

Treatment Options for Cyclic Vomiting Syndrome: A Real-World, Single-Center Experience with Systematic Literature Review and Meta-Analysis

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Abstract

The optimal therapeutic management of cyclic vomiting syndrome (CVS) remains elusive. The objective of this study was to document our clinical experience in the Pediatric Department of San Marco Hospital and to survey the literature on pediatric CVS treatment, aiming to update the guidance on the most effective treatment strategies for this not-so-uncommon condition. Data from 70 patients with CVS, admitted to our Pediatric Department between September 2011 and December 2021, were aggregated and included in the study. A systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool and the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2) method. Treatment responses, as observed both in the literature and in our own experience, are variable. In our cohort, topiramate demonstrated superiority over other pharmacological treatments, exhibiting an efficacy of 85% in the patients treated. A universally accepted treatment protocol for pediatric CVS has yet to be established. The efficacy of first-line treatments is generally suboptimal, suggesting that topiramate might serve as a safe and effective primary therapeutic option for pediatric CVS.

Keywords

amitriptyline, cyclic vomiting syndrome (CVS), cyproheptadine, migraine, pediatrics, propranolol, topiramate, valproate

Cyclic vomiting syndrome (CVS) is a debilitating, chronic disorder of the brain–gut axis, characterized by recurrent, explosive bouts of vomiting, interspersed with intercritical periods of well-being. The worldwide prevalence of CVS in children may be as high as 1.9%, but its incidence is likely to be underestimated owing to frequent delays in diagnosis and its overlap with migraines.^{1–4} It is more prevalent in females and its occurrence intensifies under physical and mental stress. Although CVS was initially considered exclusive to the pediatric population, recent observations have shown that individuals of any age can be affected; however, episodes typically commence during childhood and tend to decrease in frequency as the individual ages.¹ The episodic vomiting can be triggered by stressful events and fatigue, with each episode potentially lasting several days. If left untreated, these episodes will resolve on their own. CVS poses a considerable disease burden for both patients and their families, resulting in psychological strain, escalating healthcare costs, frequent visits to emergency departments, increased school absence, and an overall diminished quality of life (QoL).^{1,5–8}

Diagnostic tools specific to CVS are lacking, and current diagnoses primarily depend on the North

American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) clinical diagnostic criteria, as delineated in their 2008 consensus statement, as well as the International Headache

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Table 1. Our Experience with Pediatric CVS

	Group case 1	Group case 2	Group case 3	Group case 4	Group case 5
Type of drug received	Amitriptyline	Cyproheptadine	Propranolol	Topiramate	Valproate
Number of patients	14	14	14	14	14
Age (months)	54-168	13-66	12-177	18-101	21-122
Sex	6 males 8 females	8 males 6 females	5 males 9 females	8 males 6 females	7 males 7 females
Clinical presentation severe enough to require hospitalization	5	7	11	12	14
Abnormal EEG	No	No	2	4	2
Family history of migraine	8	10	13	10	11
Dosing regimen	1 mg/kg/day	0.25-0.5 mg/kg/day	1 mg/kg/day	4 mg/day	10-40 mg/kg/day
Duration of treatment (months)	14	10	17	15	11
Complete responder*	4	3	1	9	3
Clinical improvement**	4	5	2	3	2
Non-responder***	6	8	11	2	9
Side effects	4	3	2	6	8
Ineffectiveness of previous therapy	3	0	12	11	10

CVS, cyclic vomiting syndrome.

*"Complete responder", complete remission of the vomiting episodes.

**"Clinical improvement", defined as a >50% remission of the vomiting episodes in terms of duration and/or frequency.

***"Non-responder", defined by a <50% reduction in the duration and/or frequency of vomiting episodes.

Society's 2004 Classification.^{9,10} There is no established pharmacological therapy proven to be effective for CVS. Nonetheless, considering the profound impact of this condition, identifying a potent prophylactic medical intervention is crucial in either preventing or shortening the attacks, thereby offering patients an enhanced QoL.^{11,12} According to NASPGHAN, cyproheptadine is the recommended first-line prophylactic treatment for children under 5 years of age, whereas amitriptyline is preferred for children older than 5 years and for adolescents. Propranolol has also been suggested as a second-line prophylactic treatment for CVS.¹³

As noted earlier, owing to the presumed pathogenic mechanisms and clinical similarities with other nonepileptic paroxysmal disorders, such as headaches and abdominal migraines, several antiepileptic drugs (AEDs) are frequently prescribed to treat children with CVS. However, there are no aggregated data in the literature regarding the efficacy or potential side effects of these medications. Furthermore, treatment for CVS varies considerably among pediatric departments, reflecting individual institutional protocols, expertise, and the absence of unified guidelines. Given this current gap in our knowledge regarding optimal treatment options for pediatric CVS, our aim is to conduct this study to provide additional real-life data on the outcomes of varying treatment protocols for pediatric CVS. We also undertook a systematic review of existing literature on the subject to refresh the

current clinical understanding and to seek updated evidence (eg, a reduction in episode frequency, an extension of the intercritical phases, and decreased school absence) that might support the use of AEDs as potential first-line treatment options.

Methods

Our Experience

Data from 70 children admitted to the Pediatric Department of San Marco University Hospital (Catania, Italy) between September 2011 and December 2021 for CVS were retrospectively collected by accessing the patient registry (Table 1).

Ethical approval was obtained from the ethics committee of the Medical Faculty at the University of Catania, Sicily, Italy. All research activities were conducted in line with applicable guidelines and regulations. Informed consent was secured from the parents of all participating patients. This research was conducted in accordance with the Declaration of Helsinki guidelines.¹⁴

The inclusion criteria were:

- Patients aged <18 years;
- Patients with chronic or recurrent vomiting symptoms that cannot be attributed to other medical conditions after appropriate evaluation;
- Patients experiencing 2 or more stereotypical bouts of nausea and emesis, each lasting hours or days over

a 6 month period, and returning to their baseline health status between episodes, meeting the diagnostic criteria of NASPGHAN, the Rome IV Committee, and the International Headache Society^{15,16};

- Patients treated with standard therapy (amitriptyline, cyproheptadine, and/or propranolol);
- Patients treated with one of the 2 AEDs, topiramate or valproate. Other AEDs were not included in the analysis because of the absence of data in the literature and the fact that none of our patients received different AEDs for CVS.

