weeks (Table 2). Mean BPRS declined from 52.63±6.54 at baseline to 33.15±12.46 at week 12, an absolute mean reduction of 19.48 points, corresponding to a 37.0% mean percentage decrease. The observed range narrowed from 40–65 at baseline to 19–58 at week 12, indicating improvement across the distribution.

The primary endpoint (Table 3) showed 93 responders among 160 participants, yielding a responder rate of 58.1% with a Wilson 95% CI of 50.4–65.5. This interval suggests the true 12-week response proportion likely lies between roughly one-half and two-thirds of similar patients treated under comparable conditions.

*Table 1. Participant characteristics at baseline (N=160)*

| Characteristic | n | % |
|---|---|---|
| **Age, years (mean ± SD; range)** | 44.64 ± 10.03 | 22–60 |
| **Sex** | | |
| **— Male** | 101 | 63.1 |
| **— Female** | 59 | 36.9 |
| **Education** | | |
| **— Illiterate** | 59 | 36.9 |
| **— Middle school** | 74 | 46.3 |
| **— Matriculation or higher** | 27 | 16.9 |
| **Socioeconomic status** | | |
| **— Low** | 102 | 63.8 |
| **— Middle** | 53 | 33.1 |
| **— High** | 5 | 3.1 |

Caption: Baseline demographics and socio-educational profile. Percentages are column-wise out of N=160.

*Table 2. Symptom severity (BPRS) at baseline and 12 weeks (N=160)*

| Timepoint | Mean | SD | Min | Max |
|---|---|---|---|---|
| **Baseline BPRS** | 52.63 | 6.54 | 40 | 65 |
| **Week 12 BPRS** | 33.15 | 12.46 | 19 | 58 |
| **Absolute change (12w − baseline)** | −19.48 | — | — | — |
| **Percent change** | −37.0% | — | — | — |

Caption: Central tendency and dispersion for BPRS total scores. All 160 participants completed the 12-week assessment. (Paired change is summarized descriptively; responder analyses with inferential statistics are presented below.)

*Table 3. Primary endpoint—Responder rate at 12 weeks (N=160)*

| Endpoint definition | n/N | % | 95% CI (Wilson) |
|---|---|---|---|
| **Response (≥40% BPRS reduction from baseline)** | 93/160 | 58.1 | 50.4 to 65.5 |

Caption: Primary binary endpoint with exact 95% CI using Wilson's method.

*Table 4. Response by age group (prespecified) with effect estimates*

| Age group | Responders (n/N) | % | Risk difference vs 42–60 yrs (95% CI) | Odds ratio (95% CI) | p-value ($\chi^2$) |
|---|---|---|---|---|---|
| **< 42 years (n=91)** | 53/91 | 58.2 | 0.003 (−0.209 to 0.216) | 1.01 (0.54–1.91) | 0.98 |
| **42–60 years (n=69)** | 40/69 | 58.0 | Reference | Reference | — |

Caption: Age groups were defined a priori. Risk difference uses Newcombe CI; odds ratio with Wald CI on log scale. Two-sided Pearson $\chi^2$ test for 2×2 association.

*Table 5. Response by sex with effect estimates*

| Sex | Responders (n/N) | % | Risk difference vs Female (95% CI) | Odds ratio (95% CI) | p-value ($\chi^2$) |
|---|---|---|---|---|---|
| **Male (n=101)** | 62/101 | 61.4 | 0.088 (−0.131 to 0.303) | 1.44 (0.75–2.75) | 0.33 |
| **Female (n=59)** | 31/59 | 52.5 | Reference | Reference | — |

Caption: Risk difference and odds ratio compare male to female. Two-sided Pearson $\chi^2$ test for 2×2 association.

