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PRACTICE GUIDELINE

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition 2025 guidelines for management of cyclic vomiting syndrome in children

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Abstract

Background: Cyclic vomiting syndrome (CVS) is a disorder recognized for its unique intensity of vomiting attacks and inordinate impact on quality of life. There is considerable symptom overlap with migraine. Due to the lack of evidence-based treatment algorithms, current management strategies vary.

Objective: These evidence-based guidelines were formulated to replace prior expert consensus recommendations and to assist patients and clinicians in the management of pediatric CVS.

Methods: Guidelines were developed by a multidisciplinary panel of experts and a patient representative who prioritized questions relevant to medical providers and patients. The guidelines were developed based on systematic reviews with assessment of certainty of the evidence, following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, including indirect evidence from pediatric migraine headache literature to strengthen the recommendations in areas with limited evidence. The panel used GRADE Evidence-to-Decision frameworks to formulate recommendations, which were subject to public comment.

Results: The panel formulated 16 recommendations on the management of pediatric CVS using nonpharmacological and pharmacological approaches. Recommendations were subdivided into abortive (acute) and prophylactic (preventive) interventions.

Conclusions: A strong recommendation was formulated for the use of anti-migraine agents in aborting CVS episodes in patients with a personal or family history of migraine. Conditional recommendations for abortive CVS therapies included the use of oral and intravenous (IV) 5-hydroxytryptamine 3 (5-HT_3) and neurokinin 1 (NK-1) receptor antagonists and early presentation when requiring IV intervention. Conditional recommendations for prophylactic CVS

[Correction added on 9 May 2025, after the first online publication: Headings have been updated.]

CME module may be found at https://learnonline.naspghan.org/jpgn2

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therapies included nonpharmacological treatments such as trigger avoidance, supplements, and various biobehavioral and neuromodulation interventions. Conditional recommendations for prophylactic pharmacological therapies included the use of beta-blockers, NK-1 and 5-hydroxytryptamine 2A (5-HT_{2A}) receptor antagonists, and tricyclic antidepressants. The panel cautioned regarding potential side effects with several pharmacological agents and the use of anti-convulsants only in refractory CVS.

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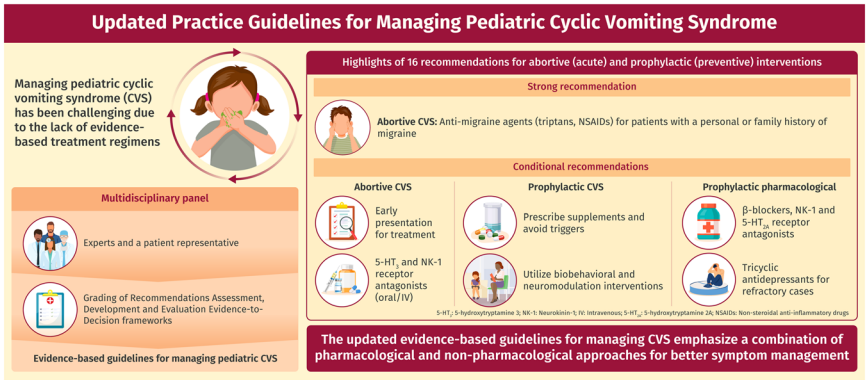

KEYWORDS
GRADE, pediatric cyclic vomiting syndrome, pediatric disorders of gut–brain interaction, pediatric migraine disorder, periodic syndrome, practice guidelines

1 | BACKGROUND AND SUMMARY OF RECOMMENDATIONS

Cyclic vomiting syndrome (CVS) is a disorder prevalent in 1.9%–2.3% of children.[1–4] CVS has considerable impact on quality of life (QoL) and incurs a substantial healthcare burden due to recurrent emergency department (ED) visits, hospitalizations and school-related disability.[5] Affected children experience stereotypical attacks of emesis that closely resemble migraine.[6] There is insufficient knowledge of exact pathophysiology and lack of evidence-based treatment algorithms. Therefore, there is inconsistency and poor consensus among practitioners on the management of pediatric CVS.[7,8] Therapies are typically empiric and/or targeted towards common comorbidities, with substantial focus on pharmacological interventions. The aim of these guidelines was to replace the 2008 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) expert consensus recommendations[9] with evidence-based guidelines that supersede the former recommendations with best practices for the management of pediatric CVS. Note that guidelines on the diagnosis of pediatric CVS are published separately. These NASPGHAN 2025 guidelines are based on updated and original systematic reviews of evidence, conducted by a panel of multidisciplinary experts, following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess certainty in evidence and formulate recommendations.[10–14] The guidelines panel

What is Known

- Cyclic vomiting syndrome (CVS) is a disabling disorder with substantial medical burden
- Management strategies vary considerably
- There are no practice guidelines for evidence-based management of pediatric CVS

What is New

- Evidence supports the use of anti-migraine agents such as nonsteroidal anti-inflammatory drugs and triptans for aborting CVS episodes
- Conditional recommendations for abortive therapies include 5-hydroxytryptamine 3 (5-HT_3) and neurokinin 1 (NK-1) receptor antagonists
- Conditional recommendations for prophylactic therapies include nonpharmacological strategies and drugs such as beta-blockers, NK-1, and 5-hydroxytryptamine 2A (5-HT_{2A}) receptor antagonists and tricyclic antidepressants with attention to potential side effects

followed best practices for guideline development as recommended by the Institute of Medicine and the Guidelines International Network (GIN).[10–12,14] Based on the overlap with migraine and scarcity of high-quality evidence, the panel performed a separate search of pediatric migraine literature to assist in treatment recommendations.

2 | INTERPRETATION OF STRONG AND CONDITIONAL RECOMMENDATIONS

The strength of a recommendation is expressed as either strong (the guideline panel recommends…), or conditional (the guideline panel suggests…) and based on the interpretation outlined in Table 1.[10]

2.1 | Recommendations

A summary of all treatment recommendations and relevant remarks is shown in Table 2.

2.2 | Values and preferences and other considerations

The guideline panel rated the following outcomes as most critical in formulating the guideline recommendations: reduction in frequency, duration, and/or severity of CVS episodes, reduction in ED visits and hospitalizations, improved disability, QoL, and patient satisfaction, as well as avoidance of treatment side effects. The panel also took into consideration resource use and cost-effectiveness, impact on health equity, acceptability, and feasibility of interventions when formulating the recommendations.

3 | INTRODUCTION

3.1 | Aim of these guidelines and specific objectives

The purpose of these guidelines is to provide up-to-date, evidence-based recommendations that supersede the prior 2008 NASPGHAN expert consensus statement[9] on the best management of pediatric CVS. These include pharmacological and nonpharmacological preventive management strategies, lifestyle interventions, abortive and acute care management as well as treatment of comorbid conditions. The overall goal is to reduce the high burden on QoL and substantial healthcare spending associated with pediatric CVS.

The target audience includes patients, general pediatricians, pediatric subspecialists, including gastroenterologists, neurologists, emergency medicine providers, psychologists, and pain specialists, along with other clinicians and policy decision-makers. Policymakers include those involved in developing local, national, or international plans with the goal of reducing the significant costs and functional impairment associated with CVS as

TABLE 1 Interpretation of strong and conditional recommendations.

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

TABLE 2 Summary of recommendations grouped by abortive versus prophylactic and nonpharmacological versus pharmacological therapeutic interventions.

Abortive Interventions (nonpharmacological)

Recommendation 1: The guideline panel suggests using nonpharmacological therapies (i.e., neuromodulation, acupuncture, behavioral interventions) for treatment of acute CVS episodes in children and adolescents who prefer nonpharmacological approaches and/or who experience side effects of pharmacological agents (conditional recommendation, very low certainty in the evidence of effects).

Remarks

While there was very low certainty of evidence, patient preferences for avoiding pharmacotherapy coupled with likely low harm of these interventions may warrant a self-limited trial. Evidence on topical capsaicin use was extrapolated from pediatric CHS and may be considered for CVS given the overlapping clinical features and plausible mechanistic role of the endocannabinoid system in CVS.

Abortive Interventions (pharmacological)

Recommendation 2: The guideline panel recommends using anti-migraine agents (e.g., NSAIDs, triptans) for treatment of acute CVS episodes in children and adolescents with a personal or family history of migraine (strong recommendation, moderate certainty in the evidence of effects).

Remarks

The panel highlighted the close overlap of CVS and migraine and that evidence from pediatric migraine literature strongly supports the use of NSAIDs and triptans as abortive agents *at first onset of symptoms*.

Recommendation 3: The guideline panel suggests using NK-1 receptor antagonist (i.e., aprepitant) for treatment of acute CVS episodes in children and adolescents (conditional recommendation, very low certainty in the evidence of effects).

Remarks

Acute treatment with NK-1 receptor antagonist should be continued for 3 consecutive days. The panel determined that the desirable effects are bolstered by positive clinical experience among the expert panel, possibly mitigating some of the very low-quality evidence. However, a strong recommendation could not be supported due to very low certainty evidence, cost and feasibility issues.

Recommendation 4: The guideline panel suggests using 5-HT_3 receptor antagonists (i.e., ondansetron) for treatment of acute CVS episodes in children and adolescents (conditional recommendation, very low certainty in the evidence of effects).

Abortive Interventions (IV)

Recommendation 5: The guideline panel suggests early presentation and immediate IV fluids for treatment of acute CVS episodes in children and adolescents not responding to outpatient abortive therapies (conditional recommendation, very low certainty in the evidence of effects).

Remarks

Early presentation and immediate IV fluid treatment for aborting a CVS episode is necessary when outpatient therapies failed as opposed to continued watch and wait when not responding to rescue medications. Urgent care centers, infusion centers, or home IV therapy may be alternatives to ED care to provide early intervention and expedited IV access.[a]

Recommendation 6: The guideline panel suggests IV fluid rehydration for treatment of acute CVS episodes guided by patient age, symptom severity, and degree of dehydration (conditional recommendation, very low certainty in the evidence of effects).

Remarks

There is no research evidence regarding the use of D10 versus D5 IV fluids in the setting of acute CVS episodes. No recommendations for specific IV fluids are made due to lack of evidence and potential for delay in treatment if specialized fluids are utilized. IV fluids should be determined by the evaluating physician and provided similarly to other children presenting with acute onset vomiting, with goals of rehydration and alleviation of electrolyte disturbances and ketosis.

Recommendation 7: The guideline panel suggests using an IV NK-1 receptor antagonist (e.g., fosaprepitant) for treatment of acute CVS episodes in children and adolescents not responding to outpatient abortive therapies (conditional recommendation, very low certainty in the evidence of effects).

Recommendation 8: The guideline panel suggests using an IV 5-HT_3 receptor antagonist (e.g., ondansetron) for treatment of acute CVS episodes in children and adolescents not responding to outpatient abortive therapies (conditional recommendation, very low certainty in the evidence of effects).

Prophylactic Interventions (nonpharmacological)

Recommendation 9: The guideline panel suggests trigger avoidance (i.e., proper sleep habits) for preventing CVS episodes in children and adolescents (conditional recommendation, very low certainty in the evidence of effects).

Remarks

Although other potential trigger avoidance (e.g., fasting, dehydration, overexertion, and specific foods) was viewed as potentially relevant for individual patients, there was no substantial research evidence to provide evidence-based guidance.

Recommendation 10: The guideline panel suggests using certain supplements (e.g., coenzyme Q10, riboflavin, magnesium) for preventing CVS episodes in children and adolescents (conditional recommendation, very low to moderate certainty in the evidence of effects).

Remarks

Coenzyme Q10: The panel highlights the importance of shared decision-making and consideration of cost-effectiveness. The likely trivial harm, small desirable benefits, moderate costs, and variable bioavailability warrant a time-limited trial (e.g., 3–6 months) and assessment of response (conditional recommendation, very low certainty in the evidence of effects).

Riboflavin: The panel suggests use of higher, twice daily dosing based on studies in pediatric migraine in a time-limited trial and assessment of response (conditional recommendation, moderate certainty in the evidence of effects).

Magnesium: The panel cautions that certain forms of magnesium (e.g., Magnesium oxide and Magnesium citrate) are more likely to cause loose bowel movements compared to Magnesium glycinate (conditional recommendation, very low certainty in the evidence of effects).

L-carnitine: The panel did not find evidence of efficacy other than when used in combination with coenzyme Q10 and cautioned against use based on concerns for atherosclerosis in animals.

Recommendation 11: The guideline panel suggests using nonpharmacological therapies for preventing episodes and for treating comorbidities in children and adolescents with CVS (conditional recommendation, very low certainty in the evidence of effects).

(Continues)

TABLE 2 (Continued)

Prophylactic Interventions (nonpharmacological)
Remarks These include various psychological therapies, lifestyle management, and treatment adherence interventions.
Prophylactic Interventions (pharmacological)
Recommendation 12: The guideline panel suggests using beta-blockers (e.g., propranolol) for preventing CVS episodes in children and adolescents (conditional recommendation, low certainty in the evidence of effects).
Remarks Propranolol is noted to be widely used across ages, including infants. The panel cautioned for use in patients with reactive airway disease.
Recommendation 13: The guideline panel suggests using 5-HT_{2A} receptor antagonists (e.g., cyproheptadine) for preventing CVS episodes in children and adolescents (conditional recommendation, very low certainty in the evidence of effects).
Remarks The panel cautioned for side effects such as drowsiness and weight gain. The panel noted experience using this drug effectively in children over age 5. Although pizotifen, which is not available in the United States, has similar activity upon 5-HT_{2A} receptors, no relevant data were reviewed.
Recommendation 14: The guideline panel suggests using NK-1 receptor antagonists (e.g., aprepitant) for preventing CVS episodes in children and adolescents (conditional recommendation, very low certainty in the evidence of effects).
Recommendation 15: The guideline panel suggests using TCAs (e.g., amitriptyline) for preventing CVS episodes in children and adolescents (conditional recommendation, very low certainty in the evidence of effects).
Remarks The panel suggests that this medication be reserved for those with more frequent and severe diseases who have not responded to therapies with more favorable side effect profiles. Caution for possible behavioral changes, including suicidality, is indicated in all children and adolescents.
Recommendation 16: The guideline panel suggests not using anticonvulsants (e.g., topiramate or valproate) for preventing CVS episodes in children and adolescents, except for *refractory* CVS (conditional recommendation, very low certainty in the evidence of effects).
Remarks The panel suggests that these medications be reserved for patients with more frequent and severe symptoms who have not responded to therapies with more favorable side effect profiles.

