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Management of Cyclic Vomiting Syndrome in Adults: Evidence Review

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ABSTRACT

Background. This evidence review was conducted to inform the accompanying clinical practice guideline on the management of cyclic vomiting syndrome (CVS) in adults.

Methods. We followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework and focused on interventions aimed at prophylactic management and abortive treatment of adults with CVS. Specifically, this evidence review addresses the following clinical questions: (1) Should the following pharmacologic agents be used for prophylaxis of CVS: amitriptyline, topiramate, aprepitant, zonisamide/levetiracetam, or mitochondrial supplements? (2) Should the following pharmacologic agents be used for abortive treatment: triptans or aprepitant?

Results. We found very low-quality evidence to support the use of the following agents for prophylactic and abortive treatment of CVS: amitriptyline, topiramate, aprepitant, zonisamide/levetiracetam, and mitochondrial supplements. We have moderate certainty of evidence for the use of triptans as abortive therapy. We found limited evidence to support the use of ondansetron and the treatment of co-morbid conditions and complementary therapies.

Conclusions. This evidence review helps inform the accompanying guideline for the management of adults with CVS which is aimed at helping clinicians, patients and policy makers, and should improve patient outcomes.

Key words: cyclic vomiting, technical review, treatment

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INTRODUCTION

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Cyclic vomiting syndrome (CVS) is a chronic, debilitating illness that is characterized by recurrent episodes of intense nausea and vomiting. Although the true prevalence of CVS in adults in the general population remains uncertain, it is not a rare disorder. A recent population-based study noted that the US prevalence was 2% among adults, mirroring prevalence estimates in children. (1) Another estimated that ~10% of outpatients presenting to a tertiary gastroenterology clinic met the Rome III criteria for the illness.(2) But even in this clinical setting, CVS was considered as a potential diagnosis in only a small minority of these patients. This finding highlights the poor recognition of CVS in adults by clinicians, with many patients continuing to suffer for several years before receiving a diagnosis of CVS. Concerted messaging and increased awareness campaigns should minimize this clinical recognition gap. Recognizing CVS in adults is critical, as there are several fairly effective prophylactic and abortive therapies to treat the disorder.

This evidence review represents a foundational effort by the American Neurogastroenterology and Motility Society (ANMS) and the Cyclic Vomiting Syndrome Association (CVSA) to develop recommendations based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to provide a robust guideline for best practices in the management of CVS. This review addresses focused clinical questions on the use of pharmacologic agents for prophylactic and abortive therapies for the management of patients with CVS and was used to inform the development of the accompanying clinical practice guidelines. Panel members were selected by the CVS guidelines committee task chair (T.V.), Co-Chair (B.L.), former ANMS council member (B.M.) and the CVSA based on their clinical and methodological expertise. All members of the panel underwent a thorough vetting process for potential conflicts of interest.

METHODS

Overview

This evidence review was developed using the GRADE framework to develop clinically focused questions, and identify, synthesize, and evaluate the quality of the supporting evidence to inform a recommendation. (3)

Formulation of Clinical Questions

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Through an iterative process, the panel developed focused clinical questions on the role of specific therapeutics in the management of CVS. The PICO format was used which frames a clinical question by defining a specific Population (P), Intervention (I), Comparator (C), and Outcomes (O) (**Table 1**). The *population* was adult patients with CVS. The *intervention* was one of numerous therapies used in CVS. The preferred *comparator* was placebo. Relevant *patient-centered outcomes* were considered and rated in terms of importance. All PICO questions formed the basis for a literature search which is detailed below.

Outcomes

Outcomes were grouped into two broad categories for prophylactic and abortive therapies. We arrived at a consensus as to what measurements would be acceptable for each outcome. Outcomes were rated by the group on a scale of 1 (not important) to 9 (critically important) for medical decision making. It was understood that data on all outcomes would not be available in the published literature.