Exclusion criteria were:

- Patients aged ≥ 18 years;
- Patients with non-CVS disorders, including malrotation with volvulus, neoplastic lesions of the central nervous system, some metabolic disorders, and gastrointestinal, neurological, and endocrine conditions;
- Patients treated with different medications;
- Patients with cannabinoid hyperemesis.

All 70 patients with CVS admitted to our pediatric department between 2011 and 2021 were enrolled to the study.

Clinical data retrieved from the selected patient database included anamnestic, clinical, and electroencephalographic information. For each patient, medical records were meticulously reviewed by 2 authors (B.S. and A.D.C.). We assessed the urgency of each case by examining the triage color codes upon admission, clinical data at the time of admission, and the discharge diagnosis.

Beyond the routine workup conducted during the initial presentation, all patients were evaluated by pediatric gastroenterologists and neurologists during their hospitalization. An abdominal ultrasound was performed for every patient to rule out differential diagnoses. Endoscopy was only undertaken for those with abnormal abdominal ultrasounds or when there was uncertainty regarding an underlying gastrointestinal condition. An electroencephalogram (EEG) was conducted for all patients during their hospital stay, even if there was no prior history of epileptic disorders. In instances where sinus or central nervous system (CNS) issues were suspected, sinus series and brain computed tomography (CT) scans were performed.

Prophylactic therapy was determined by the head of the department, taking into consideration patient characteristics, anamnesis, and clinical evaluation. Treatment options included amitriptyline (1 mg/kg/day), cyproheptadine (0.25-0.5 mg/kg/day), propranolol (1 mg/kg/day), topiramate (2 mg/kg twice daily), or valproate (10-40 mg/kg/day). Of the 70 patients enrolled, precisely 14 received each medication.

The average duration of treatment was 12 ± 3 months. During the treatment period, patients had follow-up visits at 2 weeks, 1 month, and then every 3 months subsequently. Each medication was initiated at the minimum effective dose. If the response was suboptimal, the dosage was incrementally increased to the maximum allowable dose over a period of 3 months. For patients who remained symptom free for at least 9 months, the medication dosage was reduced by 25% every 20 days until eventual discontinuation.

After discontinuation, patients were followed up at 6 months, then annually, and subsequently every 2 years. Only a minority of patients (N = 21) completed the follow-up, making the data on long-term treatment efficacy potentially biased and, therefore, unsuitable for inclusion in the analysis.

The primary end point aimed to evaluate the efficacy of each medication. We classified the results of their administration into 3 groups to standardize our findings in comparison with the existing literature:

- “Complete response,” defined by a complete remission of the vomiting episodes;
- “Clinical improvement,” conventionally defined as a $\geq 50\%$ remission of the vomiting episodes in terms of duration and/or frequency. This definition is derived from other reports in the literature on CVS treatment and establishes a threshold above which patients perceive the medication as effective.^{1,5,7,9} During each follow-up evaluation, data from diaries maintained by patients and their families at home were collected and documented;
- “No response,” defined by a $\leq 50\%$ reduction in the duration and/or frequency of vomiting episodes.

Moreover, for each patient, familial anamnesis, EEG recordings, comorbidities, treatment side effects, and data from radiological examinations were compiled with the aim of discerning a potential correlation between these variables and the response to a specific medication.

Systematic Review of the Literature

Search Strategy. A systematic search of the PubMed, MEDLINE, and Embase databases was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following search terms were utilized: “cyclic vomiting syndrome children,” “cyclic vomiting syndrome treatment,” “cyclic vomiting syndrome treatment AND amitriptyline,” “cyclic vomiting syndrome treatment AND cyproheptadine,” “cyclic vomiting syndrome treatment AND propranolol,” “cyclic vomiting syndrome treatment AND topiramate,” and “cyclic vomiting syndrome treatment AND valproate.”