Abbreviations: 5-HT_{2A}, 5-hydroxytryptamine 2A; 5-HT_3, 5-hydroxytryptamine 3; CVS, cyclic vomiting syndrome; IV, intravenous; NK-1, neurokinin 1; NSAID, nonsteroidal anti-inflammatory drug; TCA, tricyclic antidepressant.

[a]See Supporting Information S1: Supplement 1 for a sample ED protocol template.

well as research funding agencies. The recommendations in these guidelines include off-label use of drugs. Off-label drug use remains an important public health concern in children. A policy statement by the American Academy of Pediatrics recommend that drug use be based on sound scientific evidence, expert medical judgment or published literature whenever possible.[15] None of the included drugs or therapies are currently labeled by the US Food and Drug Administration (FDA) specifically for use in children with CVS. However, both nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans are FDA-approved for treatment of pediatric migraine while enteral and intravenous (IV) neurokinin 1 (NK-1) receptor antagonist is FDA- approved for children with chemotherapy-induced nausea and vomiting (CINV). While we did not address multiple intervention comparisons in the systematic reviews and the formulation of recommendations, for rank ordering of treatment recommendations suggested prioritizations are included in Figure 1. This treatment algorithm is based on CVS severity and driven by expert consensus considering available evidence and possible adverse effects.

3.2 | Description of the health problem(s)

CVS is characterized by recurrent, stereotypical attacks of disabling nausea and vomiting that last from a few hours to a week. The prevalence of pediatric CVS is estimated between 1.9% and 2.3% with an incidence of 3.2 per 100,000 children/year.[1–3,16] CVS peaks among school-aged children and often evolves into migraine headaches in adolescent years.[17] A large subset develops chronic symptoms of autonomic dysfunction in adolescence, contributing to confusion in diagnosis and management.[18] Based on a study assessing long-term outcomes, 56% of children experience resolution of CVS during a median follow-up of 29 months (range 6 months to 7 years).[17] CVS often persists into adulthood and even throughout life, resulting in long-term disability and escalating healthcare utilization.[19,20] Transitioning to adult care often presents challenges including identification of a new and knowledgeable clinical team, increased autonomy, requirement for self-management, and challenging psychosocial factors.[21,22] Due to its resemblance to migraine and efficacy of migraine-targeted interventions, CVS has been termed a migraine-equivalent disorder.[23,24] However, it appears to be more heterogeneous with both non-migraine and other subtypes discussed below.[6,25] Cannabinoid hyperemesis syndrome (CHS) is a condition related to prolonged, excessive cannabis use.[26] Legalization of cannabis has resulted in increased prevalence of CHS and may be under-recognized in adolescents, adding to the healthcare burden.[27,28]

CVS is associated with substantial healthcare utilization and costs due to the common need for acute care in ED and hospital settings.[29,30] QoL is significantly impaired due to the severity of attacks and comorbid anxiety, resulting in complete functional impairment and extensive school absences.[5,31]

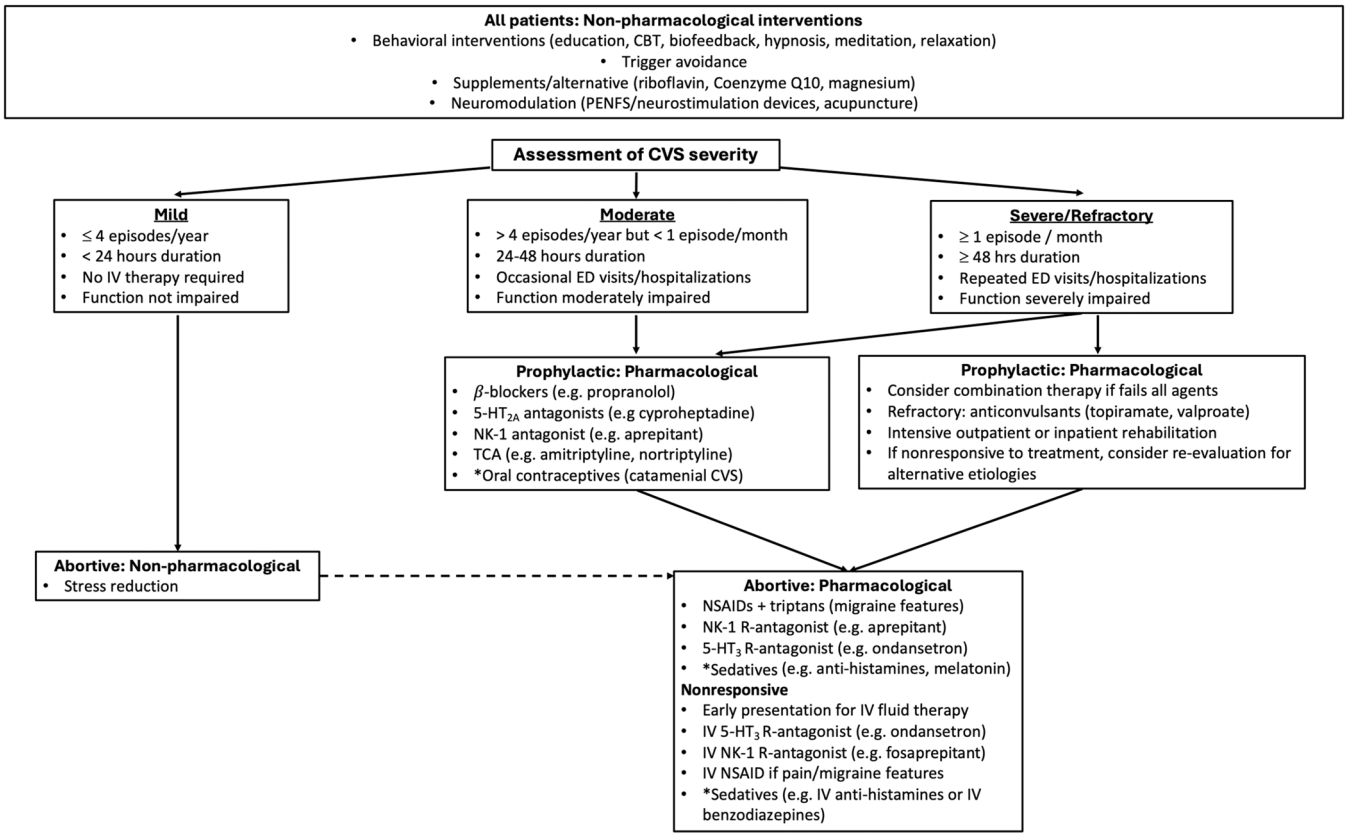

FIGURE 1 Suggested CVS management algorithm based on GRADE evidence and expert consensus recommendations. Suggested severity categorization if majority of each bulleted criterion is met. Mild: symptoms manageable by lifestyle interventions, nonpharmacological approaches, and/or abortive therapies. Moderate: failed lifestyle and abortive interventions; symptoms warrant prophylactic therapy and consideration of treating comorbid conditions. Functioning moderately impaired (frequently missed school). Severe/Refractory: condition worsened by psychosocial factors and difficult to control despite behavioral interventions and pharmacotherapy. Functioning severely impaired (significant missed school/functional disability). CBT, cognitive behavioral therapy; ED, emergency department; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PENFS, percutaneous electrical nerve field stimulation; R, antagonist–receptor antagonist; TCA, tricyclic antidepressant. *Recommendation based on expert consensus.

Comorbid mental health problems and school absences are linked to worse family health-related QoL, highlighting the importance of multimodal management strategies.[32] Emerging data support the need for addressing comorbidities using a biopsychosocial approach and nonpharmacological treatment interventions.[33–36]

3.3 | Description of the target populations

The target population for these guidelines includes children of all ages with symptoms consistent with CVS. The diagnostic considerations and recommended symptom-based criteria are described in a separate document. To date, diagnostic criteria and exclusionary medical workup to strengthen a diagnosis of CVS have been driven by expert consensus recommendations.[9] There is lack of direct evidence in support of any specific diagnostic testing for disorders mimicking pediatric CVS unless suspected by clinical alarm signs. Extensive diagnostic workup such as screening for metabolic conditions, brain pathology, or mucosal GI disease is documented to be of low yield and unlikely to change management for patients who fit symptom-based criteria.[37,38]

Specific CVS subgroups include migraine-related, catamenial, calendar-timed, and Sato-variant CVS.[25] Autonomic nervous system dysfunction is documented in several studies.[39–41] It remains unclear if this is a subset or a common underlying mechanism. Pediatric CHS is considered a related but at this time, a separate category.[26]

3.3.1 | Migraine

A large subgroup of CVS carries a striking resemblance to migraine headaches (pallor, lethargy, photo- and/or phonophobia, etc.), further supported by response to migraine-targeted therapies and shared mitochondrial DNA polymorphisms.[6,42] A personal and/or family history of migraine is described in up to 82% of children with CVS.[6]

A long-term follow-up study demonstrated progression to migraine in 26% of those with pediatric CVS.[17] While there is significant symptom overlap with both migraine and abdominal migraine, CVS is the preferred diagnosis when the predominant symptom is vomiting.[6] Yet, the diagnoses of CVS and abdominal migraine can be difficult to separate. Patients with migraine headaches generally do not experience the severe abdominal pain that is characteristic of abdominal migraine or the intense autonomic response (diaphoresis, salivation, etc.) that is common to CVS.[43]

3.3.2 | Catamenial

A smaller subgroup of those with CVS experience vomiting attacks precipitated by menstrual periods. While poorly characterized, the attacks are thought to be precipitated by a decline in estrogen similar to that in menstrual migraine.[44] Small reports suggest that low-dose estrogen or progesterone birth control pills may be effective in preventing catamenial CVS.[45,46]

3.3.3 | Calendar-timed

A predictable, calendar-type pattern is described in a subset that can predict the start of an emetic cycle within 1–2 days.[25,47] While this subtype may be more refractory to typical therapies, recognition of this predictable pattern can allow for abortive interventions before symptom onset.

3.3.4 | Sato-variant

A smaller subset of patients with CVS displays a clinical and biochemical profile of an overreactive hypothalamic–pituitary–adrenal axis, first described by Sato et al.[48] This subtype manifests elevated levels of adrenocorticotropin hormone, cortisol, antidiuretic hormone, catecholamines, and prostaglandin E_2, consequently presenting with hypertension and profound lethargy.[25] While there is no published data for guidance, electrolyte monitoring is warranted, and episodic hypertension is generally managed by short-acting agents such as lisinopril or labetalol.

3.3.5 | Autonomic dysfunction

Emerging data demonstrate dynamic vagal dysfunction during the inter-episodic wellness phase in children with CVS compared to healthy controls.[41] An underlying autonomic dysregulation is also supported by clinical features during attacks (diaphoresis, listlessness, palpitations, and peripheral vasoconstriction), and a study shows that 40% of pediatric patients with CVS develop chronic dysautonomia during adolescence.[18] While several of these mechanisms may be at play, there are likely interactions of different pathophysiologic processes.

3.3.6 | Cannabinoid hyperemesis syndrome

Based on evidence and guidelines recommendations in adult patients, CHS is considered a probable subtype of CVS that presents after prolonged and excessive cannabis use.[26] Legalization of cannabis across the United States has caused a rise in CHS cases, including in adolescents.[27,49] The nearly identical symptom presentation can result in misclassification of CVS as CHS and underutilization of standard therapies. Topical capsaicin, benzodiazepines, and droperidol or haloperidol have all been proposed as possible treatments for acute CHS episodes.[50] It remains unclear whether standard CVS therapies are effective for CHS or whether topical agents (e.g., capsaicin) used in CHS are equally effective in CVS.[26] Although there is no pediatric data, adult guidelines recommend that CHS patients be offered the same therapies as CVS patients. While the exact duration is unknown, expert consensus suggests cannabis cessation for at least 6 months or a period equivalent to three emetic cycles (with concurrent improvement) can aid in the diagnosis of CHS.[26] Complete cannabis cessation is the only known effective long-term treatment for CHS.

3.4 | Methods

The guideline panel developed and graded the recommendations and evaluated the certainty of supporting research evidence using the GRADE approach.[10,13] The guideline-development process, including panel formation, management of any potential conflicts of interest, internal and external review, and organizational approval, was guided by NASPGHAN policies and procedures derived from the GIN-McMaster Guideline Development Checklist (https://macgrade.mcmaster.ca/resources/gin-mcmaster-guideline-development-checklist/). The guidelines development process was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and GIN, and we report the guidelines using a standardized structure meeting established reporting criteria.[11,12,14,51,52]

3.5 | Organization and panel composition

Project oversight and approval were provided by the NASPGHAN Clinical Care and Quality Committee and NASPGHAN Council, who vetted and approved

individuals to the guideline panel. A guideline methodologist (WW) coordinated the recommendations and guideline-development process according to the GRADE approach. The panel included pediatric specialists in the fields of gastroenterology, emergency medicine, metabolic genetics, psychology, and neurology, who all had clinical and research expertise on the guideline topic. A patient representative was also part of the panel (KA). The panel chair (KK) and vice-chair (BL) were content experts. The panel's work was completed using Web-based tools (www.gradepro.org and www.covidence.org) and online meetings. Supporting Information S2: Supplement 2 presents details of the panel membership and conflict of interest process, funding, selection of questions and outcomes of interest, and evidence review with the preparation of GRADE Evidence-to-Decision (EtD) tables. Supporting Information S3: Supplement 3 presents the literature search strategies for the systematic reviews.

3.6 | Development of recommendations

During online conference calls and communications, the panel developed recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel used a population perspective and reached consensus via discussions and voting on the following: the balance of benefits and harms of the management options, the certainty in the evidence, and the considerations about patients' values and preferences associated with the health outcomes. The guideline panel also considered the extent of resource use associated with alternative management options as well as cost-effectiveness. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or by voting when required (an 80% majority was required for a strong recommendation). The final guidelines, including all recommendations, were reviewed and approved by all members of the panel.

3.7 | Interpretation of strong and conditional recommendations

The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" for conditional recommendations. The guideline summary and Supporting Information S2: Supplement 2 provide GRADE's interpretation of strong and conditional recommendations by patients, clinicians, healthcare policymakers, and researchers.