Systematic Review Process

Search Strategy: The literature search was performed initially in June 2016, and updated in February 2018, with the aid of a research librarian (C.S.). Details of the search strategy are reported in the **Online Supplement**. Individual studies were identified via searches of three bibliographic databases: *Pubmed* (includes MEDLINE), *SCOPUS* (a large, multidisciplinary database), and *CINAHL* (the Cumulative Index to Nursing and Allied Health Literature). Given the acknowledged possibility of diagnostic misclassification, individual search strategies included the following terms: *cyclic vomiting; cyclical vomiting; cannabinoid hyperemesis; functional vomiting; abdominal migraine* and *periodic syndrome.* The searches excluded animal-only studies and non-English language studies. The search strategy was iteratively developed through refinement with author input to maximize sensitivity. Given the limited total literature, a single search was conducted for all PICO Questions.

For all PICOs, the a priori intent was to rely upon high-quality systematic reviews for evidence synthesis, particularly those that synthesized data from Randomized Control Trials (RCTs). If systematic reviews of RCTs were not available, we would then look to individual RCTs to generate summary estimates if possible. In the absence of systematic reviews of RCTs or individual RCTs, systematic reviews of observational studies and observational studies were

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then considered to inform the evidence. Case series of fewer than 10 individuals were excluded, as were narrative reviews.

Study Selection Criteria: The reviewers utilized the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to develop the review. A PRISMA flow diagram is included in **Figure 1**. The titles/abstracts from the database searches were uploaded to Covidence (http://covidence.org), a web-based application that facilitates screening and reviewing studies for systematic reviews. All titles and abstracts were screened by two researchers (R.S., S.S.) with disagreements regarding inclusion and exclusion resolved by discussion. Inclusion criteria included any articles that might be relevant to the included PICO questions. Exclusion criteria were principally around study design as mentioned above. 1469 non-duplicate articles were found and 572 full text articles were then reviewed. One author (R.S.) extracted data from full text articles into a standardized data collection form with accuracy of data extraction confirmed by several members of the systematic review committee. Study characteristics and data extraction are reported in **Table 2a & b**.

Statistical Analysis

Given the size and heterogeneity of included studies, the majority of results were suitable to narrative summary. Quantitative outcomes were calculated using Open Meta (http://www.cebm.brown.edu/openmeta/).

Quality or Certainty of Evidence

The GRADE approach was used to rate the certainty in the evidence. In this approach, direct evidence from RCTs starts at high quality and can be rated down to levels of moderate, low, and very low quality, based on risk of bias in the body of evidence (or study quality), indirectness (addressing a different but related population, intervention, or outcome, from the one of interest), imprecision (of the summary estimate and boundaries of 95% CI), inconsistency (or heterogeneity in the results of the included studies), and/or publication bias. Due to inherent limitations in observational studies (selection bias, unmeasured confounding, etc.), evidence derived from observational studies starts at low quality and then is potentially downgraded based on the aforementioned factors or upgraded in case of dose-response relationship and large magnitude of effect. High-quality evidence suggests that we are confident of the quality of the evidence and/or the direction and magnitude of the effect estimate and any

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new data are unlikely to alter this. Moderate certainty suggests that we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty suggests that our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Finally very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Judgments about the certainty in the evidence were made via discussion amongst the panel and any disagreements were resolved by group consensus.

Evidence-to-Decision Framework

Information from this review was used in combination with factors such as patients' values and preferences, cost-effectiveness data (if available), and resource utilization to inform the development of the clinical guideline.

RESULTS

Overview

Study details are presented in **Table 2a &b** and summarized for each PICO question in the accompanying evidence profiles. The team acknowledges the limited evidence for CVS with few randomized control trials or high quality observational studies leaving us with low or very-low quality certainty in the evidence across outcomes. Given the paucity of literature on the topic, studies of all populations (adult and pediatric) were included with the assumption that the pathophysiology of CVS was similar in adults and adolescents, and that the effects of the various interventions may be generalizable across some populations. Finally, there was variability in criteria used to diagnose CVS, medication exposures (e.g. dosage and length of treatment) that were not consistently reported, and variable definitions for "response to treatment" used by authors across studies.

Prophylactic Therapy

Should Tricyclic Antidepressants (TCAs) be used as prophylactic therapy in adults with CVS?