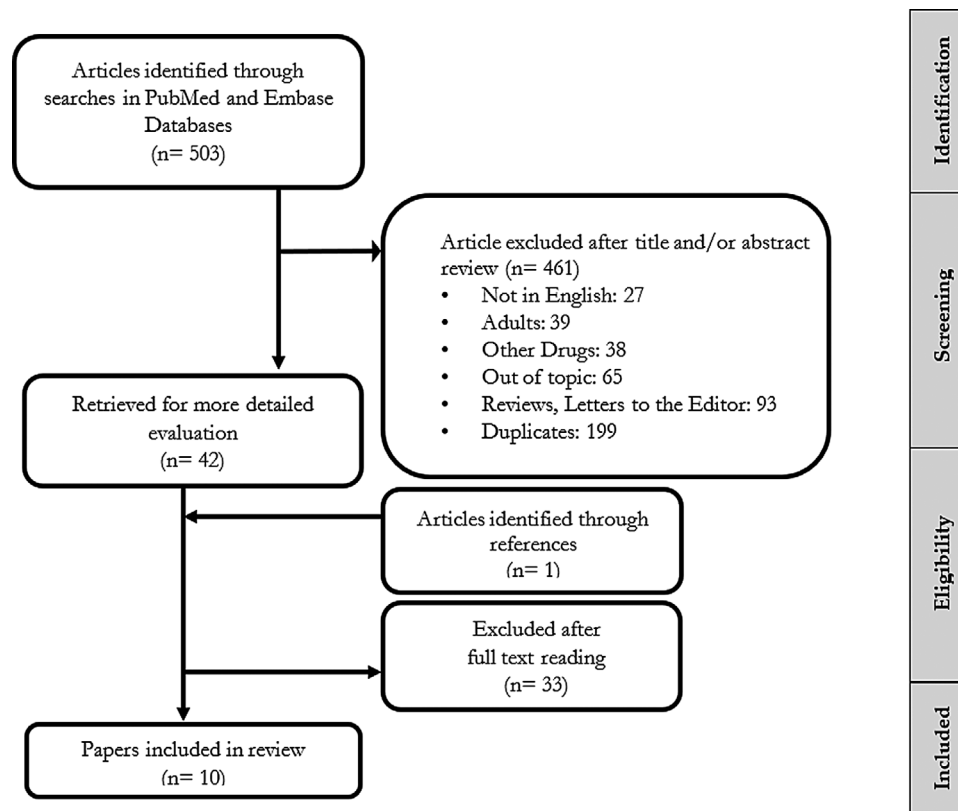


Figure 1. Search results, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology.

All results are up to date until April 2022. Filters were applied to restrict the search to pediatric patients aged <18 years. Additionally, references from articles obtained through this search strategy were reviewed to identify any further relevant publications.

Inclusion and Exclusion Criteria. Inclusion criteria were:

- Studies reporting on patients with CVS;
- Studies reporting on patients with CVS treated with valproate and/or topiramate;
- Studies reported in English only.

Exclusion criteria were:

Editorials, letters to the editor, expert opinions, comments, reviews, systematic reviews, guidelines, and meta-analysis;

Studies that reported experiences of a combination therapy (eg, topiramate and/or valproate plus other drugs);

Studies that reported on patients aged ≥ 18 years or where the age could not be clearly stated in the text were excluded. The decision to exclude adults stemmed from our clinical experience being solely with pediatric patients. Additionally, although pediatric and adult patients may share a common pathogenetic basis,

we believe that they are considerably heterogeneous, especially in terms of comorbidities and concurrent treatments with other medications that might influence the pharmacokinetics and pharmacodynamics of CVS treatment options.

Study Selection

The search using the aforementioned search terms identified 503 studies, of which 42 were selected for reading in full if the title and/or abstract were related to our clinical aspects of interest (Figure 1).

Titles and abstracts were initially screened by 3 independent reviewers, in accordance with the recommendations of the Cochrane Collaboration. Each researcher unanimously decided on the articles to include during the pre-selection phase based on the established inclusion criteria. Complete consensus was reached regarding the articles to be included in the study. Duplicates were removed. The reasons for exclusion are detailed in Figure 1. A total of 10 studies met the inclusion criteria and were subsequently included in the review. The full texts of these studies were read by the same authors. Data from these articles were extracted, organized in an Excel table (Microsoft, Redmond, WA, USA), and discussed among the group to evaluate quality indicators and reliability.

Studies	Risk of bias				Applicability concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Andersen et al.	Low	Low	Low	Unclear	Low	Low	Unclear
Olmez et al.	High	Low	Low	Unclear	High	Low	Unclear
Haghighat et al.	Low	Low	Unclear	Low	Low	Low	Unclear
Hikita et al.	Low	Unclear	Low	Low	Low	Low	Unclear
Felton et al.	High	Unclear	Low	Unclear	High	Low	Unclear
Hikita et al.	Low	Unclear	Low	Low	Low	Low	Unclear
Sezer et al.	Low	Unclear	Low	Low	Low	Low	Unclear
Haghighat et al.	Low	Low	Unclear	Low	Low	Low	Unclear
Badihian N et al	Low	Unclear	Low	Low	Low	Low	Unclear
Bagherian et al.	Low	Low	Unclear	Low	Low	Low	Unclear

Low	High	Unclear
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Figure 2. Quality assessment of included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.

Risk of Bias and Quality Assessment

All included studies were evaluated using Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2), a tool designed to determine the quality of primary diagnostic accuracy studies included in systematic reviews. This tool assesses the risk of bias and the applicability of study results. Judgments regarding risk of bias are based on predefined signaling questions related to 4 domains: patient selection, index test, reference standard, and flow and timing. Applicability judgments are determined by how bias in any domain might impact the questions posed in the review. The risk of bias and concerns about applicability were categorized as “low,” “high,” or “unclear.” The results of this quality assessment, using the QUADAS-2 tool, are outlined in Figure 2, and the proportions of studies with risk of bias and applicability concerns are illustrated in Figure 3.¹⁸ Generally, there was a low risk of bias observed in the domains of “patient selection” and “flow and timing.” Regrettably, there was a moderate risk related to the index test, reference standard for bias, and reference standards for applicability, largely because the reference standard (pertaining to the response to medications) differed across studies and was not consistently and clearly defined. Regarding applicability concerns, 5 out of the 10 articles demonstrated a low risk in the index test domain. Two of the 10 articles were case reports, making the risk of bias and applicability concerns in patient selection high. We assigned a high or unclear risk for applicability to studies in which the diagnostic pathway leading to the diagnosis of CVS was either not provided or was ambiguously described. Additionally, based on the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2) score, this work was evaluated as a “moderate quality review.”¹⁹

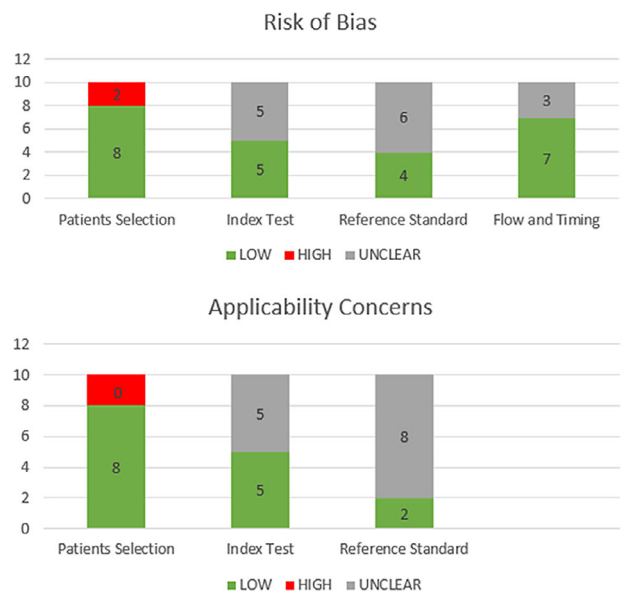


Figure 3. Percentage of the studies with risk-of-bias and applicability concerns in different domains of the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.

