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Original Article

Aprepitant Use in Pediatric Cyclical Vomiting Syndrome: A Scoping Review of Current Evidence

Hooria Rehman[1], Muhammad Talha[2], Nabeel Ahmad[1], Ghias ul Hassan[1], Hassan Suleman[1], Muhammad Shahid[1]

1. *Lahore General Hospital, Lahore, Pakistan*
2. *Ameer Ud Din Medical College, Lahore, Pakistan*

Abstract:

Objective: To map and characterize the available evidence on the use of aprepitant in pediatric cyclic vomiting syndrome (CVS), including study designs, reported outcomes, and gaps in knowledge.

Methods: We conducted a scoping review in accordance with PRISMA-ScR guidelines. PubMed, Embase, Scopus, Web of Science, and the Cochrane Library were searched upto 15 January 2025 for researches reporting aprepitant use in children (<18 years) with CVS. Two reviewers screened studies independently and charted data on study characteristics, treatment regimens, and reported outcomes. Descriptive approach was used to summarize the findings.

Results: Three studies were found to meet inclusion criteria. Evidence was heterogeneous in design, patient population, and outcome reporting. The largest cohort study found no reduction in short-term readmission rates with aprepitant use, while smaller uncontrolled studies reported symptomatic improvement in a majority of patients. Adverse events were infrequently reported and generally mild.

Conclusion: Available evidence on aprepitant use in pediatric CVS is limited and heterogeneous. Current data are insufficient to determine its efficacy, and findings are primarily derived from observational and anecdotal reports. Further prospective studies are needed to clarify its role in clinical practice.

Keywords: Cyclic vomiting syndrome, Aprepitant, pediatric, Neurokinin-1 receptor antagonist, Scoping review

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Corresponding Author: Hooria Rehman **Email:** drhooria39@gmail.com

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Introduction:

Cyclical vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder marked by stereotyped bouts of intense vomiting that has intervals in between the attacks that are symptom-free [1]. stereotypical episodic nature of nausea and vomiting makes patients undergo immense distress and repeated fluid resuscitations impacting daily life including missed school, increased health care expanses, and poor quality of life[2]. In children, estimated prevalence ranges from ~1–2%, and CVS is increasingly recognized in adults[3]. Comorbidities often include migraines,

autonomic dysfunction, and psychiatric conditions [4].

Despite its impact, evidence-based treatment guidelines for pediatric CVS are limited. A 2008 NASPGHAN consensus recommended cyproheptadine for under five years old and amitriptyline for children older than five years as prophylaxis, with ondansetron or sumatriptan for abortive therapy[4,5]. More recent reviews note that clinicians frequently try various strategies including lifestyle modification, supplementation, and multiple drug classes, owing to heterogeneous response[4]. Notably, neurokinin-1 (NK1) receptor antagonists such as aprepitant have emerged as a novel option for refractory cases. Aprepitant blocks the action of substance P in brainstem vomiting centers and is approved for chemotherapy- and postoperative nausea [6,7,8]. Its use has been described for intractable CVS in adults [9], but pediatric experience is sparse.

Given the limited and heterogeneous evidence base, we conducted a scoping review to map and characterize the existing literature on aprepitant use in pediatric cyclic vomiting syndrome, including study designs, reported outcomes, and gaps in current knowledge.

Methods

Eligibility Criteria:

We included any study including clinical trial, observational study, case series, or case report of **pediatric CVS** patients defined by accepted clinical criteria treated with aprepitant. Studies must report on outcomes after aprepitant use. We included prophylactic or abortive use, oral or IV routes, any dosage. We excluded studies of adults only, animal studies, reviews or editorials. We conducted a scoping review in accordance with the Preferred Reporting Items for Systematic Reviews and Scoping Reviews (PRISMA-ScR) guidelines.

Search Strategy:

We systematically searched PubMed, Embase, Scopus, Web of Science, and the Cochrane Library from database inception to 15 January 2025 for studies evaluating aprepitant in pediatric cyclic vomiting syndrome. The search strategy combined terms related ("cyclic vomiting syndrome" OR "cyclical vomiting syndrome" OR "CVS") AND ("aprepitant" OR "neurokinin-1 receptor antagonist" OR "NK-1 antagonist" OR "substance P antagonist"). Reference lists of included studies were manually screened for additional eligible articles.