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Key Message: There is very low certainty in the evidence that TCAs should be used as prophylactic therapy in CVS. See **Table 3** for full evidence profile.

Potential Benefits/Harms: Fourteen studies met inclusion criteria and were used to inform this question: these included 2 randomized trials and 12 observational studies.(4-14) Data from the randomized trials were converted to a single arm cohort of amitriptyline for inclusion into a summary estimate for amitriptyline's symptomatic effect. A summary estimate from all included data revealed that approximately 70% of patients with CVS exhibited a symptom response (variably defined for variable durations). Six studies were from pediatric populations, four studies from adult populations, and 4 studies from mixed adult/pediatric populations (see **Table 2 a&b**). Across these studies, 413/600 (70%) of patients reported complete or partial improvement with a decrease in frequency, duration, or severity of CVS symptoms when treated with a TCA, most commonly amitriptyline. Hejazi et al. in an open-label study of 46 adult patients demonstrated not only a marked reduction in the number of CVS episodes from 17 to 3, and in the duration of a CVS episode from 6 to 2 days, but also a reduction in the number of ED visits/hospitalizations from 15 to 3.3 with AT. Nine studies reported on adverse events, the most common being sedation and weight gain. Boles et al. 2010 had one of the largest patient cohorts and noted that 72/139 pediatric patients and 39/54 (72%) adults experienced TCA-related side effects and 29/137 pediatric patients and 13/61 (21%) adult patients discontinued amitriptyline because of side effects.(7) However adverse events leading to treatment discontinuation were not systematically reported across the studies.

Certainty of Evidence**:** The overall certainty of the evidence was judged to be very low. Risk of bias was a concern (lack of control group and possible selection bias in the observational studies, and lack of obvious blinding and an intention to treat analysis in the randomized trials). There was also concern regarding inconsistency, indirectness (many of the studies included only pediatric patients) and imprecision (for a few of the outcomes).

Should Topiramate be used as prophylactic therapy in adults with CVS?

Key Message: There is very low certainty in the evidence that topiramate should be used as prophylactic therapy in CVS. See **Table 4** for full evidence profile

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Potential Benefits/Harms: One study met inclusion criteria that investigated the role of topiramate in CVS.(15) Sezer et al investigated the use of topiramate (n=16) and propranolol (n=22) in 38 pediatric patients with CVS in a retrospective cohort study in Turkey. At baseline, the topiramate group (compared to the propranolol group) had significantly fewer episodes of vomiting/cycle before treatment, fewer attacks/year after treatment, decreased median duration of cycles, and fewer peak number of emeses/hour during an attack. As such, patients in the topiramate group might have been less severe prior to treatment than the propranolol group. Patients were followed for 1 year. At follow-up, responder rates (patients who had zero attacks in the year following treatment or patients that a ≥ 50% reduction in attacks) were significantly higher in the topiramate group 15/16 (94%) compared to the propranolol group 18/22 (81%). In the topiramate arm, 81% became episode free and 13% showed at least ≥ 50% reduction in number of episodes. Per the study, the four patients who were non-responsive to propranolol were treated with topiramate, and all of them had a "satisfactory response", though this was not clearly defined by the authors. The one patient who was non-responsive to topiramate was also non-responsive to other medications, including propranolol, amitriptyline and cyproheptadine. One additional study reported on topiramate use in adults (Kumar et al); in this study, 18/92 adults were treated with topiramate, but not enough detail was provided to discern the efficacy of topiramate alone, as patients in this cohort also received treatment with amitriptyline and mitochondrial supplements. (12)

In the study by Sezer et al., there were no dropouts from adverse events, and no statistically significant difference in adverse events between the propranolol and topiramate groups.(15) Two patients experienced drowsiness and dizziness with topiramate and mean weight loss after the end of 12 months was 1.1 ± 0.5 kg (2.9%).

Certainty in Effects: The overall certainty in the effects was very low due to concerns about study quality, imprecision (few events and small sample size) and indirectness (the study population was pediatric patients)

Should Aprepitant be used as prophylactic therapy in adults with CVS?