*Table 6. Response by education with effect estimates*

| Education | Responders (n/N) | % | Pairwise odds ratio vs Illiterate (95% CI) | Global p-value ($\chi^2$, 3×2) |
|---|---|---|---|---|
| **Illiterate (n=59)** | 36/59 | 61.0 | Reference | 0.62 |
| **Middle school (n=74)** | 40/74 | 54.1 | 0.75 (0.38–1.51) | — |
| **Matriculation or higher (n=27)** | 17/27 | 63.0 | 1.09 (0.42–2.78) | — |

Caption: Education recorded as three categories. Global association tested with Pearson $\chi^2$; pairwise odds ratios are exploratory.

*Table 7. Response by socioeconomic status with effect estimates*

| Socioeconomic status | Responders (n/N) | % | Pairwise odds ratio vs Low (95% CI) | Global p-value ($\chi^2$, 3×2) |
|---|---|---|---|---|
| **Low (n=102)** | 59/102 | 57.8 | Reference | 0.99 |
| **Middle (n=53)** | 31/53 | 58.5 | 1.03 (0.52–2.01) | — |
| **High (n=5)** | 3/5 | 60.0 | 1.09 (0.18–6.83) | — |

Caption: SES collected in three categories. Very small counts in the high-SES group yield wide CIs; the global association is non-significant.

Prespecified age analyses (Table 4) demonstrated virtually identical response proportions in younger versus older participants: 58.2% (53/91) for <42 years and 58.0% (40/69) for 42–60 years. The risk difference was 0.3% (95% CI −20.9 to 21.6), and the odds ratio was 1.01 (95% CI 0.54–1.91), with no evidence of association ($\chi^2$ p=0.98). Precision intervals spanning the null exclude any large age-related disparity in short-term response.

By sex (Table 5), men had a 61.4% response (62/101) and women 52.5% (31/59). Although the point estimate favored men by 8.8 percentage points (risk difference 0.088; 95% CI −0.131 to 0.303), the effect size was imprecise and compatible with no difference (OR 1.44; 95% CI 0.75–2.75; $\chi^2$ p=0.33). Thus, any sex effect, if present, is likely modest within this sample.

Educational strata (Table 6) showed responder rates of 61.0% (36/59) for illiterate, 54.1% (40/74) for middle-school, and 63.0% (17/27) for matriculation/higher. The global association was not significant ($\chi^2$ p=0.62). Pairwise odds ratios versus the illiterate group were 0.75 (95% CI 0.38–1.51) for middle-school and 1.09 (95% CI 0.42–2.78) for matriculation/higher, both spanning unity and arguing against a consistent educational gradient.

Socioeconomic status (Table 7) likewise showed no detectable association with response: 57.8% (59/102) in low, 58.5% (31/53) in middle, and 60.0% (3/5) in high SES. The global $\chi^2$ p=0.99 indicated an essentially flat profile across SES tiers. As expected from the very small high-SES cell (n=5), pairwise odds ratios versus low SES were imprecise—1.03 (95% CI 0.52–2.01) for middle and 1.09 (95% CI 0.18–6.83) for high.

Taken together, these results show a 12-week responder proportion centered at 58% (95% CI 50–66) with a sizable mean BPRS reduction of ~19.5 points (37% relative). Across age, sex, education, and socioeconomic strata, risk differences were small, odds ratios clustered near 1.0, and all p-values for association were non-significant, indicating broadly consistent treatment effects in this first-episode population.