3.7.1 | Document review

Draft recommendations were reviewed by all members of the panel, revised, and underwent NASPGHAN organization review by stakeholders. The document was revised to address pertinent comments, but no changes were made to the recommendations. On July 7, 2020, the NASPGHAN Council approved the defined guideline-development proposal. On January 3, 2025, the NASPGHAN Clinical Care and Quality Committee and Council approved the submission of the guidelines for publication under the imprimatur of NASPGHAN. The guidelines also underwent peer review by the *Journal of Pediatric Gastroenterology, Hepatology & Nutrition*.

3.7.2 | How to use these guidelines

The NASPGHAN clinical practice guidelines and position papers are evidence-based decision-making tools for managing health conditions. This document is not a disease management requirement or rule and should not be construed as establishing a legal standard of care or as encouraging, advocating for, mandating, or discouraging any particular diagnostic methodology or treatment. Our clinical practice guidelines and position papers should also not be used in support of medical complaints, legal proceedings, and/or litigation, as they were not designed for this purpose. The NASPGHAN clinical practice guidelines and position papers should also not be utilized by insurance companies or pharmacy benefit managers to deny treatment that is deemed medically necessary by a patient's physician. The healthcare team, patient, and family should make all decisions regarding the care of a patient, after consideration of individual specific medical circumstances. While NASPGHAN makes every effort to present accurate and reliable evidence-based information, these clinical practice guidelines and position papers are provided "as is" without any warranty of accuracy, reliability, or otherwise, either express or implied. NASPGHAN does not guarantee, warrant, or endorse the products or services of any firm, organization, or person. Neither NASPGHAN nor its officers, directors, members, employees, or agents will be liable for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, nor consequential damages, incurred in connection with the clinical practice guidelines and/or position papers or reliance on the information presented.

Figure 1 provides a treatment algorithm based on the GRADE recommendations and according to disease severity grading to guide practitioners on how to select the proper interventions. This treatment algorithm also incorporates expert consensus-driven suggestions such as the use of oral contraceptives for

TABLE 3 Recommended treatment interventions and dosages based on systematic review (underlined) and expert consensus.

Abortive Therapy (Nonpharmacological)

Behavioral therapies (stress reduction, biofeedback)

Neuromodulation (acupuncture, peripheral neurostimulation therapies)

Capsaicin: 0.025%–0.075% TOP q 4–6 h prn to abdomen

Abortive Therapy (pharmacological)

Antimigraine/analgesic

Ibuprofen 10 mg/kg PO q 6–8 h (max 600 mg)

Ketorolac 0.5 mg/kg/dose (max 15 mg) IV/intramuscular q 6–8 h, 1 mg/kg/dose (max 10 mg) PO q 8 h

Sumatriptan/naproxen[a] 30/180 mg (20–39 kg), 85/500 mg (≥40 kg) PO

Sumatriptan

Tablets: 25 mg (20–39 kg), 50–100 mg (≥40 kg) PO

Nasal spray: 5–10 mg (20–39 kg), 20 mg (≥40 kg) NS

Subcutaneous injection: 6 mg (≥40 kg) subcutaneously

Rizatriptan[b] 5 mg (<40 kg), 10 mg (≥40 kg) PO

Zolmitriptan[a]

Oral: 2.5 mg (20–39 kg), 5 mg (≥40 kg) PO

Nasal spray: 2.5 mg (20–39 kg), 5 mg (≥40 kg) NS

Almotriptan[a] 6.25 mg (20–39 kg), 12.5 mg (≥40 kg) PO

Frovatriptan (longer ½ life) 2.5 mg (≥40 kg) PO

Naratriptan 1 mg (20–39 kg), 2.5 mg (≥40 kg) PO

Eletriptan 20 mg (20–39 kg), 40 mg (≥40 kg) PO

Antiemetics

Ondansetron 0.15 mg/kg (max 8 mg) per dose q 4–6 h PO/ODT/TOP/IV

Granisetron 40 mcg/kg/dose q 12 h PO (IV q 24 h)

Aprepitant[c] (use as needed or in a 3-day regimen)

80 mg PO (Day 1), 40 mg PO q 24 h (Days 2 and 3) (<15 kg)

80 mg PO q 24 h × 3 days (15–20 kg)

125 mg PO (Day 1), 80 mg PO q 24 h (Days 2 and 3) (>20 kg)

Fosaprepitant 4 mg/kg (max 150 mg) IV Day 1 (aprepitant PO q 24 h Days 2 and 3)

Sedatives

Melatonin 4 mg (<40 kg), 8 mg (≥40 kg) PO × 1

Diphenhydramine 1.25 mg/kg/dose (adolescents 25–50 mg) PO/IV q 6 h

Hydroxyzine 12.5 mg (or 0.5 mg/kg/dose) (<6 years) PO q 6 h, 12.5–25 mg (≥6 years) PO q 6–8 h

Lorazepam 0.05–0.1 mg/kg/dose (adolescents 1–2 mg) PO/IV q 6 h

Diazepam 0.5 mg/kg (2–5 years), 0.3 mg/kg (6–11 years), 0.2 mg/kg (≥12 years) PR × 1

Prophylactic Therapy (Nonpharmacological)

Trigger avoidance

Lifestyle, behavioral and psychological interventions

Neuromodulation

Percutaneous Electrical Nerve Field Stimulation (4–6 week intervention)

Supplements

Riboflavin 100 mg (<40 kg), 200 mg (≥40 kg) PO q 12 h

Coenzyme Q10 100 mg (<40 kg), 200 mg (≥40 kg) PO q 24 h (or divided q 12 h)

Magnesium glycinate/oxide 9 mg/kg/day (adolescents 400 mg) PO nightly

Prophylactic Therapy (pharmacological)

Propranolol 0.5–3 mg/kg/day PO divided q 8–12 h, 10-40 mg (>7 years) PO q 8 h or extended-release 60–80 mg PO q 12 h

Cyproheptadine 0.25–0.5 mg/kg/day PO divided q 8–24 h (max 12 mg/day)

Aprepitant 40/40/40 mg (<40 kg), 80/80/80 mg (40–60 kg), 125/80/80 mg (>60 kg) PO 3×/week

Amitriptyline titrate from 0.5 to 1–1.5 mg/kg/day PO nightly

alternatives: nortriptyline (liquid form), doxepin

Anticonvulsants

Topiramate titrate from 0.5 to 2.0 mg/kg/day PO divided q 12 h (<12 years), titrate from 25 mg PO q 24 h to 50 mg q 12 h (≥12 years)

Valproate 10–40 mg/kg/day (<40 kg) PO divided q 12 h, 250 mg q 12 h (≥40 kg)

Other

Oral contraceptives (catamenial CVS)

Note: Separate sumatriptan and naproxen tablets may be more affordable than combination formulations. A sumatriptan/naproxen 10/60 mg dose was studied but not brought to market (only marketed doses are included). Single-dose aprepitant may be more feasible and sufficient to abort CVS episodes. Extended-release beta blocker formulations may facilitate medication adherence. Once nightly cyproheptadine dosing is recommended in case of sedative side effects.

Abbreviations: CVS, cyclic vomiting syndrome; FDA, Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IV, intravenous; NS, nasal spray; ODT, oral disintegrating tablet; PR, per rectum; TOP, topical.

[a]Approved by the FDA for ages ≥12 years (Note: zolmitriptan nasal spray form).

[b]Approved by the FDA for ages 6–17 years (Note: rizatriptan rapid dissolving tablet form).

[c]Approved by the FDA for chemotherapy-induced nausea and vomiting ages 0.5–17 years.

catamenial CVS and IV sedatives for patients not responding to typical abortive agents. The panel notes that select pharmacologic agents such as alternate antidepressants (e.g., selective serotonin reuptake inhibitors and tetracyclic antidepressants) may be considered based on individual comorbidities.

Table 3 categorizes treatment options and dosage recommendations for abortive and prophylactic interventions.

3.8 | Recommendations

The below sections summarize the research evidence supporting each recommendation, along with specific remarks, subgroup considerations and implementation considerations for each recommendation. Therapies are grouped by abortive interventions for acute episodes and prophylactic management strategies for prevention of CVS attacks.

3.8.1 | Abortive interventions (nonpharmacological): Recommendation 1

The guideline panel suggests using nonpharmacological therapies (i.e., neuromodulation, acupuncture, and behavioral interventions) for treatment of acute CVS episodes in children and adolescents who prefer nonpharmacological approaches or who experience side effects of pharmacological agents (conditional recommendation, very low certainty in the evidence of effects).

Remarks

While there was very low certainty of evidence, patient preferences for avoiding pharmacotherapy coupled with likely low harm of these interventions may warrant a self-limited trial. Evidence on topical capsaicin use was extrapolated from pediatric CHS and may be considered for CVS given the overlapping clinical features and plausible mechanistic role of the endocannabinoid system in CVS.

3.8.1.1 | *Background and summary of the evidence*

There were no studies that directly addressed this question in pediatric or adult CVS. *Indirect evidence from pediatric migraine* studies was considered but limited by variable methodology and interventions assessed. These included a post hoc analysis of an open-label trial[53] and two open-label, cohort studies.[54,55] Included studies assessed effects on pain severity such as pain relief or pain freedom at 1–2 h post-intervention or immediate effects on pain scores as well as any adverse effects. Indirect evidence from one study of CHS was also considered.[56]

3.8.1.2 | *Benefits*

The panel rated the desirable effects as small. The post-hoc analysis of an open-label trial for pediatric migraine using remote electrical neuromodulation with a transcutaneous device to stimulate nociceptive fibers in the upper arm found greater acute pain freedom in intervention vs. standard of care drugs (37% vs. 9%).[53] Two small, open-label pediatric migraine studies using auricular acupuncture and noninvasive vagal nerve stimulation of the neck using a handheld device documented pain freedom in 74% and 40%, respectively.[54,55] A retrospective review of capsaicin (0.025%) cream for CHS found that the capsaicin group (vs. no capsaicin) required less rescue medication (unadjusted odds ratio [OR]: 1.44; 95% confidence interval [CI]: 0.586–0.820, $p < 0.001$) and had a shorter time to discharge (3.72 vs. 6.11 h, $p = 0.001$).

3.8.1.3 | *Harms and burden*

The panel rated any undesirable effects as trivial.

3.8.1.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on imprecision, indirectness in the population and variable interventions assessed, as well as risk of bias in the studies such as due to lack of blinding. The cost of neuromodulation devices was noted to be fairly high ($600) and lack of insurance coverage may limit access. The panel judged that the balance of effects and cost-effectiveness does not favor either the intervention or the comparison and that health equity is probably reduced due to unequal access to therapies. The interventions were judged to be probably acceptable with variable feasibility. The EtD framework is available here.

3.8.1.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence for a net health benefit. The evidence included indirect data from pediatric migraine studies and CHS. While studies support the efficacy of remote electrical neuromodulation, auricular acupuncture, noninvasive vagal nerve stimulation, and topical capsaicin, results and research methodology were variable with most studies limited by small sample sizes, and lack of blinding and control groups.

3.8.1.6 | *Subgroup considerations*

Patients who want to avoid pharmacotherapy and those who cannot tolerate adverse effects of pharmacotherapy may benefit from use of these nonpharmacological interventions despite the lack of higher certainty evidence. Topical capsaicin 0.025% could be considered in a subgroup of CVS patients based on data extrapolated from CHS, especially those with hot bathing behaviors.

3.8.1.7 | *Monitoring and evaluation*

Time-limited trial warranted due to lack of high certainty evidence.

3.8.1.8 | *Research priorities*

The panel recommends blinded trials with control interventions to assess the specific effects of non-pharmacological interventions for acute CVS episodes.

3.8.2 | Abortive interventions (pharmacological): Recommendation 2

The guideline panel recommends using anti-migraine agents (e.g., NSAIDs, triptans) for treatment of acute CVS episodes in children and adolescents with a personal or family history of migraine (strong recommendation, based on moderate certainty in the evidence of effects).

Remarks

The panel highlighted the close overlap of CVS and migraine and that evidence from pediatric migraine literature strongly supports the use of NSAIDs and triptans as abortive agents *at first onset of symptoms*.

3.8.2.1 | *Background and summary of the evidence*

The panel identified three studies that addressed this question in pediatric CVS: a small prospective study and a retrospective study (sumatriptan) as well as a retrospective study in abstract form (NSAIDs).[6,57,58] Three case series/reports of sumatriptan for adult CVS were also considered.[59–61]

Indirect evidence from pediatric migraine was used to inform the recommendation. This included a network meta-analysis of 20 randomized trials assessed as having low risk of bias (19 placebo-controlled) of 14 different drugs for acute treatment of migraine in children and adolescents.[62] Published recommendations and evidence syntheses from guidelines for the acute treatment of migraine in children and adolescents were also reviewed. These guidelines were jointly issued by the American Headache Society and the American Academy of Neurology and reviewed the literature and adverse events in acute treatment trials in pediatric migraine.[63] Outcomes of interest from studies in the meta-analysis included pain freedom and pain relief at 2 h, while practice guidelines also assessed relief of nausea and vomiting at 2 h.