Key Message**:** In patients with CVS, there is very low certainty in the evidence for the use of aprepitant as prophylactic therapy in CVS. See **Table 5** for full evidence profile

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Potential Benefits/Harms: One observational study investigated the use of aprepitant both as abortive *and* prophylactic therapy in CVS.(16) This study by Cristofori et al., published in 2014, included pediatric patients and was retrospective in design, collecting data from administrative, pharmacy, and clinical databases as well as telephone interviews with parents of patients. The 41 included patients met NASPGHAN criteria for diagnosis of CVS and had failed or could not tolerate past treatments (**Table 2a&b**). Forty-one children and adolescents were included with 25 being administered aprepitant as an abortive medication and 16 as prophylaxis. Some adolescents in this group weighed > 60 kg. There was no control group. Patients were given an "abortive" regimen of aprepitant if they had a prodromal phase that suggested an imminent CVS attack. With respect to co-interventions, individuals were also being treated with propranolol 9/15 (60%), amitriptyline 7/15 (46%), coenzyme Q10 5/15 (33%),and L-carnitine 3/15 (20%).(16)

The outcomes were complete response (no CVS episodes), partial response (≥ 50% reduction in both frequency and intensity of CVS symptoms), no response (< 50% reduction in CVS frequency and intensity), CVS episodes/year, hospital admissions/year, duration of episodes, number of vomits/episode, duration of interspersed period (days), and percentage of school attendance. All outcomes (for abortive and prophylactic groups) were measured at a 12 month follow up time point.

In the prophylactic group, at 12-month follow-up, 19% of individuals achieved a complete response (3/16) and 62% (10/16) achieved a partial response. Overall, 82% (13/16) achieved either complete or partial response. Two children failed to respond (2/16, 19%).

With respect to adverse events, in the prophylaxis group, one patient discontinued therapy due to severe migraine (1/16, 6%). Other side effects noted included hiccups (3/16, 19%), asthenia/fatigue (2/16, 12.5%), increased appetite (2/16, 12.5%), and mild headache (1/16, 6%).

Certainty of Evidence: The certainty in the evidence was very low due to concern for risk of bias (lack of a control population, possible selection bias and confounding). There was also concern regarding indirectness, given that the study included a population that failed prior CVS treatments, and was on several concomitant medications. Some adolescents were at an adult weight (> 60kg) in the prophylactic group, and were dosed accordingly, making this less of a concern.

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Should zonisamide or levetiracetam be used as prophylactic therapy in adults with CVS?

Key Message: In patients with CVS, there is very low certainty in the evidence for the use of zonisamide or levetiracetam as prophylactic therapy. See **Table 6** for full evidence profile

Potential Benefits/Harms: One retrospective study met inclusion criteria.(17) Clouse et al. reviewed outpatient records and conducted interviews of 20 adult patients with CVS who had received prophylactic zonisamide (median dose, 400 mg/day) or levetiracetam (median dose, 1000 mg/day) when tricyclic antidepressants (TCAs) alone had failed, were intolerable, or unsuitable. Sixteen patients were treated with zonisamide and four with levetiracetam for CVS prophylactic therapy. Median follow up after initiation of the intervention was 10 months.

Outcomes measured included episode frequency and change in symptoms. A score ≥2 was required for a "favorable" clinical response. "Better" as a clinical response was not defined. The study used the following Likert scale: 0=no significant improvement or worse; 1=slight improvement, requiring treatment changes; 2=moderate improvement, regimen stable but symptoms not completely resolved; 3=clinical remission and complete patient satisfaction with therapy. Twelve out of 16 patients in the zonisamide group and 3 out of 4 in the levetiracetam group reported a favorable clinical response. Frequency of vomiting episodes decreased significantly after initiation of either zonisamde or levetiracetam from 1.3 to 0.5 episodes/month. In total, 18/20 (90%) stated that they were better on drug therapy (2 unchanged, 0 worse). There were no data on number of hospitalizations or ED visits.