Searches were limited to human studies. included studies and relevant reviews were manually screened to identify additional eligible publications.

Study Selection and Data Charting:

Two independent reviewers screened titles/abstracts and then full texts for inclusion. Disagreements were resolved by discussion. The database search identified a total of **247 records** (PubMed: 102; Embase: 119; Cochrane Library: 26). After removal of **61 duplicate records**, **186 records** remained for title & abstract screening. Of these, **169 records were excluded** for clearly not meeting inclusion criteria (adult-only populations, unrelated conditions, review articles, editorials, conference abstracts without full data, or studies not involving aprepitant). **Seventeen full-text articles** were assessed for eligibility. Of these, **14 were excluded** for the following reasons: adult-only CVS populations (n = 6), no aprepitant exposure (n = 4), review or guideline articles without original data (n = 3), and insufficient outcome data (n = 1). Ultimately, **three studies** met inclusion criteria and were included in the scoping review. From each included study, we charted: study design, setting and country, patient demographics (age, sex), CVS diagnostic criteria used, aprepitant regimen (dose, timing, duration), comparator or control (if any), and outcomes (clinical response defined as change in episode frequency/severity, hospital admissions, duration, and any reported side effects).

Risk of Bias Assessment:

In keeping with scoping review methodology, formal risk of bias assessment was not used to exclude studies but findings were interpreted in the context of study design and inherent methodological limitations.

Protocol Registration and Reporting Standards:

This scoping review was conducted and reported in accordance with PRISMA-ScR guidelines. A formal protocol was not registered. A completed PRISMA 2020 checklist is provided as Supplementary File 1. The review protocol was not registered in PROSPERO because no prospective registration was performed prior to study initiation.

Synthesis of Results:

Given the limited number of studies and substantial heterogeneity in study design, patient populations, and outcome measures, findings were summarized descriptively. No quantitative synthesis was attempted, consistent with the objectives of a scoping review.

Results

Study Selection:

Our search identified a small number of relevant studies. Three studies met the inclusion criteria after careful screening as per the study protocol, including one retrospective cohort study, one retrospective case series, and one case report. The eligible database had 1,775 children hospitalized with CVS, but only 138 patients across all studies were directly treated with aprepitant.

Study Characteristics and Findings:

- **Thavamani et al. (2024)(1)** A retrospective cohort study was performed using the US pediatric hospital database (PHIS), 2016–2019. Children <18 years hospitalized with a primary diagnosis of CVS were identified (n = 1775); 96 (5.4%) received aprepitant during the index hospitalization. Aprepitant was given as an abortive therapy during acute episodes (route not explicitly stated). The control group (n = 1679) did not receive aprepitant. Baseline demographics and comorbidities were broadly similar, although the aprepitant group trended toward more severe illness. The primary outcome was 7-day CVS-related readmission rate. Before matching, the aprepitant group had longer hospital stays (median 5 vs. 3 days) and higher costs (median $11,790 vs. $6,380)(1), suggesting more severe index admissions. Seven-day readmission was 17% for aprepitant users vs. 16% for controls (p = 0.91)(1). Propensity-score matched analysis (1:5 ratio) similarly showed no significant difference: 7-day readmission 17% vs. 16% (not significant), and no improvement at 30 days either. The authors concluded aprepitant did not reduce short-term readmission. Adverse events were not reported in this database study.

- **Cristofori et al. (2014)(10)** reported a retrospective single-arm cohort from a UK tertiary pediatric gastroenterology center. They reviewed n = 41 children (median age 8 years) with CVS refractory to conventional therapy, treated with aprepitant either prophylactically (RegP, n = 16) or acutely at prodrome (RegA, n = 25). Doses were 125 mg on day 1 followed by 80–85 mg on days 2–3, repeated as needed. No control group was available. Over 12–60 months follow-up, 81% of the RegP group (13/16) achieved a complete or partial response (62% partial, 19% complete), and 76%

of the RegA group (19/25) responded (64% partial, 12% complete). All measured outcomes improved significantly in responders: mean annual CVS episodes, hospital admissions, episode duration, and vomiting rate per hour decreased, while symptom-free interval and school attendance increased (10). Side effects occurred only in the prophylactic group (5 of 16, 31%), all mild: hiccups (19%), fatigue (12.5%), increased appetite (12.5%), headache (6%), and migraine (6%). No patients discontinued due to side effects except one (RegP) for severe migraine. This study reported substantial clinical benefit in most of the treated children. However, it lacked a control group and thus selection of patient's refractory to treatment limited the confidence of study.