3.8.2.2 | *Benefits*

The panel judged the desirable effects as moderate. In the small ($n = 11$) pediatric CVS study, 82% (9 out of 11) reported some response to sumatriptan (subcutaneous [SC] or intranasal [IN]), and 54% of attacks were classified as responsive. In this and the retrospective CVS study ($n = 214$), a twofold higher response rate was observed in those with a family history of migraine.[6,57] The other retrospective CVS study ($n = 41$) found a higher response (80%) to migraine-targeted interventions (NSAID + prokinetic) compared to standard therapy (40% response) but is limited by only being published in abstract form.[55] In the adult CVS case series, a total of 24 episodes ($n = 5$ patients) were all successfully aborted with sumatriptan IN, SC, or oral (PO) forms.[59–61]

The pediatric migraine network meta-analysis concluded that most triptans and NSAIDs were effective in achieving pain freedom or pain relief.[62] The most effective treatment for complete pain freedom was sumatriptan combined with naproxen sodium PO; efficacy estimates versus placebo: OR (95% CI) 2.92 [1.88–4.54]; $p < 0.001$. Other highly effective agents compared to placebo included zolmitriptan IN (2.12 [1.54–2.93]; $p < 0.001$), sumatriptan IN (1.63[1.25–2.11]; $p < 0.001$), and rizatriptan PO (1.57 [1.23–2.00]; $p < 0.001$). Ibuprofen was the most effective agent to achieve pain relief. Practice guidelines recommendations similarly rated high confidence for pain freedom at 2 h for sumatriptan/naproxen PO and zolmitriptan IN along with moderate confidence for sumatriptan IN and ibuprofen PO.[63] Nausea relief at 2 h was rated as moderate confidence for sumatriptan/naproxen PO and for sumatriptan IN. Vomiting relief at 2 h was rated as moderate confidence for sumatriptan IN. Additionally, one open-label, randomized trial found the efficacy of melatonin for acute migraine attacks but no difference between high- versus low-dose melatonin (<40 kg: 4 mg vs. 1 mg; ≥40 kg: 8 mg vs. 2 mg): 2 h pain relief rate 94% versus 80%.[64]

3.8.2.3 | *Harms and burden*

The panel judged any undesirable effects as small. Ibuprofen was associated with 10% of adverse events similar to placebo (11%). Nasal sumatriptan (5 and 20 mg) was associated with a 23%–32% rate of nonserious adverse events (vs. 6% placebo). Other than for disturbed taste, adverse events were equivalent between sumatriptan IN and placebo. Sumatriptan PO was also similar to placebo. For sumatriptan plus naproxen PO, adverse events were noted in 9%–13% (vs. 3%–8% in placebo) and included nasopharyngitis, jaw/throat/neck tightness, and drowsiness. For zolmitriptan IN, nonserious adverse events were documented in 16% (vs. 9% placebo), mostly due to disturbed taste. Subcutaneous sumatriptan has a substantially higher rate of adverse effects compared to PO and IN formulations.

3.8.2.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as moderate based on low risk of bias randomized trial data in pediatric migraine. The panel noted that indirect migraine data are directly applicable in up to 80% of pediatric CVS (reported rate of migraine family history).[6] The panel determined that the balance of effects favors the interventions and that the interventions are probably cost-effective due to overall low costs and savings from preventing ED visits and hospitalizations. Combination

tablets were noted to be more expensive (~$50/tablet in United States) [65] and along with some forms of triptans, may not be accessible due to lack of coverage. Yet, the panel judged that health equity is probably increased as NSAIDs are widely available over the counter and the combination drugs can be prescribed separately. The interventions were judged to be acceptable and probably feasible. The EtD framework is available here.

3.8.2.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is moderate certainty evidence for a net health benefit. The pediatric migraine evidence was considered sufficiently direct due to the likely substantial overlap in pathophysiology.[66] The panel noted that a family or patient history of migraine is sufficient to warrant therapy with anti-migraine agents administered as early as possible, ideally while symptoms are still mild,[67] during the onset of a CVS attack. While migraine data support pain relief with NSAIDs in isolation, the strongest evidence favors NSAIDs in combination with triptans. Sumatriptan was noted to be effective alone or in combination with naproxen for relief of nausea and vomiting. The treatment was judged to be acceptable to both patients and providers.

3.8.2.6 | *Subgroup considerations*

Evidence on therapeutic response in CVS with migraine features supports sub-classifying CVS patients based on a personal or family history of migraine. Targeting therapy with anti-migraine agents is likely cost-effective in this subset. Patients with migraine features could benefit from a trial of melatonin to induce sleep at the onset of acute episodes.

3.8.2.7 | *Implementation considerations*

The panel recommends early/immediate administration of anti-emetics to facilitate oral administration of NSAID (ibuprofen 10 mg/kg) as a first step, followed by as needed triptan treatment as early as possible at the onset of attack. Trialing a series of drugs in a stepwise approach, different types of triptans and different routes of administration (PO, nasal, SC) are warranted. IN sumatriptan is a particularly effective form of triptan delivery in children with CVS who may not tolerate oral formulations and experience anxiety with SC forms. Dosing considerations:

Sumatriptan + Naproxen sodium PO: 10/60 mg; 30/180 mg; 85/500 mg
Sumatriptan IN: 5/10/20 mg
Zolmitriptan IN: 2.5/5 mg
Rizatriptan PO: If <40 kg: 5 mg; If ≥40 kg: 10 mg
Almotriptan PO: 6.25 mg or 12.5 mg

3.8.2.8 | *Monitoring and evaluation*

NSAIDs (ibuprofen, naproxen, and naproxen/sumatriptan combination) are FDA-approved for children with migraine. Rizatriptan is FDA-approved in children ≥6 years, while naproxen/sumatriptan, zolmitriptan, and almotriptan are approved in children ≥12 years. Caution regarding use of any triptans in patients with underlying cardiac conduction defects such as Wolff–Parkinson–White, or history of uncontrolled hypertension, stroke, or ischemic vascular disease. If patients consistently need to use triptans on >9 days/per month and/or NSAIDs on >14 days per month, their preventive treatment plan may need adjustment. Observational data in adults suggests that frequent use may lead to medication-overuse headache.[68]

3.8.2.9 | *Research priorities*

Clinical trials evaluating the efficacy of triptans with NSAIDs versus placebo for the acute treatment of CVS across different pediatric age groups.

3.8.3 | Recommendation 3

The guideline panel suggests using NK-1 receptor antagonist (i.e., aprepitant) for treatment of acute CVS episodes in children and adolescents (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

Acute treatment with NK-1 receptor antagonist should be continued for three consecutive days. The panel determined that the desirable effects are bolstered by positive clinical experience among the expert panel, possibly mitigating some of the very low-quality evidence. However, a strong recommendation could not be supported due to very low certainty evidence, cost, and feasibility issues.

3.8.3.1 | *Background and summary of the evidence*

The panel found one retrospective study that addressed this question in pediatric CVS ($n = 25$).[69] The study assessed episode frequency, duration, intensity (number of vomits/hour), symptom-free periods, hospitalization rates, school attendance, and risks.

3.8.3.2 | *Benefits*

The panel rated the desirable effects as moderate. The study demonstrated that abortive use of aprepitant resulted in significant improvement in several measures.[69] At 12-month follow-up, 76% of children achieved either complete (12%; no episodes) or partial (64%; ≥50% decrease in both frequency and duration of CVS episodes) responses. The median (interquartile range) number of hospitalizations decreased by more than two-thirds, school attendance increased by 15%, and symptom-free days doubled. Overall, the certainty of these estimated effects is very low owing to the risk of bias due to

retrospective design, non-blinding, and imprecision due to small sample sizes.

3.8.3.3 | *Harms and burden*

The panel rated the undesirable effects as trivial based on no reported side effects.

3.8.3.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on risk of bias and imprecision in effects given the small number of observations. The balance of effects was judged to probably favor the intervention based on moderate benefits and trivial harm. The panel judged that high costs and lack of insurance coverage may limit access to therapy. Yet, moderate cost savings due to the prevention of ED visits and hospitalizations were thought to be cost-effective, probably acceptable, and probably favor the intervention. The impact on health equity and feasibility were judged to be variable as a result of variable insurance coverage and access to the drug across states. The EtD framework is available here.

3.8.3.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence for a net health benefit. Nevertheless, the panel determined that there was a moderate therapeutic benefit and trivial harm, warranting the use of aprepitant for aborting pediatric CVS episodes. While high costs may limit access, the intervention was judged cost-effective due to potential moderate savings from reduced ED visits and hospitalizations. The medication was judged to be probably acceptable to both patients and treating providers.

3.8.3.6 | *Subgroup considerations*

Not applicable.

3.8.3.7 | *Implementation considerations*

Implementation considerations include potential drug interactions including decreased efficacy of oral contraceptives.[70] In those who are unable to tolerate enteral aprepitant in a timely fashion before the onset of emesis or who have not responded to a trial of an IV 5-HT_3 receptor antagonist, a trial of IV fosaprepitant (4 mg/kg; max 150 mg) by itself or added to ondansetron may be appropriate. Although not formally reviewed, the use of short-term IV fosaprepitant and the addition of aprepitant to ondansetron is supported by a body of literature and practice guidelines in pediatric CINV.[71,72] This literature supports the equivalent effect of aprepitant and fosaprepitant,[73] higher efficacy when added to ondansetron compared to ondansetron alone,[71,74] efficacy and safety data as young as 11 months of age.[75–77] Both enteral aprepitant and IV fosaprepitant are approved by the US FDA for CINV prophylaxis and therapy in pediatric patients down to 0.5 years.

3.8.3.8 | *Monitoring and evaluation*

Periodic re-evaluation of the efficacy of abortive therapies is critical to ensure cost-effectiveness, acceptability, and appropriate balance of effects.

3.8.3.9 | *Research priorities*

The panel recommended prospective, double-blind, placebo-controlled trials assessing the efficacy and safety of NK-1 receptor antagonists in pediatric CVS.

3.8.4 | Recommendation 4

The guideline panel suggests using 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists (e.g., ondansetron) for treatment of acute CVS episodes in children and adolescents (conditional recommendation, based on very low certainty in the evidence of effects).

See related recommendation #8 on IV 5-HT_3 receptor antagonists below for summary of the evidence and decision criteria. The EtD framework is available here.

3.8.4.1 | *Implementation considerations*

An individualized CVS Action Plan to optimize both acute and preventive care and guide families in stepwise management during acute attacks may improve outcomes.[78]

3.8.5 | Abortive interventions (IV): Recommendation 5

The guideline panel suggests early presentation and immediate IV fluids for treatment of acute CVS episodes in children and adolescents not responding to outpatient abortive therapies (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

Early presentation and immediate IV fluid treatment for aborting a CVS episode are necessary for patients who have not responded adequately to outpatient therapies, as opposed to a continued "watch and wait" approach. Urgent care centers, infusion centers or home IV therapy may be alternatives to ED care to provide early intervention and expedited IV access. See Supporting Information S1: Supplement 1 for a sample ED protocol template.

3.8.5.1 | *Background and summary of evidence*

The panel reviewed pertinent evidence from one retrospective pediatric CVS study.[79] The study assessed factors that predict hospital admission from the ED during a CVS attack.

3.8.5.2 | *Benefits*

The panel judged the desirable effects to be moderate, considering impact on preventing hospitalization. Factors that predict hospital admission included male sex, age, prolonged wait time in the ED before antiemetic therapy, and delayed (>24 h) presentation to the ED following the onset of symptoms (strongest independent risk predictor).

3.8.5.3 | *Harms and burden*

The panel assessed the undesirable effects as small and mostly related to the invasiveness of IV fluid interventions, which may be traumatic for younger children. This supports the recommendation for utilization of lower-level care services such as urgent care or infusion centers, or home IV therapy to mitigate the potential emotional stress on children and families.

3.8.5.4 | *Decision criteria and additional considerations*

The certainty of these estimated effects is very low owing to the retrospective study design and not controlling for confounders. Aside from delay in presentation to the ED, the impact of various treatments is unclear. The panel agreed the benefits of early presentation outweigh the potential harms and that the benefits probably favor the intervention. The panel noted the possible reduction in overall healthcare costs by preventing hospital admission and judged it to be cost-effective. The intervention was probably acceptable and feasible and would likely facilitate health equity. Cost and access concerns could be addressed using urgent care centers with IV fluid administration. Early intervention would be facilitated by use of an individualized CVS protocol provided to the parents. The EtD framework is available here.

3.8.5.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is low certainty evidence for a net health benefit, including one study. Despite the low certainty of the evidence, the panel judged that there was a moderate therapeutic benefit and small harm, warranting early presentation for IV intervention in patients refractory to abortive therapy. This was deemed cost-effective due to potential cost savings by preventing hospitalizations. The intervention was judged probably acceptable and feasible, particularly with the use of individualized CVS protocols.

3.8.5.6 | *Subgroup considerations*

Patients refractory to outpatient interventions and with historically prolonged episodes requiring repeated IV intervention.

3.8.5.7 | *Implementation considerations*

Cost and physical/emotional burden should be considered when recommending early presentation to the ED. Utilizing lower levels of medical services (urgent care centers, infusion centers, or home IV therapy) may mitigate these potential harms. Due to the invasiveness of IV therapy, the panel advocates individualized risk assessment with the patient and parents.

3.8.5.8 | *Research priorities*

The panel recommended prospective, controlled, multicenter treatment trials on the efficacy of timed early intervention with IV fluids and medications (e.g., if patient does not respond within 2–4 h of receiving other medications at home and continues to have severe symptoms).

3.8.6 | Recommendation 6

The guideline panel suggests IV fluid rehydration for treatment of acute CVS episodes guided by patient age, symptom severity, and degree of dehydration (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

There is no research evidence regarding use of D10 vs. D5 IV fluids in the setting of acute CVS episodes. No recommendations for specific IV fluids are made due to lack of evidence and potential for delay in treatment if specialized fluids are utilized. IV fluids should be determined by the evaluating clinician and provided similarly to other children presenting with acute onset vomiting, with goals of rehydration and alleviation of electrolyte disturbances and ketosis.

3.8.6.1 | *Background and summary of the evidence*

In a prior pediatric expert consensus statement for the management of pediatric CVS in the acute care setting, dextrose 10% (D10) IV fluids were recommended over standard dextrose 5% (D5). However, the guideline panel found no published evidence supporting this practice.

3.8.6.2 | *Benefits*

The panel was unable to judge the desirable effects of D10 versus D5, given the lack of evidence.

3.8.6.3 | *Harms and burden*

The panel judged any undesirable effects as trivial and mostly related to practical considerations and potential delay in care with the administration of specialized rather than standard IV fluids.

3.8.6.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on lack of original research. The panel thought there was probably no impact on equity or costs associated with D10 versus D5 IV fluids. Either is likely to be acceptable, but D10 is probably not feasible. The EtD framework is available here.

3.8.6.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence (no direct evidence) on whether D10 or D5 containing IV fluids should be used in children with an acute CVS exacerbation. Standard practice for IV rehydration should be implemented, with a focus on the rapidity of intervention. Alternate/specific regimens may be used at the discretion of the examining clinician based on clinical and biochemical findings.

3.8.6.6 | *Subgroup considerations*

In patients with known or suspected metabolic disorders, higher glucose infusion rates should be considered.

3.8.6.7 | *Implementation considerations*

There is no evidence to support specialized IV fluids, which may delay care compared to the use of routine IV fluids.