Results

Summary of Single Center Analysis

In our clinical experience at the Pediatric Department of San Marco Hospital’s in Catania, the initial coding search identified 70 patients: 14 treated with amitriptyline, 14 treated with cyproheptadine, 14 treated with propranolol, 14 treated with topiramate, and 14 treated with valproate. Of these 70 patients, 34 (49%) were male and 36 (51%) were female. The age range of the patients at the time of diagnosis spanned from 12-177 months.

Of the 14 patients treated with amitriptyline, 4 were complete responders (28%; odds ratio, OR 0.38), 4 were partial responders (28%, OR 0.38), and 6 did not

respond (42%). Three of these patients had previously failed treatment with cyproheptadine. Notably, none of them exhibited abnormal EEG at the time of diagnosis. Amitriptyline-associated side effects, which included drowsiness and weight gain, were observed in 28% of these patients.

For those treated with cyproheptadine, an optimal response was observed in 21% of cases (OR 0.26), a partial response was observed in 36% (OR 0.56), and no response was observed in 43%. Furthermore, 21% of cyproheptadine-treated patients developed side effects, notably drowsiness and weight gain. None of the patients had abnormal EEG readings at the time of their diagnosis.

It is worth emphasizing that none of the patients treated with either amitriptyline or cyproheptadine exhibited EEG abnormalities. Moreover, 42% required hospitalization owing to dehydration. Side effects related to treatment were reported in 28% and 21% of the patients treated with amitriptyline and cyproheptadine, respectively.

The therapeutic response to propranolol was found to be unsatisfactory. Its administration resulted in a complete response in only 1 case (7%, OR 0.07) and in clinical improvement in 2 others (14%, OR 0.16). Notably, 2 of these patients had abnormal EEG readings, characterized by the presence of spike-wave complexes, and did not show any treatment response. Furthermore, a significant 78% (11 out of 14) experienced a severe clinical course of the disease, necessitating hospital admission for dehydration during the initiation of propranolol treatment. Two patients (14%) reported side effects. It is noteworthy that 12 of these patients had not responded to prior first-line treatments with either amitriptyline or cyproheptadine.

Topiramate administration yielded a complete response in 9 out of 14 patients (64%, OR 1.77) and clinical improvement in 3 out of 14 patients (21%, OR 0.26), demonstrating an overall efficacy in 93% of the included patients. The use of topiramate is frequently associated with adverse effects, including asthenia, restlessness, somnolence, tremors, and, notably, weight loss. As these side effects can often be mitigated by gradually increasing the dose, topiramate was initiated at the lowest effective dosage. Nevertheless, mild weight loss (up to 2.6% of the initial body weight) was observed in 43% of our patients. None of the reported side effects were severe enough to necessitate the discontinuation of the treatment. It should be highlighted that 11 of the included patients had previously not responded to first-line treatments with amitriptyline and/or cyproheptadine.

Valproate administration led to a complete response in 3 out of 14 patients (21%, OR 0.26) and to clinical improvement in 2 out of 14 patients (14%, OR 0.16).

Adverse effects, encompassing weight gain, lethargy, and irritability, were documented in 57% of the patients. Notably, 71% of these had not benefited from prior treatment with amitriptyline and/or cyproheptadine. It is essential to note that all the included patients exhibited severe symptoms at the initiation of valproate and had been unresponsive to previous treatments with first-line medications in 10 out of 14 cases. A familial history of migraine was present in 11 out of 14 cases. EEG abnormalities were detected in 2 patients: one exhibited spike complexes and the other showed high-amplitude, synchronous 3-4 Hz sharp-wave discharges. Among these 2 patients, one responded favorably to valproate after not benefiting from amitriptyline. Of the 2 patients who showed clinical improvement, one had an abnormal EEG and had been unresponsive to cyproheptadine, whereas the other had a normal EEG, a positive familial history for migraine, and had not responded to prior treatment with amitriptyline.

No severe side effects were recorded in any of the included patients.

Interestingly, a family history of migraine was recorded in up to 70% of the patients included.

Abnormal EEG findings were identified in 8 (11.4%) of the included patients, in the absence of a personal history of seizures; the same patients were treated with propranolol ($n = 2$), topiramate ($n = 4$), and valproate ($n = 2$). The ages of both responders and non-responders varied widely, suggesting that age does not represent a statistically significant variable in predicting the response to a certain medication.

Treatment of CVS Comparing Standard Therapy with AEDs in the Pediatric Population in the Systematic Review and Meta-Analysis

A systematic review of the literature permitted the identification of 597 pediatric patients with CVS across 10 distinct studies, which comprised 2 randomized controlled trials (RCTs), 4 prospective studies, 2 retrospective studies, and 2 case reports. The effectiveness of each medication is detailed below, with results summarized in Table 2.

Of the 10 studies included, amitriptyline was administered to 170 patients (with doses ranging from 0.1-1.9 mg/kg/day). This resulted in a complete response in 107 patients (62%), clinical improvement in 16 patients (9.4%), and no response in 47 patients (28.6%).²⁰⁻²⁵ The most commonly reported side effects were drowsiness, sedation, and weight gain.