- **Nivatsi et al. (2021) (11)** demonstrated a single case of a 13-year-old girl with intractable CVS in Greece. Her vomiting did not respond to oral ondansetron requiring hospitalization each time. While being in her prodromal phase she received oral aprepitant 125 mg on day 1 and subsequently 85 mg on days 2–3, **no further vomiting episodes occurred**, and she remained symptom-free afterwards. Along with that no systemic adverse effects were reported. This being anecdotal but it highlights the aprepitant's role in abortive therapy of an acute attack and thus possibly breaking the cycle in severe cases.

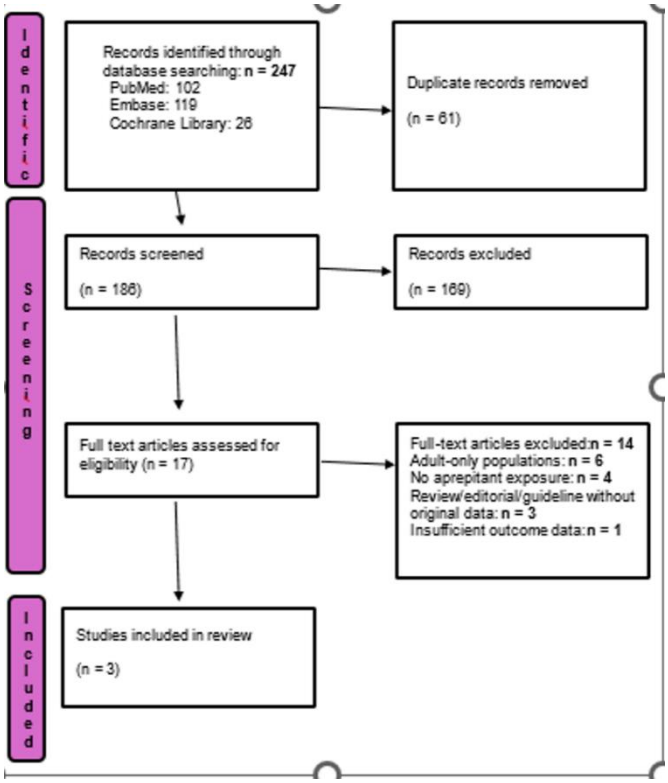

Figure 1. PRISMA flow diagram of study selection.

Efficacy Outcomes: Overall, the clinical improvement from aprepitant seen in the studies were very inconsistent in both size and in methodology of each study. The most inclusive study contained in this review demonstrated no difference in short term CVS-related readmission rates compared to those who did not receive aprepitant; however, many smaller studies containing uncontrolled cohorts reported a symptomatic improvement in approximately 50-70 % of patients. Due to the lack of randomization used within the larger datasets as well as the reliance upon subjective assessment for symptomatology within the smaller datasets, any positive results must be viewed with caution and therefore it would be inappropriate to assume that there exists a direct correlation between symptoms improved via the administration of aprepitant and a decrease in healthcare utilization. Most

importantly, the largest collection of data reviewed here did not document statistical significance regarding a positive impact from aprepitant relative to its primary endpoint. However, even when the patients treated with aprepitant appeared to be at least as ill as those in the control groups based upon propensity score matching analysis failed to identify reduced readmission rates either over 7 days or 30 days. These findings suggest that if there does exist some degree of symptomatic improvement associated with the administration of aprepitant that said improvement may not correlate with an improvement in short term healthcare usage or alternatively that present methods of administrative documentation utilized to measure outcomes do not adequately capture patient centered response.

Adverse Events:

None of these studies documented any serious adverse reactions. Cristofori et al. (10) identified only mild side effects in the aprepitant prophylactic cohort including hiccups, fatigue, changes in appetite, headaches, migraines with a recurrence rate of migraines of 6%. No side effects were identified within the aprepitant abortive cohort. There was no documentation of any adverse events within the case report. Thavamani et al. (11) failed to provide information related to safety since such details were not available within the administrative databases. As a general rule, NK1 receptor antagonists appear to be well tolerated in paediatric populations although the possibility for somnolence, headaches or alterations in liver enzymes has been described within the context of oncologic therapy. Hepatotoxicity was not reported within the paediatric CVS reviews. Therefore, based on the existing literature it appears that aprepitant is safe. However, systematic safety data are needed particularly for repeated or chronic use.