3.8.6.8 | *Monitoring and evaluation*

Patient-specific concerns about hypo- or hyper-glycemia can be evaluated with bedside blood glucose monitoring or other standard techniques in the acute care setting.

3.8.6.9 | *Research priorities*

The panel recommended research evaluating whether dextrose-containing IV fluids are superior to non-dextrose containing IV fluids for children with acute CVS exacerbation.

3.8.7 | Recommendation 7

The guideline panel suggests using an IV NK-1 receptor antagonist (e.g., fosaprepitant) for treatment of acute CVS episodes in children and adolescents not responding to outpatient abortive therapies (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

The panel noted that the desirable effects are bolstered by positive clinical experience among the expert panel, possibly mitigating some of the lack of evidence. However, a strong recommendation could not be supported due to very low certainty evidence, cost, and feasibility issues.

3.8.7.1 | *Background and summary of evidence*

The panel found no studies that addressed this question in pediatric CVS. Fosaprepitant is a highly selective substance P/NK-1 receptor antagonist antiemetic agent, most widely used for highly emetogenic CINV. Fosaprepitant is a phosphorylated, water-soluble prodrug of aprepitant. It is rapidly metabolized into the active aprepitant form and its antiemetic efficacy is fully attributed to aprepitant.[80,81] Therefore, indirect evidence on the enteral form in pediatric CVS was considered.[69] Although not formally reviewed, indirect evidence from pediatric CINV was also used to assist in the decision-making. This included recent randomized, placebo-controlled trials and pediatric CINV clinical practice guidelines.[72–74] Studies assessed the additive effects of fosaprepitant to standard chemotherapy regimens, the comparative effects of IV and enteral forms, and adverse effects.

3.8.7.2 | *Benefits*

The panel judged the desirable effects as moderate. Fosaprepitant as a single IV 150 mg dose is superior to standard anti-emetics and placebo for acute and delayed CINV.[82] A single fosaprepitant dose blocks >90% of NK-1 receptors in the central nervous system for at least 48 h, sufficient to control delayed CINV for 2–5 days.[80,83] A double-blind RCT demonstrated the efficacy of fosaprepitant over placebo when added to standard chemotherapy regimens in children ages 1–12 years.[74] Complete response rates were higher with fosaprepitant versus added placebo during both acute (< 24 h; 86% vs. 60%) and delayed (24–120 h; 79% vs. 51%) CINV phases. A non-randomized, observational study also demonstrated the efficacy of a single dose of IV fosaprepitant (4 mg/kg; max 150 mg) in addition to IV $5HT_3$ receptor antagonist versus $5HT_3$ receptor antagonist alone for both acute and delayed phases of CINV in children ages 0.5–18 years.[76] Clinical practice guidelines for pediatric CINV strongly recommend a triple regimen including fosaprepitant over dual antiemetic regimens based on high-quality evidence.[72] A randomized trial in pediatric CINV demonstrated the superiority of single-dose IV fosaprepitant over oral aprepitant × 3 days in the acute phase but equivalent effects for delayed CINV.[73] Practice guidelines suggest that either formulation can be considered for delayed CINV based on tolerance and resources.[72]

3.8.7.3 | *Harms and burden*

The panel judged the undesirable effects trivial based on no reported serious side effects. In 2018, the US

FDA approved IV fosaprepitant for CINV prophylaxis and therapy in pediatric patients ages 0.5–17 years.

3.8.7.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on risk of bias, indirectness and imprecision in effects. The balance of effects was judged to probably favor the intervention based on moderate benefits and trivial harm. The panel noted high costs ($342–398 for one 150 mg powder injection) but the average cost of $0.2/mg is actually lower than the enteral formulation.[65] However, the added cost of IV access may limit access to therapy. Due to the potential prevention of hospitalizations, the intervention was considered to be cost-effective, probably acceptable, and probably favor the intervention. The panel felt there was variable impact on health equity and feasibility due to variability in access. The EtD framework is available here.

3.8.7.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence for a net health benefit. Nevertheless, the panel determined that there was a moderate therapeutic benefit based on indirect evidence and trivial harm, warranting the use of IV fosaprepitant for aborting pediatric CVS episodes. Indirect evidence from data on the enteral form in pediatric CVS along with equivalent efficacy of IV and enteral forms further support its use. While there are moderate costs due to the need for IV access and potential feasibility issues, it was judged cost-effective due to potential savings from reduced hospitalizations. The medication was to be probably acceptable to both patients and treating providers. Implementation considerations include potential drug interactions with hormonal contraceptives, serotonergic antidepressants, and benzodiazepines.[70,84] In patients unable to tolerate enteral aprepitant in a timely fashion at the onset of emesis or who have not responded to home interventions or a trial of IV 5 HT_3 receptor antagonist, a trial of single-dose IV fosaprepitant by itself or added to ondansetron may be appropriate. Although not formally reviewed, the use of short-term IV fosaprepitant and the addition of aprepitant to ondansetron is supported by a body of literature and practice guidelines in pediatric CINV.[71,72] This literature supports the equivalent effects of aprepitant and fosaprepitant,[73] higher efficacy when added to ondansetron compared to ondansetron alone,[71] and safety data in patients as young as 10 months of age.[75–77]

3.8.7.6 | *Subgroup considerations*

Consider patients who have not responded to home-based interventions and/or standard IV anti-emetics such as 5-HT_3 receptor antagonists.

3.8.7.7 | *Implementation considerations*

Potential drug interactions need consideration although these are less relevant with short-term use in the ED.[70,84] In patients unable to tolerate enteral aprepitant in a timely fashion before the onset of emesis or who have not responded to home-based interventions and/or standard IV anti-emetics, IV fosaprepitant 4 mg/kg (max 150 mg) by itself or added to ondansetron may be appropriate.

3.8.7.8 | *Monitoring and evaluation*

Periodic re-evaluation of efficacy is essential to ensure cost-effectiveness, acceptability, and appropriate balance of effects.

3.8.7.9 | *Research priorities*

The panel recommended trials assessing the efficacy of fosaprepitant for pediatric CVS in the acute care setting.

3.8.8 | Recommendation 8

The guideline panel suggests using an IV 5-HT_3 receptor antagonist (e.g., ondansetron) for treatment of acute CVS episodes in children and adolescents not responding to outpatient abortive therapies (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

The panel noted that ondansetron is readily available, familiar and widely used both in home and ED settings. It is considered probably effective, especially in those patients with lower-intensity attacks. Part of its apparent efficacy may result from treatment bias or placebo effect. Decreasing nausea and vomiting may dampen anticipatory anxiety that can trigger recurrent CVS attacks.[7] It may also facilitate the maintenance of hydration and concomitant oral anti-migraine medication such as NSAIDS, triptans, and sedatives such as diphenhydramine that may facilitate sleep. Alternate formulations, including orally dissolving tablets and topical forms, were noted to be effective based on positive clinical experience by the expert panel. Early intervention with a topical formulation may provide relief of nausea and facilitate tolerance for subsequent oral abortive agents including aprepitant.

3.8.8.1 | *Background and summary of the evidence*

Ondansetron is a potent, highly selective serotonin 5-HT_3 receptor antagonist with established antiemetic efficacy and tolerability in the prevention of pediatric CINV.[85,86] Oral ondansetron is rapidly absorbed from the gastrointestinal tract and has lower bioavailability compared with the IV form.[87] Systematic reviews and meta-analyses conclude that ondansetron (oral or IV) is effective for aborting vomiting induced by acute

gastroenteritis and reduces the need for IV hydration and hospital admission.[88,89] Ondansetron is widely used in the acute management of CVS,[90] where it not only quells vomiting but facilitates retention of other oral medications as part of a multistep treatment plan. There is a paucity of literature on the efficacy of 5-HT_3 receptor antagonists for CVS or migraine. The panel found only one pediatric study that indirectly addressed this question as part of an ED CVS order set.[91] *Indirect evidence from pediatric migraine* based on one retrospective study of acute migraine management was used to assist in the decision-making.[92]

3.8.8.2 | *Benefits*

The panel judged the desirable effects as moderate. The judgment was mostly based on indirect evidence in acute gastroenteritis and one retrospective study in pediatric migraine, demonstrating 90% efficacy in controlling vomiting (formulation not specified).[92]

3.8.8.3 | *Harms and burden*

None of the studies reported on the side effects of 5-HT_3 receptor antagonists. The panel judged the undesirable effects as small, owing to reported side effects of constipation, headache, transaminitis, and QTc interval prolongation, particularly with concomitant use of agents that affect cardiac conductivity.[93–95]

3.8.8.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on indirectness and risk of bias. The balance of effects was judged to probably favor the intervention based on moderate benefits and small harm. Due to the prevention of hospitalizations, it was considered to be cost-effective. It was judged probably acceptable and feasible with probably no impact on health equity. The EtD framework is available here.

3.8.8.5 | *Conclusions and implementation considerations*

The guideline panel determined that while the certainty of evidence is very low, the use of IV ondansetron is supported by its indirect efficacy, broad availability and safety in a diversity of settings. Much of these data also applie to the use of enteral 5-HT_3 receptor antagonists. Despite its widespread use there is a paucity of high-quality evidence as to its effectiveness. The intervention was judged to have neutral effects on health equity and probably be acceptable and feasible, particularly when used within individualized protocols.

3.8.8.6 | *Subgroup considerations*

Patients whose disease is refractory to outpatient interventions and requiring IV intervention.

3.8.8.7 | *Implementation considerations*

Potential drug interactions and risks of QTc interval prolongation need consideration. One study suggests that for most younger patients, dose ranges between 0.13 and 0.26 mg/kg showed no major outcome differences.[96]

3.8.8.8 | *Monitoring and evaluation*

Periodic re-evaluation of efficacy is essential to ensure cost-effectiveness, acceptability, and appropriate balance of effects.

3.8.8.9 | *Research priorities*

The panel recommended trials assessing the efficacy of ondansetron singly or as part of a multi-drug protocol for pediatric CVS in both the home and acute care setting. The panel also recommends head-to-head comparison trials between IV 5-HT_3 receptor antagonists and NK-1 receptor antagonists.

3.8.9 | Prophylactic interventions (nonpharmacological): Recommendation 9

The guideline panel suggests trigger avoidance (e.g., proper sleep habits) for preventing CVS episodes in children and adolescents (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

Although other potential trigger avoidance (e.g., fasting, dehydration, overexertion, and specific foods) was viewed as potentially relevant for individual patients, there was no substantial research evidence to provide evidence-based guidance.

3.8.9.1 | *Background and summary of the evidence*

There were no studies that directly addressed this question in pediatric CVS. *Indirect evidence from pediatric migraine* studies was used to inform the recommendation. This included a cross-sectional, internet-based survey on later school start times[97] and an open-label trial of a sleep hygiene intervention.[98] Indirect evidence from three additional cross-sectional studies assessing lifestyle factors associated with pediatric migraine was also considered.[99–101] Included studies assessed the effects of a sleep hygiene education on headache frequency, duration, and severity [98] while others examined the association of self-reported lifestyle factors (sleep habits, physical activity, and eating habits) on headache frequency.[97,99–101]

3.8.9.2 | *Benefits*

The panel rated the desirable effects as moderate. Later compared to earlier school start time was associated with reduced headache frequency.[97] The open-label trial of sleep hygiene education intervention compared to no

education found improvement in headache frequency (lower number of patients with >1 attack/week) and headache duration over a 6-month period.[98] Two large, cross-sectional studies on lifestyle factors associated higher physical activity with less frequent headaches.[99,100] Sedentary lifestyle was associated with increased odds of recurrent headaches (OR: 1.4; 95% CI: 1.1–1.7).[99] There were mixed findings in cohort studies evaluating the association of eating and sleep habits in relation to headache frequency.[99,101]

3.8.9.3 | *Harms and burden*

The panel rated any undesirable effects as trivial and related only to the potential harms of altering diet without evidence or socioeconomic constraints that prevent lifestyle changes.

3.8.9.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on risk of bias, imprecision and indirectness. The panel judged that the balance of effects probably favors the intervention based on moderate benefits and trivial harm. The interventions were judged as having negligible costs and savings, to probably have variable impact on equity and to probably be both acceptable and feasible. The EtD framework is available here.

3.8.9.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence for a net health benefit. The evidence included indirect data from pediatric migraine studies, mostly evaluating the association of headaches with specific lifestyle practices. Despite these limitations, the panel determined that there were moderate desirable effects in relation to sleep habits (later school start time and sleep hygiene education). While increased physical activity was thought to be potentially beneficial, this has not been tested in clinical studies. No evidence was found to advise patients to avoid certain types of foods, maintain a particular level of hydration, or follow specific diets to prevent CVS episodes.

3.8.9.6 | *Implementation considerations*

The guidelines panel agreed that there are likely moderate effects of sleep hygiene interventions.

3.8.9.7 | *Monitoring and evaluation*

Monitoring the impact of the interventions would be necessary for judging overall effectiveness.

3.8.9.8 | *Research priorities*

The panel recommends prospective trials with rigorous data collection, outcomes monitoring, and credible control interventions to assess the specific effects of sleep hygiene on CVS episode frequency. The mixed findings from cohort studies regarding eating habits also require further clinical study.

3.8.10 | Recommendation 10

The guideline panel suggests using certain supplements (e.g., coenzyme Q10, riboflavin, magnesium) to prevent CVS episodes in children and adolescents (conditional recommendation, based on very low to moderate certainty in the evidence of effects).

1. *Coenzyme Q10*: The guideline panel suggests using coenzyme Q10 for preventing CVS episodes in children and adolescents with a time-limited trial and assessment of response (conditional recommendation, based on very low certainty in the evidence of effects).
2. *Riboflavin*: The guideline panel suggests using riboflavin for preventing CVS episodes in children and adolescents (conditional recommendation, based on moderate certainty in the evidence of effects).
3. *Magnesium*: The guideline panel suggests using magnesium for preventing CVS episodes in children and adolescents (conditional recommendation, based on very low certainty in the evidence of effects).
4. *Vitamin D*: The guideline panel suggests using vitamin D for preventing CVS episodes in children and adolescents as an adjunct therapy in combination with treatments (conditional recommendation, based on very low certainty in the evidence of effects).
5. *L-carnitine*: The guideline panel notes there is insufficient evidence for making recommendations on the use of L-carnitine for preventing CVS episodes in children and adolescents.