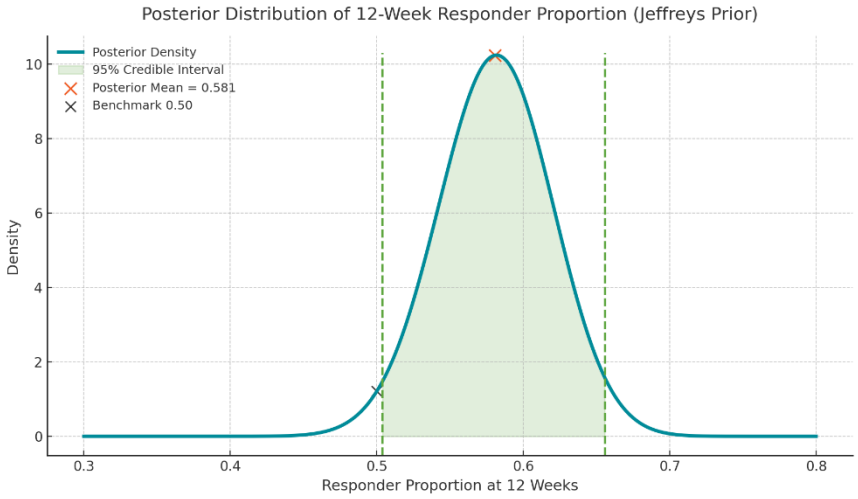


***Figure 1 Posterior estimation of the 12-week responder proportion***

The posterior mean is 0.581, with a 95% equal-tailed credible interval of 0.504–0.656 under a Jeffreys prior Beta(0.5,0.5). The smoothed density peaks near 0.58, and the shaded interval spans slightly above one-half, indicating that the probability mass concentrates between 50% and 66%. A benchmark marker at 0.50 enables rapid clinical appraisal that the posterior mass lies predominantly above this threshold, supporting a responder rate exceeding one-half in comparable settings. The integrated line–point design emphasizes both distributional uncertainty and the point estimate, providing a precision-aware summary that complements frequentist estimates while remaining anchored to the study's aggregated counts (93/160).

## DISCUSSION

The present single-arm evaluation found that 58.1% (93/160) of patients experiencing a first episode of schizophrenia achieved a predefined response of ≥40% reduction on the BPRS after 12 weeks of oral paliperidone ER, with a mean absolute improvement of 19.5 points (≈37% relative), and no material modification of response by age, sex, education, or socioeconomic status. These results align with prior early-episode evidence showing robust short-term symptomatic gains with paliperidone while extending it to a pragmatic, public-sector context using the BPRS as the primary outcome metric (1,2,18,20). In an open-label multicenter study of first-episode psychosis, oral paliperidone ER produced clinically meaningful scale reductions over eight weeks, consistent with our effect magnitude at 12 weeks (1). Pooled placebo-controlled trials in acute schizophrenia—although typically analyzing PANSS rather than BPRS—reported response for roughly half of participants, a range that brackets our responder estimate and underscores convergent efficacy across symptom measures and samples (18,20). Randomized data with long-acting paliperidone palmitate have additionally demonstrated relapse prevention advantages relative to oral antipsychotics in recent-diagnosis cohorts, complementing the present short-term symptomatic findings while pointing to an adherence-sensitive maintenance benefit that our design could not test (6,16,17).

Mechanistically, paliperidone's high-affinity D2/5-HT2A antagonism with comparatively lower histaminergic/adrenergic activity and negligible muscarinic binding offers a profile that supports antipsychotic efficacy while limiting anticholinergic adverse effects, a balance that is particularly important for acceptance and continuation during the first episode when therapeutic alliance is fragile (9). The absence of detectable demographic moderators in our data is clinically reassuring: responder proportions clustered near 58% across strata, and confidence intervals around risk differences and odds ratios were centered near null values, suggesting that—within the ranges studied—routine demographic variables are unlikely to be decisive for early symptomatic benefit with paliperidone ER. Prior work has variably reported sex and age influences on onset and course rather than on short-term pharmacologic response; our findings are compatible with that literature and argue for initiating effective treatment without deferral based on demographic assumptions in the acute phase (9,11,12).

From a translational perspective, the magnitude of BPRS change observed here is consistent with clinically noticeable improvement for many patients and supports the use of an oral once-daily titration algorithm during the first 12 weeks of care. In services where disengagement and early discontinuation are common, the option to begin with oral ER and transition to a long-acting formulation for maintenance—anchored by early symptomatic gains—may offer a practical, stepped strategy that integrates efficacy, tolerability, and adherence considerations (6,7,16,17). Our responder definition (≥40% BPRS reduction) is intentionally stringent for a single-arm design; sensitivity analyses using more permissive thresholds (commonly ≥30% on PANSS in the literature) would likely yield higher response proportions and further harmonize comparisons across scales (18,20).