Methodological Considerations and Limitations of Included Studies: Each of the studies included in this review had important methodological limitations due to their study designs. The study conducted by Thavamani et al., while large, was retrospective and non-randomized thereby creating the likelihood of confounding by indication. More specifically, confounding by indication could occur because more severely affected CVS patients may have preferred to receive aprepitant. The single case cannot establish causality and is subject to publication bias (only positive cases tend to be reported). Overall, the evidence base is limited by retrospective designs, small sample sizes, heterogeneity in outcome measures, and reliance on anecdotal reports, confounding by indication, inconsistency of outcome measures, and reliance on retrospective and anecdotal data. Formal GRADE assessment was not performed because no randomized or comparable controlled studies were available.

Discussion:

This scoping review identified only three studies of aprepitant in pediatric CVS: one large retrospective cohort, one small retrospective series, and one case report. The controlled cohort (Thavamani et al.) did not demonstrate a reduction in 7-day readmissions with aprepitant (1). However, as a population study it measured a surrogate outcome (readmission) rather than direct symptom relief, and patients receiving aprepitant had more severe illness[1]. By contrast, the smaller case series (Cristofori et al.) reported that the majority (≈80%) of children refractory to standard therapy improved with either abortive or prophylactic aprepitant[10], with significant reductions in episode frequency, hospitalizations, and improved functional outcomes. The single published case echoed these positive results[11]. Taken together, the available evidence describes variable outcomes, with some studies reporting symptomatic improvement, while the largest

dataset did not demonstrate benefit in short-term healthcare utilization as it seems consistent with what adult experienced with similar therapies keeping in line with the consensus recommendations [12]. Important consideration is that no serious safety concerns emerged in the pediatric cases; adverse events were mild and comparable to known effects of NK1 antagonists[10]. Although the available data does not allow inference regarding the efficacy of aprepitant in pediatrics population with CVS. Observed improvements seen in literature may reflect the natural relapsing and remitting course of the disease, placebo effects, or concurrent supportive interventions. The absence of randomized comparisons substantially limits internal validity.

Recent clinical guidelines mention NK1 receptor antagonists as a potential option for refractory pediatric CVS; however, these recommendations are explicitly conditional and based on low certainty evidence, largely derived from the same observational studies summarized in this review. Interpretation of efficacy is further complicated by substantial heterogeneity in outcome measures across included studies.

Limitations: This review is limited by the extremely small number of available studies and the uniformly low methodological quality of the evidence. No randomized controlled trials were identified. Heterogeneity in dosing strategies, treatment timing, and outcome definitions further limited comparability and precluded the analysis. Finally, publication bias is likely, as negative case experiences may be underreported.

Implications: Despite limitations, the available literature indicates that aprepitant has been used in refractory pediatric CVS, with variable reported outcomes. for pediatric CVS, especially in severe or refractory cases. The recent 2025 NASPGHAN guidelines conditionally recommend abortive use of NK1 antagonists based on indirect evidence and expert opinion[12]. Clinicians might consider aprepitant when first-line agents fail, recognizing that insurance coverage and cost can be barriers. The drug's pharmacology and theoretical risks warrant caution. Families should be counseled about limited evidence and monitored for side effects. No studies from Pakistan or South Asia were identified, highlighting a regional gap in the literature and the need for context-specific research.

Future Research: There is an urgent need for prospective studies. A randomized controlled trial or even a well-designed cohort study could compare aprepitant to placebo or standard care in refractory CVS. Important questions include optimal dosing especially for children, duration of prophylaxis, and long-term outcomes. Comparative effectiveness should be explored. Patient reported outcomes and quality-of-life measures should be included. Given CVS's overlap with migraine pathophysiology, mechanistic studies could identify biomarkers predicting aprepitant response.

Conclusion: Current evidence on aprepitant use in pediatric cyclic vomiting syndrome is limited, heterogeneous, and primarily derived from observational and anecdotal reports. While some studies describe symptomatic improvement, the largest available dataset did not demonstrate benefit in short-term outcomes. The existing evidence is insufficient to guide routine clinical use. Prospective studies and controlled trials are needed to clarify the role of aprepitant in Pediatrics population.

Conflict of Interest:

The authors declare no conflicts of interest in conducting this study.

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