Cyproheptadine was used in 38 patients (with doses ranging from 0.1-0.3 mg/kg/day), yielding a complete response in 20 patients (52%), clinical improvement in 9 patients (24%), and no response in 9 patients (24%).^{21,24} Side effects, namely drowsiness and sedation, were frequently observed. Badihian et al compared the efficacy

Table 2. Review of the Literature

	Andersen et al 1997	Haghighat M et al., 2007	Olmeze et al 2006	Haghighat et al 2007	Felton et al 2009	Hikita et al 2016	Sezer et al 2016	Haghighat et al 2017	Badhian et al 2018	Bagherian et al 2019
Type of article	RS	CR	PS	PS	CR	PS	RS	PS	RCT	RCT
Patients (n)	22	1	81	10	1	15	16	206	32	36
Age (months)	24-168	114	18-168	39-127	84	3-179	108-156	3-174	60-144	106
Sex	16 M	F	88 M	6 M	F	N/A	5 M	127 M	16 M	17 M
Patients requiring hospitalization	11 F		93 F	4 F			11 F	79 F	16 F	19 F
Abnormal EEG	16	1	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A
Family history of migraine	N/A	1	N/A	2	1	NR	9	N/A	N/A	N/A
Comorbidities	3	No	43	N/A	No	13	N/A	N/A	N/A	N/A
Drug	2 DD, 5 D, 1 NS, 1 AD	No	N/A	N/A	E, DD, GRD	N/A	N/A	N/A	N/A	N/A
Doses (mg/kg/day)	A C	T	A	V	A	V	T	P	A	T
Duration of treatment (months)	0.2-1.9	5	1	10-40	N/A	N/A	25-75	1-3	0.5-1	1-2
Complete responder ^a	N/A	24	N/A	0.5-98	18	10-135	16.8 ± 2.2	N/A	N/A	3
Clinical improvement ^b	16	1	46	2	1	9	13	191	21	14
Non-responder ^c	4	1	N/A	7	0	0	2	16	8	16
Side effects	2	0	N/A	1	0	6	1	15	3	8
Previous failed treatments	Yes	N/A	Yes	No	N/A	N/A	2	0	3	2
			(N = N/A)							
			C, PHB	A, C, P, PHB	N/A	N/A	N/A	No	N/A	N/A

Total patients (N = 597). A, amitriptyline; AD, anxiety disorder; C, cyproheptadine; CBZ, carbamazepine; CR, case report; D, depression; DD, developmental delay; E, epilepsy; F, female; GRD, gastroesophageal reflux disease; M, male; N, number; N/A, not available; NS, Noonan syndrome; P, propranolol; PHB, phenobarbital; PS, prospective study; RCT, randomized controlled trial; RS, retrospective study; T, topiramate; V, valproate.

^a Complete response: no attacks.
^b Clinical improvement: ≥50% decrease.
^c No response: <50% decrease/no response.

of cyproheptadine with the other first-line treatment, amitriptyline, in an RCT.²⁴ They concluded that both amitriptyline and cyproheptadine are efficacious in the prophylaxis of CVS, with neither demonstrating statistically significant superiority. According to their results, 21 out of 32 patients (65.6%) in the amitriptyline group and 16 out of 32 patients (50%) in the cyproheptadine group reported a cessation of attacks. Patients unresponsive to either treatment typically presented with severe symptoms, often necessitating repeated hospital admissions for dehydration.²¹ Both treatment groups showed similar response rates between male and female patients. Moreover, although a family history of migraine was frequently documented, it did not predict the response to either drug.

Propranolol has been introduced as an alternative to “conventional” medications. Its efficacy was evaluated in 311 patients across 2 extensive prospective studies and 1 retrospective study.^{22,26,27} Haghghat et al compared the effectiveness of propranolol with that of amitriptyline, and observed that 89% of patients treated with propranolol demonstrated a “good response” without side effects, in contrast to a 56% overall response rate in patients treated with amitriptyline.²² Furthermore, no side effects were reported among the propranolol-treated patients, unlike the amitriptyline group. This suggests that propranolol could be considered a safe and effective primary treatment for prophylaxis in pediatric patients with CVS. In 2017, the same authors again highlighted the efficacy of propranolol as first-line prophylaxis in a large prospective cohort of 206 patients.²⁷ They found that 93.2% responded to its administration, with doses ranging from 1-3 mg/kg/day. The increased efficacy in this cohort, relative to prior studies, might be attributed to the higher doses administered.

Regrettably, the design of the aforementioned studies on the efficacy of propranolol does not differentiate between “complete responders” and “clinical improvement.” Instead, it aggregates all patients that exhibited some response to propranolol treatment into an “overall response” category. This approach poses a limitation for data analysis, as it likely overestimates the effectiveness of propranolol.

Sezer and Sezer conducted a comparative study on the efficacy of propranolol versus topiramate, finding that topiramate was more effective for managing CVS.²⁶ However, the retrospective design of this study, coupled with the limited sample size, casts doubt on the reliability of these findings and underscores the need for further open-label controlled trials featuring larger sample sizes, extended treatment durations, and a broader range of test drugs.

The efficacy of topiramate was assessed in 53 patients across 3 distinct studies, comprising 1 case report,

1 retrospective study, and 1 RCT.^{25,26,28} A complete response was observed in 28 patients (53%), a partial response was observed in 18 (34%), and no response was observed in 7 (13%). Olmez et al described a 13-year-old female patient with CVS and an abnormal EEG, although she exhibited no clinical episodes indicative of seizures, apart from vomiting attacks.²⁸ Previous treatments with cyproheptadine and flunarizine had proven ineffective for this patient. However, a complete response to topiramate was achieved at a dosage of 5 mg/kg/day.

In an RCT comparing topiramate with amitriptyline, Bagherian et al noted the superiority of amitriptyline, which resulted in a full remission of attacks in 68% of the treated patients, compared with topiramate, which was effective in only 39% of cases.²⁵ Regrettably, the limitations of the study included a small patient sample, a brief 3-month follow-up period, and the administration of lower topiramate doses (1-2 mg/kg/day) relative to other trials.