Four subjects out of 20 reported "severe" side effects consisting of fatigue, confusion, headache, and dizziness, which were eliminated in 3/4 of these patients once they switched to the other antiepileptic. Two of these 4 patients were noted to have concomitant use of TCAs and 1 of the 4 patients was on a high dose of levetiracetam (3000 mg/day). Five subjects out of 20 reported depression, muscle weakness, difficulty sleeping, dizziness, poor concentration/memory, confusion, or tiredness/fatigue. One subject on levetiracetam developed angioedema, which resolved when switched to zonisamide. Only one subject out of 20 reported antiepileptic drugs intolerable in spite of switching drugs and dosages.

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Certainty in the Evidence: The certainty in the evidence was very low. We rated down for risk of bias and imprecision (small sample size, raising concern about optimal information size).

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Should mitochondrial supplements be used as prophylactic therapy in adults with CVS?

Key Message: In patients with CVS, there is very low certainty in the evidence for the use of mitochondrial supplements, such as Co-enzyme Q10, and riboflavin as prophylactic therapy. See **Table 7** for full evidence profile

Potential Benefits/Harms: The only comparative study to evaluate the efficacy of Coenzyme Q10 was conducted by Boles et al (2010).(7) In this study, the authors compared the efficacy of Coenzyme Q10 to amitriptyline in patients with CVS via an internet-based survey that asked subjects about their response to treatment. Eleven out of 22 subjects, using varying doses of Coenzyme Q10, reported a 50% reduction in episode frequency, 8/22 reported a 50% reduction in episode duration, and 8/20 reported a 50% reduction in nausea severity. Out of 28 participants on Coenzyme Q10, no side effects were reported. The survey did not allow a physician to confirm if the patient truly had CVS and was subject to recall and self-selection bias. No published studies reported on the efficacy of riboflavin in CVS patients. The Boles 2011 study included riboflavin but did not report on response for these patients.

The majority of studies that reported on the use of mitochondrial supplements was not amenable to providing estimates on the efficacy of mitochondrial supplements because these were used as co-therapy in conjunction with other agents or because lack of reporting of outcomes specific to mitochondrial therapy.(7, 8, 10, 12, 16, 18)

Data on the reported prevalence of mitochondrial supplement therapy as co-interventions is reviewed below. The Lee et al., 2012 systematic review was not used to inform this outcome because it either included studies that did not meet our inclusion criteria or included studies that as discussed below, used supplements as co-therapy.(19) Kumar 2012 conducted a retrospective analysis of 101 patients who met Rome III criteria for CVS. Of the 44/76 patients who achieved a “complete response” with medical therapy, approximately ~30% were taking Co-enzyme Q10. Of those with a “partial response” (21/76) to medical therapy, 35% taking Coenzyme Q10. Of the 11/76 patients with “no response” to medical therapy, 10% were taking Coenzyme Q10.

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Boles 2011 conducted a retrospective study in adult and pediatric populations with CVS and reported on outcomes of a 2-year case series in which 30 patients were treated with multiple agents, which often included mitochondrial supplements. Individual effect from the mitochondrial supplements could not be determined from the result, though the combination of amitriptyline, Coenzyme Q10 and L-carnitine was used most frequently. Two articles by Hejazi et al. described outcomes of an open labeled study for adults with CVS treated with TCA.(10, 20) Seventeen percent of the 46 patients took L-carnitine and/or Coenzyme Q10. The second study by Hejazi reported outcomes on 132 patients and focused on comparing non-responders and responders to TCA therapy. This study also had 17% of patients on L carnitine/Co-enzyme Q10. There seemed to be an overlap in the patient population between both of these studies. With respect to adverse effects, in the Boles 2010 study, there were no reported side effects (0/20).

Certainty of Evidence: The certainty in the evidence was deemed to be very low due to concerns about study quality, indirectness, and imprecision (retrospective design, lack of a control population, probable selection bias, pediatric population, small sample size, and confounding). No pooled effect estimate or range of effects could be calculated.

Abortive Medications:

Should triptans be used as abortive therapy in adults with CVS?

Key Message: There is moderate certainty in the evidence for the use of triptans as abortive therapy in CVS, primarily based on indirect data. See **Table 8** for full evidence profile.