Remarks

Coenzyme Q10: The panel highlights the importance of shared decision-making and consideration of cost-effectiveness. The likely trivial harm, small desirable benefits, moderate costs, and variable bioavailability warrant a time-limited trial (e.g., 3–6 months) and assessment of response.

Riboflavin: The panel suggests use of higher, twice daily dosing based on studies in pediatric migraine in a time-limited trial and assessment of response.

Magnesium: The panel cautions that certain forms of magnesium (e.g., Magnesium oxide, Magnesium citrate) are more likely to cause loose bowel movements compared to Magnesium glycinate.

L-carnitine: The panel did not find evidence of efficacy other than when used in combination with coenzyme Q10 and cautioned against use based on concerns for atherosclerosis in animals.

3.8.10.1 | *Background and summary of the evidence*

Coenzyme Q10: The panel found four studies that addressed this question. These included two CVS studies: one retrospective survey study and one case series (in combination with L-carnitine) in pediatric and adult CVS.[102,103] *Indirect evidence from pediatric migraine* included one open-label, prospective study, and one placebo-controlled, double-blind cross-over trial.[104,105] Studies assessed effects on episode frequency, duration, severity, functional disability, and any risks.

Riboflavin: Eight studies addressed this question. There were no data on riboflavin in pediatric CVS except one case series.[106] The other seven were from pediatric migraine. The *Indirect evidence from pediatric migraine* included three retrospective studies [107–109] and four double-blind, placebo-controlled trials.[110–113] Retrospective studies and two RCTs defined treatment response based on ≥50% improvement in migraine attack frequency. RCTs assessed effects on headache frequency, duration, and severity along with risks. One RCT assessed functional disability outcomes.[111]

Magnesium: Four studies addressed this question, all in pediatric migraine. There were no data in pediatric CVS. *Indirect evidence from pediatric migraine* included two open-label, prospective studies, one single-blind, non-randomized study, and one RCT.[114–117] All included studies assessed attack frequency and risks while one open-label study also assessed long-term effects on functional disability, QoL, and mental health. The single and double-blind studies also evaluated headache severity.[116,117]

Vitamin D: Three studies addressed this question, all in pediatric migraine.[118–120] One study was excluded after the panel review noted a 100-fold erroneous dosing raising methodological concerns.[121] There were no data in pediatric CVS. *Indirect evidence from pediatric migraine* included one retrospective study, one open-label observational study and one double-blind, placebo-controlled RCT.[118–120] The two latter studies used vitamin D as an adjunct to pharmacotherapy. Studies assessed headache frequency, severity, duration, and disability.[118,120] Risks were assessed in the RCT.

L-carnitine: A total of three studies addressed this question in pediatric CVS. Two were small case series of which one reported on the combination of L-carnitine, coenzyme Q10 and pharmacotherapy.[103,122] One study compared the effects of high-dose propranolol and low-dose propranolol in combination with L-carnitine.[123]

3.8.10.2 | *Benefits*

Coenzyme Q10: The panel judged the desirable effects as small. Using criteria of ≥50% improvement in outcomes of interest (CVS episode frequency, duration, severity), 31%–59% met this threshold based on one retrospective pediatric CVS study.[102] The adult CVS case series was confounded by the addition of pharmacotherapy in refractory cases.[103]

An open-label study of pediatric migraine was notable for improved headache frequency and disability concurrent with higher coenzyme Q10 blood concentrations.[104] However, the panel noted a high chance of placebo effects based on a randomized trial in pediatric migraine showing non-superiority over placebo.[105] Overall, the certainty of these estimated effects is very low due to risk of bias, non-blinding, indirectness, and imprecision.

Riboflavin: The panel judged the desirable effects as moderate. One small case series in pediatric CVS [106] and several retrospective studies of pediatric migraine suggest the possible efficacy of riboflavin at 400 mg/day.[107–109] Indirect evidence from four RCTs in pediatric migraine lends some support for higher riboflavin dosing. Of these, two smaller RCTs failed to show significant improvement with riboflavin 50 and 200 mg/day,[112,113] while a larger RCT using higher dose riboflavin 400 mg/day demonstrated improved episode frequency, duration, and functional disability in adolescent migraine (12–19 years).[111] A higher dose regimen was also supported by a large RCT comparing lower versus higher doses (100 vs. 200 mg/day) versus placebo in children; 80% on the higher dose achieved ≥50% reduction in attack frequency and duration.[110] Considering these dosing data, and data on riboflavin's absorption and pharmacokinetics,[124,125] the panel suggests a moderate benefit for children with CVS using a higher total daily dose given twice daily (e.g., 200 mg BID).

Magnesium: The panel judged the desirable effects as small. There are no data in CVS. Indirect evidence from a single-blind, pediatric migraine study suggests the possible efficacy of magnesium (400 mg/day) for migraine prevention (reduced attack frequency) and reduced intensity of attacks when combined with over-the-counter analgesics.[116] Two open-label prospective studies showed similar improvement in the frequency of migraine attacks one of which noted improvement in disability, QoL, and mental health.[114,115] However, one large double-blind RCT only demonstrated improved headache intensity.[117] Overall, the certainty of these estimated effects is very low owing to risk of bias, non-blinding, indirectness, and imprecision.

Vitamin D: The panel judged the desirable effects as small. There are no data in CVS. Indirect evidence from pediatric migraine suggests efficacy of 2000 IU daily × 2 months in those with reduced blood levels.[118] An open-label, observational study similarly showed improved headache frequency in patients with reduced blood levels who received vitamin D as an adjunct to tricyclic antidepressant (TCA) (vs. pharmacotherapy alone).[119] A double-blind RCT found that addition of

vitamin D 5000 IU daily versus placebo to topiramate reduced monthly headache frequency and disability but not severity and duration.[120] A response (>50% reduction in monthly headache frequency) was found in 76% of vitamin D versus 54% of placebo group.

L-carnitine: The panel judged there is insufficient evidence on the use of levocarnitine as a single agent for pediatric CVS.

3.8.10.3 | *Harms and burden*

Coenzyme Q10: The panel judged the undesirable effects as trivial based on no reported side effects in any of the included studies.

Riboflavin: The panel judged the undesirable effects as trivial based on few, mild side effects of polyuria, diarrhea, and urine color changes in the included studies.

Magnesium: The panel judged the undesirable effects as trivial based on a few reported side effects. The RCT noted side effects of diarrhea/loose stools in 9% versus 7% in the placebo group. The panel cautioned that certain forms (e.g., magnesium oxide, magnesium citrate) are more likely to cause this.

Vitamin D: The panel judged the undesirable effects as trivial based on no reported side effects.

L-carnitine: The panel judged there is insufficient evidence to determine the risks of levocarnitine in pediatric CVS. The panel cautioned use of L-carnitine based on concerns for atherosclerosis demonstrated in animals. Dietary L-carnitine is highly atherogenic in animals through metabolism to proatherogenic trimethylamine-N-oxide (TMAO) by intestinal bacteria.[126] The association between TMAO and cardiovascular disease has also been demonstrated in humans and pharmacologic L-carnitine supplementation raises TMAO levels in children.[127,128] Therefore, it remains a theoretical concern that long-term L-carnitine supplementation may lead to atherosclerosis in children.

3.8.10.4 | *Decision criteria and additional considerations*

Coenzyme Q10: The panel rated the overall certainty of the evidence as very low due to lack of evidence for critical outcomes, downgrading for serious imprecision, and high risk of bias. The panel judged that given the uncertainty of benefit, the balance of effects was also uncertain. The panel noted the difficulty in comparing studies as absorption may vary by type and source of preparation. Bioavailability studies suggest that liquid emulsion provides greater bioavailability over solid powder formulations and a higher plasma concentration.[129,130] Further, the panel noted that cost and impact on healthy equity vary across the population and that substantial out-of-pocket cost for this supplement needs consideration. Costs range from about $50/month, reaching up to $100–200 depending on dosing and formulation. While generally feasible and acceptable, patients and families may be subject to persuasion of using an intervention that may have low efficacy but potentially high cost. The EtD framework is available here.

Riboflavin: The panel rated the overall certainty of the evidence as moderate based on pediatric migraine studies showing effects based on larger sample sizes, more systematic outcome assessments, and greater rigor in the positive RCTs.[110,111] The panel suggested that the balance of effects probably favors the intervention based on the moderate benefits of a higher dose regimen along with trivial harm. Riboflavin was judged to contribute to moderate savings and increased healthy equity due to low costs and the potential prevention of ED visits and hospitalizations. The supplement was judged acceptable and feasible due to wide availability and low cost ($4/month). The EtD framework is available here.

Magnesium: The panel rated the overall certainty of evidence as very low based on bias due to risk of bias and imprecision in effects. The panel suggested that the balance of effects probably favors the intervention due to trivial harm and indirect positive evidence from single-blind and open-label studies in pediatric migraine as well as one RCT. Magnesium incurs negligible costs and savings based on low out-of-pocket costs and small benefits. The panel judged that the cost-effectiveness probably favors the intervention and that the intervention probably increases health equity based on affordability and small benefits. The supplement was judged acceptable and feasible due to wide availability and low cost ($4/month). The EtD framework is available here.

Vitamin D: The panel rated the overall certainty of evidence as very low based on risk of bias due to non-blinding, imprecision, and effects confounded by other therapies. The panel judged that given the very low uncertainty of evidence, small benefit, and minimal direct evidence, the balance of effects does not favor either the intervention or comparison. Vitamin D incurs negligible costs ($4/month) and savings based on low out-of-pocket costs and overall variable cost-effectiveness. The panel judged that the intervention would be acceptable and feasible but probably would have no impact on healthy equity. The EtD framework is available here.

L-carnitine: The panel concluded there is insufficient data for EtD ratings.

3.8.10.5 | *Conclusions and implementation considerations*

Coenzyme Q10: The panel determined that there is very low certainty evidence for a net health benefit. Despite the very low certainty of the evidence, the panel determined that the trivial harm may warrant a time-limited trial (e.g., 3–6 months), considering the cost-effectiveness and bioavailability of different formulations.

Riboflavin: The guideline panel determined that there is moderate certainty evidence largely from pediatric migraine for a net health benefit. The panel judged that the balance of moderate effects and trivial harm along with low costs warrants a time-limited trial (e.g., 3–6 months), followed by re-evaluation of efficacy.

Magnesium: The guideline panel determined that there is very low certainty evidence for a net health benefit based upon indirect evidence from pediatric migraine. Despite very low certainty of the evidence, the panel determined that the trivial harm and small desirable effects may warrant a time-limited trial (e.g., 3–6 months), considering the type of magnesium formulation.

Vitamin D: The guideline panel determined that there is very low certainty evidence for a net health benefit based on indirect evidence from pediatric migraine using adjunctive vitamin D. The panel suggests the use of vitamin D mainly as an adjunct to other therapies.

L-carnitine: The guideline panel concluded that there is insufficient evidence for formal EtD ratings for use of L-carnitine as a single agent in pediatric CVS. The panel noted a theoretical concern for atherosclerosis with long-term L-carnitine supplementation.

3.8.10.6 | *Subgroup considerations*

Coenzyme Q10: May benefit patients with specific comorbidities such as chronic fatigue/poor stamina and altered mitochondrial bioenergetics,[131] those with low coenzyme Q10 blood concentrations or those not tolerating or accepting pharmacotherapy.

Riboflavin: Patients with migraine-associated CVS may have greater benefit.

Magnesium: Patients with migraine-associated CVS may have some benefit.

Vitamin D: Patients with reduced blood levels and migraine-associated CVS may benefit.

3.8.10.7 | *Implementation considerations*

Coenzyme Q10: Consider time-limited trial based on cost-effectiveness and patient symptomatology.

Riboflavin: Consider time-limited trial and patient characteristics. Suggested dosing: 100 mg (<40 kg), 200 mg (≥40 kg) PO q 12 h.

Magnesium: Consider time-limited trial based on patient characteristics and type of formulation used. Suggested dosing: 9 mg/kg/day (adolescents 400 mg) PO nightly.

Vitamin D: Consider time-limited trial based on patient characteristics and reduced blood levels.

All supplements: Based on the natural course of pediatric CVS, periodic re-evaluation of the efficacy of long-term prophylactic therapies is critical to ensure cost-effectiveness, acceptability, and appropriate balance of effects. The panel cautioned for variability in the quality of supplements and, when available, recommended referring to quality control programs such as the United States Pharmacopeia for quality control information.

3.8.10.8 | *Monitoring and evaluation*

Dose titration based on Coenzyme Q10 blood concentration may be warranted based on indirect migraine data.[104]

3.8.10.9 | *Research priorities*

The panel recommended prospective, double-blind placebo-controlled trials assessing the efficacy and safety of these supplements in pediatric CVS. Specific to certain supplements (coenzyme Q10 and vitamin D) is the potential relevance of therapeutic blood levels to treatment outcomes. Efficacy and dose–response of different types of formulations (coenzyme Q10, riboflavin, and magnesium) also need further study.

3.8.11 | Recommendation 11

The guideline panel suggests using nonpharmacological therapies for preventing episodes and for treating comorbidities in children and adolescents with CVS (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

These include various psychological therapies, lifestyle management and treatment adherence interventions.