There are limited studies addressing the efficacy of valproate in treating CVS.^{29,30} Notably, in our research, 25 patients were prospectively enrolled and treated with valproate at doses ranging from 10-40 mg/kg. Complete responses were noted in 11 patients (44%), partial responses were noted in 7 (28%), and no response was noted in 7 (28%). Interestingly, the authors meticulously examined the characteristics of the included population and ascertained that no significant differences were present between risk factors and the predictability of the treatment response. These factors encompassed abdominal pain, allergic conjunctivitis, allergies, atopic dermatitis, bilious vomiting, bloody vomiting, bronchial asthma, complications, diarrhea, early morning onset, family history of migraine headaches, fever, food allergies, headache, nausea, pallor, phonophobia, photophobia, precipitating events, sex, stereotypical patterns, variations in interval durations, and vertigo.

Comparison of Our Experience and Literature Data

In addition to the findings presented in the preceding paragraphs, evidence from our patients was juxtaposed with that available in the literature. Specifically, the efficacy of each medication – categorized as “complete response,” “clinical improvement,” and “no response” (defined earlier) – was compared between literature sources and our own observations, as detailed in Table 3.

The effectiveness rates of the available drugs show considerable variance between our cohort and the general population, leading to some conflicting interpretations from this comparison. Notably, amitriptyline, cyproheptadine, and valproate manifest lower efficacy in our records, compared with the broader population.

Table 3. Comparison between Efficacy Rates in Our Experience and in the Literature

		Literature	Our experience (%)
Amitriptyline ^{20–25}	Complete response	62% (n = 107)	28
	Clinical improvement	9.4 % (n = 16)	28
Cyproheptadine ^{21,24}	No response	28.6% (n = 47)	54
	Complete response	52% (n = 20)	21
	Clinical improvement	24% (n = 9)	36
Propranolol ^{22,26,27}	No response	24% (n = 9)	43
	Complete response	N/A	7
	Clinical improvement	N/A	14
	Overall response	87% (n = 179)	21
Topiramate ^{25,26,28}	No response	13% (n = 19)	79
	Complete response	53% (n = 28)	64
	Clinical improvement	34% (n = 18)	21
Valproate ^{29,30}	No response	13% (n = 7)	25
	Complete response	44% (n = 11)	21
	Clinical improvement	28% (n = 7)	14
	No response	28% (n = 7)	65

N, number; OR, odds ratio.

Both literature and our data offer encouraging support for the utilization of topiramate in the management of CVS. Consequently, to provide a more in-depth understanding of the effectiveness of topiramate, we conducted a meta-analysis incorporating data from Bagherian's RCT,²⁵ the sole study in our review that executed a detailed comparison between topiramate and alternative drugs. Data from Sezer and Sezer and from Olmez et al were excluded from the meta-analysis because of the nature of their study designs (retrospective in 1 instance and a single case report in the other), as well as the absence of a comparison group.^{26,28} Specifically, we carried out 2 discrete meta-analyses, each focusing on either “complete response” or “clinical improvement,” with the results illustrated in separate forest plots (as discussed below).

The potential influence of publication biases was ascertained through funnel plots, which plot the precision against the effect size. The horizontal axis denotes the event effect, whereas the vertical axis represents the standard (Figures 4, 5). In scenarios with minimal publication bias, the points symbolizing the incorporated studies symmetrically surround the mean effect size.

Individual and aggregate point effects were visually summarized using forest plots employing the Mantel–

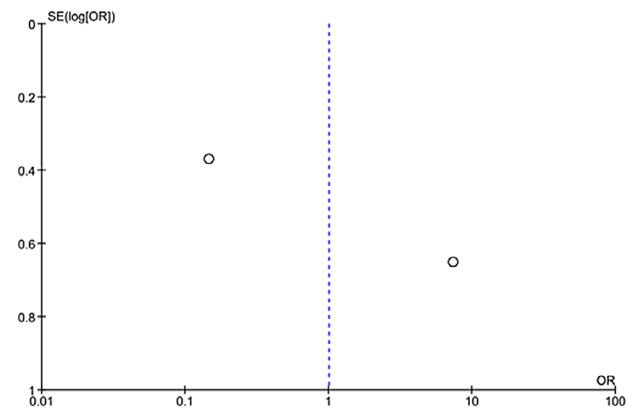


Figure 4. Funnel plot of the included studies on “complete response” after the administration of topiramate or other drugs, reflecting the heterogeneity in the number and features of patients included in each study.

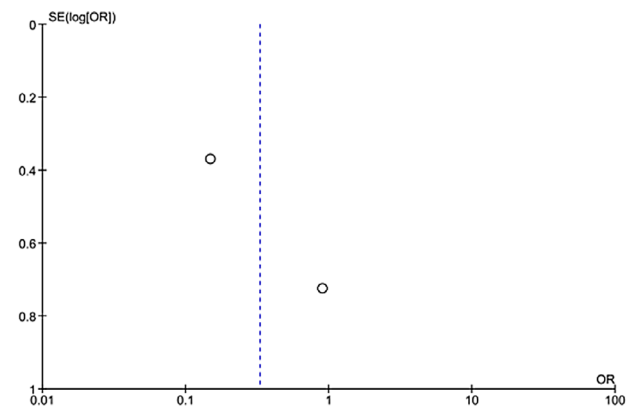


Figure 5. Funnel plot of the included studies on “clinical improvement” after the administration of topiramate or other drugs, reflecting the heterogeneity in the number and features of patients included in each study.

Haenszel OR for dichotomous data. Each study is depicted by a square and a line: the square symbolizes the OR, and its magnitude is contingent upon the weight accorded to the respective study, whereas the line delineates the 95% confidence interval. The aggregated effect is denoted by a black diamond.