Potential Benefits/Harms: We identified four studies that met inclusion criteria and that reported on the use of triptans as abortive therapy in CVS. One systematic review of treatments for CVS was not included below because it only reviewed the Hikita 2011 study.(21) We additionally looked for indirect evidence in the migraine literature to help inform outcomes, such as nausea and vomiting.(22)

Kumar 2012 conducted a retrospective review of adult and pediatric patients seen at the Medical College of Wisconsin who met Rome III criteria for CVS.(12) Data were collected on 101 patients through chart review and patient questionnaires. Response data was not available

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on all patients, though it was noted that triptan medications “aborted” CVS episodes in 64/77 (83%) of patients.

Hikita 2011 studied one adult and eleven pediatric patients in a prospective cohort study that took place at Teikyo University Hospital in Japan.(21) Patients had been diagnosed with severe CVS by a pediatric neurologist per the International Classification of Headache Disorders. Patients were given sumatriptan, as either a subcutaneous injection or nasal spray; the average dose administered was not specified. Measured outcomes included “complete response” (no vomiting after treatment), “effective response” (vomiting frequency reduced by ≥ 50%), or “noneffective response” (the treatment was not effective in preventing vomiting). For the 11 patients receiving subcutaneous sumatriptan injection, 4/11 had complete resolution, 5/11 had effective response, and 2/11 had a noneffective response. Patients with a family history migraine were more likely to respond (“complete” and “effective”). Amongst the five patients who received nasal spray, 1/5 had complete resolution, 1/5 had effective response, and 3/5 had non-effective response.

Li 1999 published a retrospective cohort study in of 214 children from Columbus Children’s Hospital with a clinical diagnosis of CVS. (23)The purpose of the study was to descriptively compare the characteristics of those with migraine-associated CVS versus those with non-migraine associated CVS. The diagnosis of CVS was made as a clinical diagnosis by treating clinicians. Median follow-up was 17.5 months. Measured outcomes included demographic characteristics, vomiting pattern, associated symptoms, triggering events, and medication response. The migraine-associated CVS group (with either self or family history of migraines) compared to non-migraine associated CVS had fewer emeses/episode, more abdominal pain, and more triggering events for their CVS episodes. Li et al found that 24/35 (69%) of children had improvement in symptoms (defined as a ≥ 50% reduction in vomiting episodes) with subcutaneous sumatriptan.

Indirect estimates for the effect of sumatriptan on symptom reduction (nausea and vomiting) were derived from the migraine headache literature. (22) In a systematic review of patients with migraine headaches, but not necessarily CVS, of 8 randomized control trials, 45% to 76% of individuals with migraine headaches experienced a reduction in nausea symptoms within 2 hours with triptans and higher rates of symptom improvement were seen in individuals receiving sumatriptan by either intranasal (50-60% range) and subcutaneous routes (76%).(22)

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Amongst the 3 studies that included data on the use of triptans as abortive therapy in CVS, no adverse events were reported. (12, 23) Furthermore, no data on adverse events leading to treatment discontinuation were provided in the Derry et al. Cochrane Systematic Review. Adverse effects were generally described as mild or moderate and self-limited. No cardiovascular problems were noted.

Certainty in the Evidence: Indirect estimates influenced the certainty of the evidence supporting the utility of triptans as abortive therapy in CVS. With regard to the outcome of relief of nausea at 2 hours, we had moderate certainty in the beneficial effect of triptans, as presented by the summary estimate yielded from a meta-analysis of eight RCTs. We downgraded for indirectness as the population studied was patients with migraine headaches (CVS is in the subgroup of periodic syndromes that include migraine and its equivalents).

With regard to the outcome of treatment response and adverse events (across the three studies in CVS patients) the certainty in the evidence was deemed to be very low. We down-graded due to risk of selection bias, imprecision (concern for fragility in the estimate due to suboptimal information size) and indirectness, because some studies were conducted in pediatric populations and some data comes from a CVS-migraine associated phenotype.

Should 5-HT3 Antagonists be used as abortive therapy in adults with CVS?

No published studies examining the use of ondansetron as abortive therapy for CVS were identified despite its widespread use in CVS. No GRADE Evidence Profile was created.