3.8.11.1 | *Background and summary of the evidence*

One case series (psychological intervention) and an open-label prospective study (percutaneous electrical nerve field stimulation [PENFS]) in pediatric CVS [47,132,133] and one RCT in adult CVS (meditation) addressed this question.[33] All studies assessed the effects on CVS episode frequency. Impact on secondary outcomes (e.g., sleep, QoL, anxiety, depression, fatigue, and coping) was addressed by one or more of the studies. *Indirect evidence from pediatric migraine* on a variety of biobehavioral therapies further informed the recommendation. This included different psychological interventions and also treatment adherence and lifestyle management interventions. Data were extracted from seven systematic reviews and/or meta-analyses of RCTs of various nonpharmacological interventions [134–140] and a pilot study of a self-management tool for pediatric migraine.[141] Literature on the impact of treating comorbidities, particularly psychiatric symptoms common to CVS,[142] was reviewed. No studies were identified that directly addressed the impact of treating comorbidities on headache/CVS episodes. In studies that reported on treatment acceptability, there was moderate to high acceptability and feasibility.[143–149] The remotely delivered interventions and digital self-management tool for pediatric headaches reported positive participant satisfaction.[134,141] Challenges with recruitment and

adherence with nonpharmacological therapies are reported, with >20% attrition rate in some studies.[33,150]

3.8.11.2 | *Benefits*

The panel rated the desirable effects as moderate. The case series of a psychological intervention resulted in symptom resolution in all at 1-year follow-up.[132] The open-label study using 6 weeks of PENFS in pediatric CVS reported decreased episode frequency and duration at 4–6 months follow-up, which correlated with improvement in trait anxiety.[47,133] There was a median duration of response of 113 days. PENFS was associated with improvement in other comorbidities such as sleep and several QoL measures.[133] The RCT of meditation and care coordination in adult CVS did not demonstrate reduction in CVS episodes, but was associated with improvements in multiple psychosocial domains.[33]

The meta-analyses/systematic reviews in pediatric migraine included multiple nonpharmacological interventions (e.g., cognitive behavioral therapy [CBT], relaxation training, coping skills, biofeedback, hypnosis, meditation, music therapy, and education), delivered individually or in combination.[135,137–139] Treatment was delivered in person, in groups, or through self-administration (internet, written/audio materials, or phone app).[138,141,136,138] Multiple meta-analyses demonstrated efficacy of CBT, relaxation training, biofeedback and stress management for the primary outcome of reduced headache frequency, duration or intensity.[135,136,138–140] One meta-analysis demonstrated large effect sizes for two self-administered interventions: relaxation and stress management (standardized mean difference [SMD]: 2.50) and biofeedback and stress management (SMD: 1.81).[138] A systematic review of 10 RCTs of nonpharmacological migraine interventions (e.g., CBT and music therapy) showed significant long-term within-group reductions in headache frequency, intensity, or reduction but no significant between-group differences.[137] Another RCT reported headache improvement with meditation versus hypnotherapy versus relaxation training with a combined 47% response rate at 9 months but no group differences.[150] In many studies, specific treatment components associated with improved outcomes could not be delineated due to different interventions being compared or multiple interventions provided concomitantly.

Secondary treatment outcomes (e.g., QoL, disability, sleep, anxiety, and depression) were not consistently reported in meta-analyses.[135,137,139,140] In two systematic reviews with limited data, no benefits were found for disability, anxiety, or depression.[134,136] In contrast, improvements in disability were reported by six pediatric migraine studies of nonpharmacological therapies (three RCTs, two open-label trials, and one case series) [141,144,149,151–153] and one adult CVS RCT.[33] Several studies in both CVS and migraine, including RCTs, have documented improved attacks and concurrent improvement in comorbidities such as depression and anxiety.[132,133,150–152,154] However, the panel noted that these associations between comorbidities and treatment outcomes are only correlational.

3.8.11.3 | *Harms and burden*

The panel rated any undesirable effects as trivial, related only to access, time, and cost burden, all mitigated by the increased availability via Internet and phone applications. No adverse events were found in the studies that reported on these interventions.[47,133,140,145,149,150]

3.8.11.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on imprecision, and indirectness variability of interventions. The panel judged that the balance of effects probably favors the interventions based on moderate benefits and trivial harm. The interventions were judged to have variable costs and savings and probably have no impact on equity. The EtD framework is available here.

3.8.11.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence for a net health benefit due to limited data in pediatric CVS. Indirect but robust pediatric migraine evidence demonstrated moderate desirable effects of nonpharmacological interventions on attack frequency, intensity, or duration and limited evidence for secondary outcomes (e.g., disability, QoL, and psychiatric comorbidities). While a wide range of nonpharmacological therapies from biobehavioral to neuromodulation devices note a positive impact on attack frequency and comorbidities, these associations are only correlational.

3.8.11.6 | *Subgroup considerations*

Nonpharmacological interventions should be considered for all pediatric CVS patients.

3.8.11.7 | *Implementation considerations*

Feasibility (cost, access), acceptability, and treatment adherence warrant consideration.

3.8.11.8 | *Monitoring and evaluation*

Monitoring treatment adherence and the long-term impact of the interventions is necessary to judge efficacy.

3.8.11.9 | *Research priorities*

The panel recommends prospective RCTs of nonpharmacological interventions, use of additional outcome variables (QoL, disability, and psychiatric comorbidities), identification of individual differences relevant to specific therapies, and further development of remote and self-administered therapies (phone/internet applications).

3.8.12 | Prophylactic interventions (pharmacological): Recommendation 12

The guideline panel suggests using beta-blockers (e.g., propranolol) for preventing CVS episodes in children and adolescents (conditional recommendation, based on low certainty in the evidence of effects).

Remarks

Propranolol is noted to be widely used across ages, including infants. The panel cautioned for use in patients with reactive airway disease.

3.8.12.1 | *Background and summary of the evidence*

The panel found 18 studies that addressed this question, of which 17 evaluated the effects of propranolol. These included four retrospective studies,[6,8,155,156] two prospective, observational studies,[157,158] and two randomized, uncontrolled trials in pediatric CVS.[115,159] *Indirect evidence from pediatric migraine* were also included based on 10 studies. These included a systemic review and network analysis of seven trials on propranolol,[160] one randomized, unblinded, uncontrolled trial on metoprolol,[161] one single blind RCT [115] and a double blind RCT on propranolol.[162] All except three studies assessed effects on episode frequency. The randomized trial in CVS also assessed the effects on episode severity.[159] In addition to episode frequency, trials in pediatric migraine assessed effects on headache duration, severity, and migraine-associated disability. Risks were assessed in all included studies except one descriptive CVS study.[6]

3.8.12.2 | *Benefits*

The panel rated the desirable effects as moderate. Retrospective studies showed high long-term efficacy of propranolol (57%–81%) when used as a first-line agent for pediatric CVS.[155,156] Two prospective, observational studies in pediatric CVS showed a high response rate to propranolol (77%–93%).[157,158] A larger ($n = 81$) randomized (uncontrolled and unblinded) trial demonstrated long-term effects of propranolol 1 mg/kg/day on both frequency and severity of CVS attacks with a 92% response rate and superiority over amitriptyline (53% response rate).[159] Another randomized (uncontrolled) trial ($n = 76$) showed the efficacy of both high-dose (titrated to 2 mg/kg/day) propranolol and low-dose (0.5 mg/kg/day) propranolol + L-carnitine in 71% and 91%, respectively (no significant group differences).[123]

Indirect evidence from a network meta-analysis in pediatric migraine demonstrated medium-sized efficacy of propranolol over placebo (SMD of 0.60 [95% CI: 0.03–1.17]) based on seven placebo-controlled, randomized trials and $n = 297$ patients.[150] However, the 95% CI was nonsignificant. One double-blind, RCT did not demonstrate the superiority of propranolol 1–3 mg/kg/day over placebo but was similarly underpowered.[162]

3.8.12.3 | *Harms and burden*

The panel rated the undesirable effects as trivial based on several studies reporting none or few side effects. The network meta-analysis of pediatric migraine reported no adverse events of propranolol compared to placebo.[160] One retrospective study ($n = 22$) reported side effects of drowsiness, nervousness, and dizziness in three patients.[156]

3.8.12.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on the risk of bias including non-blinding, indirectness, and imprecision in effects. The panel judged that the balance of effects probably favors the intervention based on moderate benefits and trivial harm. The intervention was thought to contribute to moderate savings, and the cost-effectiveness probably favors the intervention due to the low cost and prevention of ED visits and hospitalizations. The panel found that the medication would probably increase health equity and that it was acceptable and feasible due to wide availability and low cost. The EtD framework is available here.

3.8.12.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence for a net health benefit. The body of evidence included 18 studies of which the more rigorous, randomized controlled trials were indirect evidence from pediatric migraine. Despite the very low certainty of the evidence, the panel thought there was a moderate therapeutic benefit and trivial harm, warranting the use of propranolol for preventing pediatric CVS episodes. The generic form was deemed cost-effective and projected to incur moderate savings by preventing ED visits and hospitalizations. The medication was acceptable to both patients and treating providers.

3.8.12.6 | *Subgroup considerations*

Patients with migraine-associated CVS may have greater benefits based on indirect evidence extracted from pediatric migraine.

3.8.12.7 | *Implementation considerations*

Consider use in children who have more frequent and/or severe CVS and have not responded to lifestyle modifications, nonpharmacological interventions, and abortive medications. If it becomes difficult to adhere to multiple doses per day regimen, extended-release formulations may be considered. Cardio-selective beta-blockers such

as metoprolol are less likely to cause bronchoconstriction and may be preferred in some patients.

3.8.12.8 | *Monitoring and evaluation*

In children who do not respond to standard doses (e.g., propranolol 1 mg/kg/day divided BID), higher doses (up to 3 mg/kg/day) can be considered while monitoring for bedtime bradycardia and for any adverse effects. Based on the natural course of pediatric CVS, periodic re-evaluation of the efficacy of long-term prophylactic therapies is critical to ensure cost-effectiveness, acceptability, and appropriate balance of effects.

3.8.12.9 | *Research priorities*

The panel recommended prospective, double-blind placebo-controlled trials assessing the efficacy and safety of beta-blockers in pediatric CVS.

3.8.13 | Recommendation 13

The guideline panel suggests using 5-hydroxytryptamine 2A (5-HT_{2A}) receptor antagonists (e.g., cyproheptadine) for preventing CVS episodes in children and adolescents (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

The panel cautioned against side effects such as drowsiness and weight gain and noted experience using this drug effectively in children over age 5. Although pizotifen, which is not available in the United States, has similar activity upon 5-HT_{2A} receptors, no relevant data was reviewed.

3.8.13.1 | *Background and summary of evidence*

The panel found 8 studies that addressed this question. These included one RCT (non-placebo controlled) and five retrospective series in pediatric CVS.[6,8,17,38,163,164] *Indirect evidence from pediatric migraine* included one retrospective series in children and one controlled trial in adolescents and young adults.[165,166] All included studies assessed the effect on episode frequency, duration, and adverse effects.

3.8.13.2 | *Benefits*

The panel rated the desirable effect to be moderate. Using criteria of ≥50% improvement in outcomes of interest (episode frequency and duration), 55%–75% (retrospective to randomized) met this threshold. In pediatric migraine, 83% had a positive response.

3.8.13.3 | *Harms and burden*

The panel rated the undesirable effects, including sedation, appetite stimulation, and weight gain, as small but present in up to 21% of children.[8] The panel suggests caution in those overweight or concerned about weight gain.

3.8.13.4 | *Decision criteria and additional considerations*

Overall, the certainty of these estimated effects is very low owing to the risk of bias including non-blinding, indirectness, imprecision, and concerns about the study cohort in the single randomized trial. The panel also noted a high chance of placebo effects previously observed in pediatric CVS.[167] The panel judged the balance of moderate desirable effects and small undesirable effects to favor its use. The panel noted that low cost ($16–30/month) and potential reduction in health costs (ED visits and hospitalizations) rendered this a cost-effective treatment that would be acceptable and accessible to most patients and probably facilitate health equity. The EtD framework is available here.

3.8.13.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence (five studies with direct and three with indirect evidence) for a net health benefit. The panel determined that there was a moderate therapeutic benefit and small harm, warranting its use for preventing CVS episodes. The medication with its low cost was judged cost-effective due to potential moderate savings from reduced ED visits and hospitalizations. The medication was judged to be accessible, feasible, and acceptable to most patients and treating providers.

3.8.13.6 | *Subgroup considerations*

The impact of adverse effects may be perceived as greater in adolescents where weight gain considerations may be stronger.

3.8.13.7 | *Implementation considerations*

The side effects, including sedation, appetite increase, and weight gain, should be disclosed before initiating therapy. The daily dosage may be administered all at once at bedtime.

3.8.13.8 | *Monitoring and evaluation*

Follow-up of therapeutic and adverse effects should take place at least every 6 months.

An alternative agent, pizotifen, is not available for use in the United States. The panel noted the possibility of tachyphylaxis with long-term use of cyproheptadine. There were no data to suggest that tachyphylaxis occurs when used prophylactically to treat CVS and there was potential concern that a gap in administration (if cycling off to avoid tachyphylaxis) could lead to a breakthrough episode.

3.8.13.9 | *Research priorities*

The panel recommended prospective, controlled, multicenter treatment trials on efficacy that control for the substantial placebo effect in CVS [167] and the natural history of disease resolution.[168] Specific questions to be studied include the relationship between dose/kg and weight gain and incidence of tachyphylaxis over time.

3.8.14 | Recommendation 14

The guideline panel suggests using NK-1 receptor antagonists (e.g., aprepitant) for preventing CVS episodes in children and adolescents (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

The panel noted that the desirable effects are bolstered by positive clinical experience among the expert panel, possibly mitigating the very low-quality evidence. However, a strong recommendation could not be supported due to very low certainty evidence, cost, and feasibility issues.

3.8.14.1 | *Background and summary of the evidence*

The panel reviewed two retrospective studies, one each in pediatric and adult CVS, that addressed this question (total $n = 95$).[69,169] The studies assessed episode frequency, duration, and intensity along with symptom-free periods, ED visits, hospitalization rates, school attendance, and risks.

3.8.14.2 | *Benefits*

The panel rated the desirable effects as moderate. Both studies demonstrated that the use of aprepitant two or three times per week for prophylaxis resulted in significant improvement in several essential outcomes, including episode frequency, duration, intensity, symptom-free periods, hospitalization rates, and school attendance.[69,169] At the 12-month follow-up, 82% of children achieved either partial or complete treatment response. In the adult study, 71% had a global response (>50% improvement in symptoms and/or reduction in ED visits/hospitalizations).

3.8.14.3 | *Harms and burden*

The panel rated the undesirable effects as trivial based on few (hiccups, fatigue, increased appetite, headache) and no serious side effects. In the pediatric study, one patient (6%) discontinued the drug due to reported migraine, which may have been related to CVS rather than the drug.

3.8.14.4 | *Decision criteria and additional considerations*

The panel rated the overall certainty of the evidence as very low based on risk of bias, indirectness, and imprecision in effects due to a small number of observations. The balance of effects was judged to probably favor the intervention based on moderate benefits and trivial harm. The panel noted that high costs and lack of insurance coverage may limit access to therapy (27% were unable to access the medication in the adult study).[169] Yet, moderate cost savings due to the prevention of ED visits and hospitalizations were judged to be cost-effective and probably favor the intervention. The impact on health equity was judged to be variable as a result of variable insurance coverage and access to the drug across states. The intervention was judged to be probably acceptable with variable feasibility due to the high costs. The EtD framework is available here.