Statistical heterogeneity was evaluated using the λ^2 test, adopting a significance threshold of $P < .05$, and with the I^2 test, which was deemed significant for values exceeding 70%. The meta-analysis was conducted using RevMan 5.3 (<https://revman.cochrane.org>).

According to our meta-analysis, no statistically significant discrepancy was discerned in the therapeutic outcomes for “complete response” between topiramate and other drugs. Figure 6 displays a forest plot indicating no significant difference in odds between the groups (OR 1, 95%CI 0.02-48.20; χ^2 27.8; $P < .000001$; I^2 96%). Intriguingly, in evaluating patients demonstrating a “clinical improvement” – characterized by a reduction exceeding 50% in the severity and/or

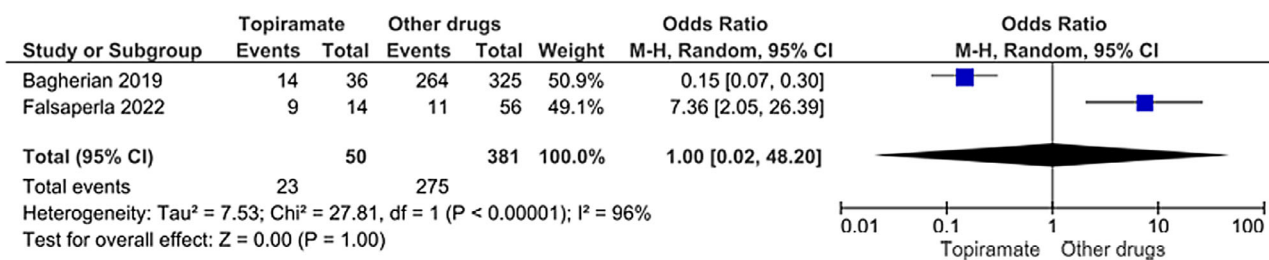


Figure 6. Meta-analysis of studies on “complete response” after the administration of topiramate or other drugs for cyclic vomiting syndrome (CVS). “Events” = number of patients with a complete response to topiramate or other drugs. “Total” = number of patients treated with each medication.

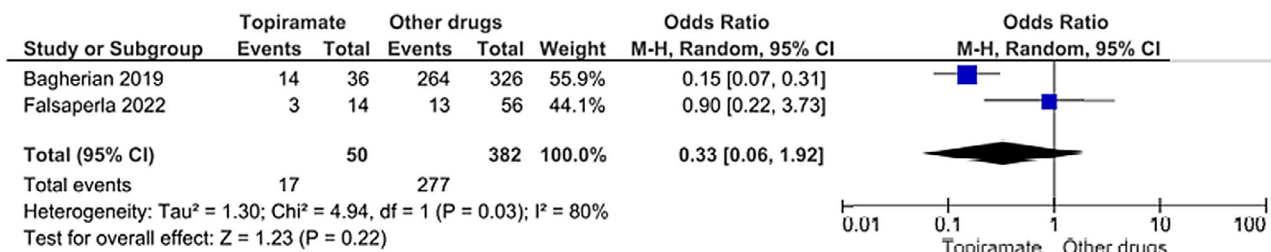


Figure 7. Meta-analysis of studies on “clinical improvement” after the administration of topiramate or other drugs for cyclic vomiting syndrome (CVS). “Events” = number of patients with a clinical improvement after treatment with topiramate or other drugs. “Total” = number of patients treated with each medication.

frequency of attacks – our meta-analysis highlighted a trend favoring the superior efficacy of topiramate relative to other drugs, as depicted in the forest plot presented in Figure 7 (OR 0.33, 95%CI 0.06-1.92; χ^2 4.94; $P < .22$; I^2 80%).

Discussion

Amitriptyline, cyproheptadine, phenobarbital, pizotifen, and propranolol are the most commonly prescribed medications for prophylaxis in CVS patients, and have demonstrated high response rates with level II evidence.²⁴ According to a study by Moses et al,²⁰ cyproheptadine and amitriptyline emerge as the preferred medications for CVS prophylaxis among pediatric patients. However, a definitive treatment for CVS remains elusive, and the superior medication remains unidentified owing to the scarcity of comparative clinical trials.

Our 10-year retrospective analysis at the Pediatric Department of San Marco’s Hospital in Catania presents data from 70 pediatric patients diagnosed with CVS who received various medications. These details are comprehensively presented in Table 1.

In our cohort, the administration of amitriptyline and cyproheptadine resulted in a complete response for 28% and 21% of patients, respectively, and in clinical improvement for 28% and 36% of patients, respectively.

There are contradictory findings regarding propranolol. Literature data predominantly endorse its use; however, it proved largely ineffective in the majority

of our patient cohort. It is worth noting that of the 3 studies in the literature appraising the effectiveness of propranolol in CVS, only 1 explicitly segmented the response to treatment into “complete response,” “clinical improvement,” and “no response.” The remaining 2 studies, which comprised the majority of the patients, vaguely documented a “general improvement” under propranolol. This could potentially encompass patients experiencing less than a 50% reduction in the duration and frequency of attacks – individuals classified as “non-responders” in other reports, including ours.

Valproate administration led to a complete response in 3 patients (21%) and to clinical improvement in 2 patients (14%). Of these, 2 exhibited abnormal EEG results, with 1 responding positively to valproate after an unsuccessful amitriptyline regimen.

Topiramate treatment resulted in a complete response for 64% of our patient group and to clinical improvement in 21%, culminating in an overall efficacy of 85%. This rate surpasses that documented in the broader literature. Notably, all 9 patients exhibiting a complete response to topiramate had a familial history of migraines, and 4 patients displayed abnormal EEG readings. In essence, all those with EEG anomalies demonstrated a complete response to topiramate. The 2 nonresponsive patients presented neither EEG irregularities nor successful prior amitriptyline treatment.