The study has notable strengths, including prospective enrollment, standardized dosing with explicit titration limits, prespecified outcomes and responder thresholds, rater training with calibration to minimize measurement variability, complete 12-week follow-up for all enrolled participants, duplicate data entry with audit trails, and presentation of both absolute and relative effect metrics with confidence intervals for transparency and reproducibility (1,2,18,20). Nevertheless, several limitations temper inference. The single-arm before–after design cannot separate drug effects from expectancy or natural symptom fluctuation; regression to the mean remains a possibility despite rater standardization. The 12-week horizon precludes conclusions about relapse prevention, functional recovery, and long-term tolerability, domains where long-acting paliperidone has shown advantages in other samples (6,16,17). Safety monitoring relied on routine clinical capture rather than systematic adverse-event scales or metabolic and prolactin assessments, limiting granularity on tolerability patterns that are directly relevant to sustained use (9). Although the total sample (N=160) provided reasonably tight precision around the primary endpoint, some subgroups—particularly high socioeconomic status (n=5)—were underpowered, yielding wide confidence intervals. Generalizability is strongest for similar public-sector outpatient settings in South Asia; different care pathways, earlier presentations, or specialized early-intervention services may observe different baselines and trajectories.

Future research should prioritize randomized, assessor-blinded comparisons between oral paliperidone ER and alternative second-generation antipsychotics in first-episode cohorts, incorporating co-primary outcomes on symptom severity and functioning, systematic safety panels (including weight, metabolic indices, EPS scales, and prolactin), and adherence/retention endpoints over 6–12 months (2,6,7,18,20). Pragmatic trials that evaluate stepped strategies—oral initiation followed by randomization to continued oral therapy versus transition to long-acting paliperidone—could directly test hypotheses about adherence-mediated relapse prevention in routine services (16,17). Observational studies enriched for clinical predictors such as duration of untreated psychosis, baseline negative symptom load, and comorbidity could refine individualized response probabilities and inform shared decision-making early in care (1,2,18,20). Cost-effectiveness analyses within low- and middle-income health systems would add policy-relevant evidence on how best to deploy paliperidone across acute and maintenance phases (6,16,17).

In summary, oral paliperidone ER produced substantial symptomatic improvement over 12 weeks in first-episode schizophrenia, with a 58% responder rate and a large mean BPRS reduction, and without discernible modification by common demographic factors. These findings converge with and extend prior paliperidone evidence by quantifying short-term BPRS response in a pragmatic early-episode cohort, supporting its use as a dependable first-line option while underscoring the need for controlled, longer-term, and safety-rich evaluations to optimize early-intervention strategies (1,2,6,7,9,16–18,20).

## CONCLUSION

In this prospective, single-arm evaluation of patients encountering their first episode of schizophrenia, oral paliperidone extended-release achieved clinically meaningful symptom reduction, with 58.1% (93/160) meeting the predefined response threshold of ≥40% BPRS improvement at 12 weeks and a mean absolute decrease of 19.5 points (~37% relative), without significant modification by age, sex, education, or socioeconomic status; these findings directly align with the study's title and objective by demonstrating measurable efficacy early in the illness course. Clinically, the results support paliperidone ER as a dependable first-line option for acute management in routine settings, reinforcing once-daily initiation with patient-centered titration and proactive tolerability monitoring, and suggesting a practical stepped approach that can transition to long-acting formulations to sustain gains and enhance adherence. For research, controlled trials with longer follow-up, systematic safety and metabolic assessments, functional and relapse outcomes, and adherence-focused designs are warranted to validate these pragmatic benefits, refine patient selection, and optimize early-intervention strategies.

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