Should Aprepitant be used as abortive therapy in adults with CVS?

Key Message: In patients with CVS, there is very low certainty in the evidence for the use of aprepitant as abortive therapy. See **Table 9** for full evidence profile

Potential Benefits/Harms: One observational study investigated the use of aprepitant as abortive *and* prophylactic therapy in CVS.(16) The study included pediatric patients and was retrospective in design, collecting data from administrative, pharmacy, and clinical databases as

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well as telephone interviews with patients' parents (see section on aprepitant as prophylactic therapy in CVS for more details). In the abortive group, at a 12-month follow up time point, 12% (3/25) achieved a complete response and 64% (16/25) achieved a partial response. Overall, 76% (19/25) achieved either a complete or partial response. Six children had no response (6/25, 24%). It was difficult to discern how often patients received the medication in the abortive group. There were no noted adverse events from aprepitant administration in the abortive group.

Certainty in the Evidence: The certainty in the evidence was deemed to be very low, for the same reasons discussed in the prophylactic group. Certainty was reduced by risk of bias (lack of a control population, possible selection bias and confounding). There was also concern regarding indirectness, given that the study included a population that failed prior CVS treatments, and was on several concomitant medications.

Should we screen for and treat co-morbid conditions, such as anxiety, depression, migraine headache, autonomic dysfunction, sleep disorders, and substance use in adults with CVS?

No published studies were found that explicitly addressed this question. No GRADE evidence profile was created.

Should meditation, relaxation and biofeedback be used as complementary therapy in adults with CVS?

No published studies were found that explicitly addressed this question. No GRADE evidence profile was created.

Areas of limited/insufficient evidence

Three recommendations (recommendations 7, 9 and 10) that are presented in the accompanying manuscript, were deemed consensus recommendations and no GRADE evidence profile was created. Recommendation 7 addresses the role of 5-HT3 antagonists, such as ondansetron, as abortive therapy for CVS. Acknowledging the lack of direct evidence to

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inform this clinical question, the committee relied on indirect evidence on the efficacy of ondansetron in patients with chemotherapy-induced nausea and vomiting (CINV) and post-operative nausea and vomiting (PONV) in treating acute, delayed and anticipatory nausea and vomiting to inform the recommendation. For recommendations 9 and 10,there was insufficient evidence in the published literature examining the role of screening and treatment of co-morbid conditions on CVS symptoms and the effects of complementary therapies on CVS symptoms. For these two recommendations, the committee made consensus-based recommendations based on their large collective experience of managing adult and pediatric CVS patients and their observations in clinical practice as well as the recognition that the treatment of CVS, a functional disorder, should be based on a biopsychosocial care model, integrating lifestyle modification, prophylactic and/or abortive medications, and evidenced based psychotherapy to address psychiatric comorbidity. Finally the guideline also includes consensus statements that address the diagnosis and workup of CVS patients as well as a narrative review and sample protocol for treatment of CVS patients in the ED.

Conclusions

This evidence review is based on the GRADE framework and was developed to inform the clinical practice guideline for the management of CVS, which should ultimately improve patient outcomes and reduce morbidity associated with this chronic and often, debilitating illness.

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Abbreviations used in this paper: AE, adverse event; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LR, likelihood ratio; OR, odds ratio; PICO, population, intervention, comparator, and outcome; RCT, randomized control trial; RR, relative risk;

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(TO THE EDITOR: TABLES 1, 2a & b and 3-8 are attached in separate Word Files)

TABLE 2 Characteristics of Included Studies

TABLE 3 Should TCAs be used as prophylactic therapy in adults with CVS?

TABLE 4 Should topiramate be used as prophylactic therapy in adults with CVS?

TABLE 5 Should aprepitant be used as prophylactic therapy in adults with CVS?

TABLE 6 Should (antiepileptics) zonisamide or levetiracetam be used as prophylactic therapy in adults with CVS?

TABLE 7 Should mitochondrial supplements be used as prophylactic therapy inadults with CVS?

TABLE 8 Should triptans be used as abortive therapy in adults with CVS?