Comparing our findings with literature data underscores the discrepancies in drug efficacy rates between

our cohort and the general populace (Figure 3). Specifically, amitriptyline, cyproheptadine, and valproate manifested diminished effectiveness in our records, compared with the general data. The limited patient count per treatment group in our study might account for this variance. Conversely, the relatively brief follow-up durations in most literature sources, juxtaposed against our more extended follow-up (ranging from 6 months to 2 years after a 12 month treatment and subsequent discontinuation), could inflate the efficacy estimates in prior publications.

Our data indicate an increased proportion of patients responding favorably to topiramate. However, our meta-analysis revealed no statistically significant variance in the therapeutic outcomes concerning a “complete response” between topiramate and other medications, suggesting parity in the ability of topiramate to induce complete CVS remission, compared with traditional drugs. Intriguingly, the OR suggested a heightened likelihood of “clinical improvement” in patients under topiramate versus alternative medications (Figures 6 and 7).

Clearly, the number of studies analyzed (2) remains limited, necessitating additional research for a dependable assessment. Examination of the funnel plots for both groups, as depicted in Figures 4 and 5, indicates that the studies qualifying for our meta-analysis are asymmetric, hinting at potential biases in data evaluation. This asymmetry might stem from heterogeneities in patient cohort sizes and attributes, limited patient numbers, and diverse methodological frameworks.

Contemporary literature does not yet permit conjectures on potential correlations among personal and familial histories, comorbidities, EEG outcomes, and treatment responses. However, from a precision medicine perspective, it is imperative that future research endeavors to identify determinants that can prognosticate specific patient responses to particular medications.

Hikita et al ascertained that the overall duration of CVS was prolonged in patients exhibiting anorexia, lethargy, and salivation during attacks, and with a family history of migraine, than in patients without these features.³⁰ However, the design of the study precludes discerning which patients responded to treatments and which did not.

Our data tentatively suggest a potential relationship between EEG abnormalities and a favorable response to AEDs, as opposed to traditional medications. Notably, patients with EEG abnormalities exhibited responses to both valproate and topiramate, with the overall response to topiramate surpassing that of valproate. Intriguingly, those patients with EEG abnormalities who responded to AEDs had not responded to initial treatments with first-line drugs like amitriptyline

and/or cyproheptadine in our cohort. This raises the possibility that conducting an EEG upon admission might help guide treatment choices. Regrettably, the literature does not provide precise assessments of these associations, as patients are often grouped together, and none of the studies included, barring case reports, specify whether patients with EEG abnormalities responded to a particular treatment. Similarly, our retrospective study design does not permit the exclusion of potential biases in our analysis.

In summary, our findings indicate a potential merit in considering topiramate administration for patients who did not respond to first-line medication. Further, it suggests the potential viability of topiramate as a primary treatment for specific patient groups, such as those exhibiting EEG abnormalities (eg, spikes or spike waves).

A thorough anamnesis is imperative for CVS patients to identify “risk factors” that could assist in predicting their responses to specific treatments.

Limitations and Strengths

The retrospective nature of our study undoubtedly represents its primary limitation. Furthermore, although most studies included in the review facilitated a consistent synthesis of results, some reported on the general efficacy of a particular medication without quantifying it. This approach can inadvertently result in an overestimation of outcomes. Additionally, both in the literature and in our findings, patients were grouped collectively without considering stratifying risk factors (eg, EEG abnormalities or familial history), preventing a statistical analysis of potential correlations between specific risk factors and responses to particular medications. Moreover, the significant differences in baseline characteristics of patient populations between the cited literature and our cohort can challenge the interpretation of comparisons across different studies. Additionally, our meta-analysis incorporated only 2 studies, both exhibiting high heterogeneity.

Conversely, our research has multiple strengths. Notably, to the best of our knowledge, this is the first study to compare the efficacy of more than 2 distinct medications for CVS concurrently. Furthermore, the various treatment groups are consistent in number, diagnostic approach, and follow-up procedures. Our study also boasts a long-term follow-up (6-24 months) after 12 months of treatment and subsequent discontinuation, a feature not commonly seen in most studies in the literature. Many of these studies limited their follow-up to the months immediately following treatment initiation, potentially leading to an overestimation of medication efficacy, which should ideally be viewed in terms of sustained remission.

Conclusions

A universally accepted and reliable treatment protocol for pediatric CVS is currently lacking. The choice of treatment predominantly depends on the experiences of individual centers and a limited body of literature, which is markedly diverse in terms of design, patients included, and therapeutic regimens.

First and foremost, there is an immediate need to conduct studies that offer deeper insights into the pathogenesis of CVS, facilitating the identification of targeted therapies.

The presently available data, as consolidated in our systematic review, suggest that the response to first-line treatment is predominantly unsatisfactory. AEDs emerge as a potentially safe and effective choice for the prophylactic treatment of pediatric CVS. This preference may be attributed to their action on the suspected epileptogenic nature of the disorder.

Our experience involving 70 pediatric patients contributes to the understanding of the safety and efficacy of treating pediatric CVS with AEDs. Specifically, topiramate proved effective in a substantial proportion (85%) of patients treated, especially in patients exhibiting EEG abnormalities. This suggests potential overlaps in the underlying mechanisms of epilepsy and CVS, and hints at the prospect of future personalized therapeutic strategies.

Further clinical studies, encompassing prospective, retrospective, RCT, and cross-sectional designs, are imperative to assess the efficacy and safety of treatment modalities and to corroborate our findings.

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Author Contributions

R.F. cared for the patients and collected clinical data. B.S. and A.D.C. wrote the article and conducted the literature search. V.G. performed the statistical analysis. B.S. edited the article. R.F., A.P., and M.R. revised the article. All authors have read and approved the final version for publication.

Conflicts of Interest

The authors declare that they have no conflicts of interest associated with this work.

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Data Availability Statement

The data and materials of this case report are available from the corresponding author, upon reasonable request.

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