3.8.14.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence for a net health benefit. The body of evidence included only two retrospective studies. Despite the low certainty of evidence, the panel determined that there was a moderate therapeutic benefit and trivial harm, warranting the use of aprepitant 3×/week for prevention of pediatric CVS episodes. While high costs may limit access, the intervention was judged cost-effective due to moderate savings from reduced healthcare utilization. The medication was judged to be probably acceptable to both patients and treating providers.

3.8.14.6 | *Subgroup considerations*

Panel experience indicated that aprepitant may be useful for intermittent short-term prophylaxis in children with regular, predictable episodes (calendar-timed CVS) where a 3-day dose regimen can be initiated a day or two before the predicted onset.

3.8.14.7 | *Implementation considerations*

Implementation considerations include potential drug interactions including decreased efficacy of oral contraceptives.[70]

3.8.14.8 | *Monitoring and evaluation*

Periodic re-evaluation of the efficacy of long-term prophylactic therapies is critical to ensure cost-effectiveness, acceptability and appropriate balance of effects.

3.8.14.9 | *Research priorities*

The panel recommended prospective, double-blind placebo-controlled trials assessing the efficacy and safety of NK-1 receptor antagonists in pediatric CVS.

3.8.15 | Recommendation 15

The guideline panel suggests using TCAs (e.g., amitriptyline) for preventing CVS episodes in children and adolescents (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

The panel suggests that this medication be reserved for those with more frequent and severe disease who have not responded to therapies with more favorable side effect profiles. Caution for possible behavioral changes, including suicidality, is indicated in all children and adolescents.

3.8.15.1 | *Background and summary of evidence*

The panel reviewed pertinent evidence from three controlled (no placebo) trials ($n = 149$) [159,170,171] and eight retrospective series ($n = 251$) in pediatric CVS.[6,8,38,102,103,155,164,172] Indirect evidence included four retrospective series in adult CVS ($n = 410$).[173–176] *Indirect evidence from pediatric migraine* included two RCTs.[165,177] All included studies assessed the effect on overall improvement (either complete remission or substantial, or ≥50% improvement in either episode frequency or duration), emergency visits, or adverse effects.

3.8.15.2 | *Benefits*

The panel judged the desirable effect to be moderate. Using the common criteria of ≥50% improvement as definition of response (complete or partial), 57% of pediatric and 81% of adult CVS patients responded. The indirect (moderate certainty) evidence from pediatric migraine was conflicting where 89% responded in one study and 52% responded in another which was not significant over placebo.[165,177] Where reported, there were also significant reductions in episode frequency and duration.

3.8.15.3 | *Harms and burden*

The panel assessed the undesirable effects, including sedation, constipation, and weight gain, as moderate. In one survey study for specific side effects, there was a moderate-to-high rate of adverse effects (50%) and a substantial number of children who consequently stopped TCAs (19%).[102] A smaller, retrospective study ($n = 14$) observed drowsiness and weight gain in 28%.[8] Similarly, 26% of adults had to terminate TCA therapy due to adverse effects.[178] Although uncommon, there is a risk of QTc prolongation and TCAs should be avoided when there is a pertinent family history of QT prolongation or sudden cardiac death. There is a black box warning regarding suicidal ideation for all children, potentially higher in those with psychiatric comorbidity.[179] Cognitive dysfunction is found with amitriptyline and other anticholinergic agents documented both short- and long-term in adults.[180,181] The risk to children and adolescents on long-term amitriptyline therapy is unknown.

3.8.15.4 | *Decision criteria and additional considerations*

The certainty of these estimated effects is very low owing to the high risk of bias due to single observers and non-blinding, indirectness, imprecision, and concerns about the study cohort in the pediatric randomized trials. The panel also noted a high rate of placebo effects previously observed in pediatric CVS trials as well as the potentially confounding natural history of disease with resolution beginning in early adolescence.[168,182] The panel judged the balance of moderate desirable effects and moderate undesirable effects to favor its use in children who had not responded to other regimens, that is, that TCAs be considered secondary/alternative preventive treatment. The panel noted that low cost ($7–11/month) and potential reduction of healthcare costs (ED visits and hospitalizations) rendered this a cost-effective treatment that would be acceptable to some and accessible to most patients, and probably facilitate health equity. The EtD framework is available here.

3.8.15.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence (10 studies with direct and 6 studies with indirect evidence) for a net health benefit. The panel determined that there was a moderate therapeutic benefit and moderate harm, reserving its use for those with frequent and severe episodes who had failed treatments with more favorable side effect profiles. The low cost medication was judged cost-effective due to potential moderate savings from reduced ED visits and hospitalizations. The medication was judged to be accessible, feasible, and acceptable to some patients and treating providers.

3.8.15.6 | *Subgroup considerations*

The panel suggests that amitripyline be reserved for children with more frequent and more severe (ED visits and hospitalizations) disease who have already tried lifestyle modifications, nonpharmacological interventions, abortive medications, and other prophylactic agents with more favorable side effect profiles. This medication may be more effective in those with a family or personal history of migraine, but that should not preclude a trial in nonmigraine-associated CVS.[183]

3.8.15.7 | *Implementation considerations*

The side effects, sedation, constipation, weight gain, and black box warning of suicidal ideation, should be fully disclosed to the parents before initiating therapy.[184] An ECG with calculated QTc should be considered before starting, with any dose titration/addition of other QTc-prolonging agents and confirmed <460 ms.[185] Caution for risk of serotonin syndrome is warranted in children treated with multiple psychotropic agents. The panel advocates individualized risk assessment with the patient and parents who may find these adverse effects beyond their level of risk tolerance.

3.8.15.8 | *Monitoring and evaluation*

Follow-up of therapeutic and adverse effects should take place at least every 6 months. In patients who do not respond to standard doses (e.g., 1.0–1.5 mg/kg/day),

higher dosing may be considered by incrementally increasing the dose, monitoring the QTc interval on ECG, and obtaining trough levels to determine whether a therapeutic level (total amitriptyline blood concentration 93–140) [186] has been achieved. Steady state blood concentration of TCAs have been found to correlate with both adverse effects and P450 genotype in patients with depression [187,188] and Clinical Pharmacogenetic Implementation Consortium Guidelines recommend dosing based on P450 genotype.[189] In patients who experience side effects at standard doses or fail to respond at higher than standard doses, P450 metabolizer status (CYP2C19 and CYP2D6) may clarify the problem. In a study of CYP2C19 status in adult patients with CVS, 4% were poor metabolizers at higher risk of side effects, and 43% were ultrarapid metabolizers, a risk of being unable to achieve a therapeutic level.[190]

3.8.15.9 | *Research priorities*

The panel recommended prospective, controlled, multicenter treatment trials on efficacy that control for the substantial placebo effect in CVS [167,182] and the natural history of disease resolution.[168] Specific questions include the relationship between weight-based dose, therapeutic blood levels, CYP microsomal genetic profile, and treatment outcomes, both upon clinical improvement and cognitive function.

3.8.16 | Recommendation 16

The guideline panel suggests not using anticonvulsants (e.g., topiramate or valproate) for preventing CVS episodes in children and adolescents, except for *refractory* CVS (conditional recommendation, based on very low certainty in the evidence of effects).

Remarks

The panel suggests that these medications be reserved for patients with more frequent and severe symptoms who have not responded to therapies with more favorable side effect profiles.

3.8.16.1 | *Background and summary of evidence*

The panel reviewed evidence from one controlled trial with topiramate ($n = 36$),[171] one prospective, open-label trial ($n = 13$),[191] and three retrospective series in pediatric CVS ($n = 43$), one as part of a systematic review and meta-analysis.[8,156,192] Indirect evidence was obtained from two retrospective adult series CVS (n = 156).[173,193] *Indirect evidence from pediatric migraine* included 18 RCTs ($n = 1897$).[177,194–197] All included studies assessed overall improvement (≥50% reduction in vomiting or headache episode frequency, duration, and severity, ED visits). Most of the data pertained to topiramate, less to valproate.

3.8.16.2 | *Benefits*

The panel rated the desirable effect to be moderate. Using the criteria of ≥50% improvement, 86% and 84% improved in pediatric CVS (topiramate and valproate), and 75% and 65% in adult CVS (zonisamide/levetiracetam, and topiramate). Retrospective data ($n = 14$) noted improvement in 85% (topiramate) and 36% (valproate) of pediatric CVS.[8] However, with moderate certainty evidence from controlled trials in pediatric migraine, the effects were mixed. Although the headache frequency was significantly reduced with topiramate (except in four of the RCTs), the ≥50% improvement outcome was nonsignificant compared to placebo, and neither the headache frequency nor the ≥50% improvement reached significance for valproate compared to placebo.

3.8.16.3 | *Harms and burden*

The panel rated the undesirable effects of topiramate, including weight loss, cognitive dysfunction, somnolence, paresthesias, dizziness, and abdominal pain, to be large. The panel's experience indicated that cognitive dysfunction was the most common reason for discontinuing the drug in children. In adults with CVS, 55% experienced side effects including cognitive dysfunction, fatigue and paresthesias, and 32% terminated therapy.[193] Among four RCTs ($n = 344$) of topiramate in pediatric migraine, 21% experienced paresthesias, 16% upper respiratory tract infections, 14% fatigue, and 11% weight loss.[195]

In pediatric migraine, 5 out of 329 patients had severe side effects to topiramate including infections and suicidal attempts.[197] In the case of valproate, side effects included upper respiratory tract infections, nausea, nasopharyngitis, and potential for severe adverse effects including pancreatitis, polycystic ovarian syndrome and teratogenicity.[197] There is a black box warning regarding suicidal ideation for most antiseizure medications.[198]

3.8.16.4 | *Decision criteria and additional considerations*

There was very low certainty evidence based on the risk of bias due to non-blinding, indirectness, and imprecision in effects. Based on moderate certainty and indirect evidence from pediatric migraine, there was a mixed effect with a reduction of headache frequency but not for a ≥50% effect compared to placebo. The panel also noted a high chance of placebo effects previously observed in pediatric CVS and natural history in which resolution begins in early adolescence.[182] The panel judged the balance of moderate beneficial effects and large side effects, including serious ones, probably favors not using these drugs in routine therapy. There may be utility in trialing these anticonvulsants when other approaches fail. There was a variable range of costs as topiramate sprinkles used in toddlers were high cost at $175/month and capsules for older children only $9/month and low to moderate costs of valproate at $18 for younger and $59 for older children. Although there

may be cost savings from the prevention of ED visits and hospitalizations, these may be mitigated by costs of hospitalization from serious adverse effects. These two medications, topiramate and valproate, were judged acceptable to some and accessible to most patients. The EtD framework is available here.

3.8.16.5 | *Conclusions and implementation considerations*

The guideline panel determined that there is very low certainty evidence (4 studies with direct and 20 studies with indirect evidence) for a net health benefit. The panel determined that there was a moderate therapeutic benefit and large harm, reserving its use for those who are refractory to other treatments. The medications were judged acceptable to some patients and treating providers and cost-effective due to potential moderate savings from reduced ED visits and hospitalizations.

3.8.16.6 | *Subgroup considerations*

The panel recommended that these medications be reserved for those with more frequent (>1/month) episodes and more severe symptoms (ED visits and hospitalizations) who have not responded to lifestyle modifications, nonpharmacological interventions, abortive medications and who are *refractory* to other prophylactic agents with more favorable side effect profiles. Caution is indicated in those with psychiatric comorbidities. These drugs may be more suitable for patients with comorbid epilepsy.

3.8.16.7 | *Implementation considerations*

The potential side effects should be fully disclosed to the parents before initiating therapy.

Topiramate should be titrated gradually from 25 mg/day or 0.5 mg/kg/day every 2 weeks by 1 mg/kg until a dose of 2 mg/kg/day divided BID is reached.

3.8.16.8 | *Monitoring and evaluation*

Follow-up of therapeutic and adverse effects including weight checks should take place at least every 6 months. Hepatic transaminases and platelets should be monitored while on valproate.[199]

3.8.16.9 | *Research priorities*

The panel recommended prospective, controlled, multicenter treatment trials on safety and efficacy that control for the substantial placebo effect in CVS and the natural history of disease resolution.[182,183]

4 | LIMITATIONS OF THESE GUIDELINES

The limitations of these guidelines are inherent in the indirectness and low or very low certainty in the evidence for the majority of the questions. Yet, this document provides the first, evidence-based practice guidelines for pediatric CVS that utilized the GRADE approach. It should be viewed as best practices for managing children with CVS as compared to other documents focusing on diagnosis and management of adults with CVS using the GRADE approach (American Neurogastroenterology & Motility Society 2019 CVS guidelines) [20] or expert opinion (American Gastroenterological Association Clinical Practice Update).[200] These guidelines should also replace prior expert recommendations in the 2008 NASPGHAN consensus statement on pediatric CVS.[9] The current guidelines provide more comprehensive, evidence-based guidance by employing systematic reviews, assessments of the certainty of evidence, consideration of additional extensive pediatric migraine research evidence, and explicit EtD judgments about the criteria that impact the direction and strength of recommendations according to the GRADE approach.

4.1 | Revision or adaptation of the guidelines

After the publication of these guidelines, NASPGHAN will maintain them by continued surveillance for new evidence, ongoing review by experts, and regular revisions. Adaptation of these guidelines should be based on the associated EtD frameworks. Depending on when such a process takes place, the following steps should be taken[201]: identifying additional, pertinent healthcare questions, critically appraising existing recommendations, surveillance of new literature, adapting to the need for changes in population, intervention or comparison, transparency in description of the judgment process and completion of GRADE EtD frameworks for each recommendation.

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CONFLICT OF INTEREST STATEMENT

Katja Karrento serves as consultant for Takeda Pharmaceuticals and AbbVie. John M. Rosen serves as consultant for Haymarket Media. Sally E. Tarbell served as consultant for Takeda Pharmaceuticals. Amy Gelfand serves as consultant for Satsuma, Biohaven, Advanced Clinical, UpToDate, the American Academy of Neurology, and the American Headache Society. B.U.K. Li serves as consultant for Takeda Pharmaceuticals, UpToDate, and GLG Consulting.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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