TABLE 9 Should aprepitant be used as abortive therapy in adults with CVS?

FIGURE 1 PRISMA Flow Diagram

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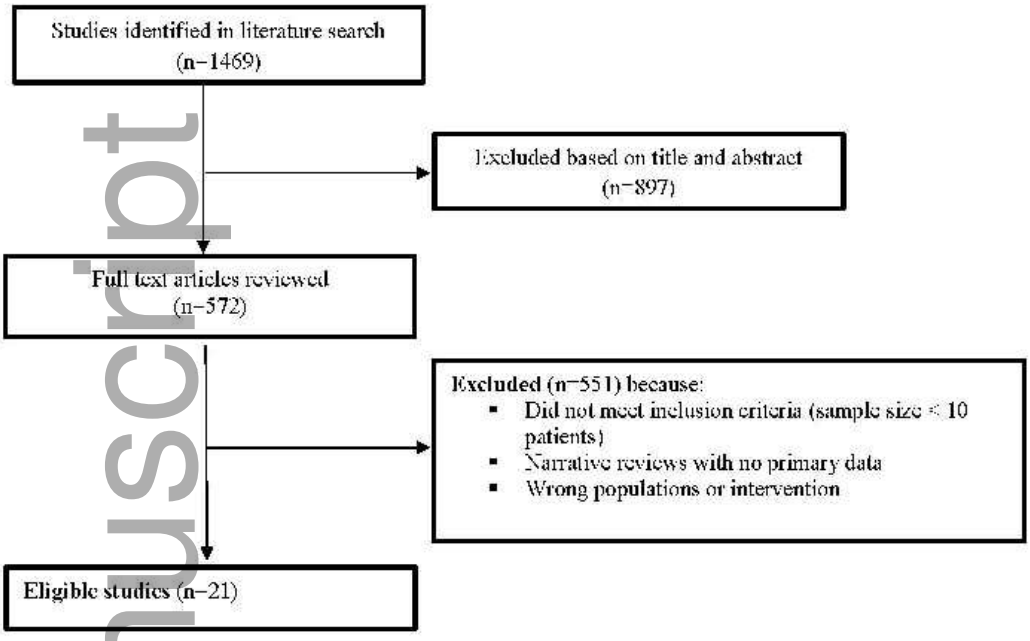

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ONLINE SUPPLEMENT

Search Strategy

PUBMED:

("cyclic vomiting" [tw] OR "cyclical vomiting" [tw] OR "Cannabinoid hyperemesis" [tw] OR "functional vomiting"[tw] OR "abdominal migraine"[tw] OR "periodic syndrome"[tw] OR ((extreme [ti] OR coalescent* [ti] OR familial [ti] OR unexplained [ti] OR recurrent [ti] OR cyclic [ti] OR cyclical [ti] OR idiopath* [ti]) AND (vomit* [ti] OR emesis [ti]))) AND English [lang] NOT ("animals" [mesh] NOT "humans" [mesh]) AND english [lang]

SCOPUS: TITLE((extreme OR coalescent* OR familial OR unexplained OR recurrent OR cyclic OR cyclical OR idiopath*) AND (vomit* OR emesis))OR TITLE(("Cyclic vomiting" OR "Cyclical vomiting" OR "functional vomiting" OR "abdominal migraine" OR "periodic syndrome" OR "Cannabinoid hyperemesis")) AND (LIMIT-TO(LANGUAGE,"English"))

CINAHL: TX (("Cyclic vomiting" OR "Cyclical vomiting" OR "functional vomiting" OR "abdominal migraine" OR "Cannabinoid hyperemesis" OR "periodic syndrome")) OR TI (

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((extreme OR coalescent* OR familial OR unexplained OR recurrent OR cyclic OR cyclical OR idiopath*) AND (vomit* OR emesis)))

TOTAL: 2054 (June 2016)

DUPLICATES: 585

REMAINING: 1,469

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PICO Questions				Method
Population	**Intervention(s)**	**Comparator**	**Outcomes**	
Prophylactic Therapy				
Adults with CVS	1. TCAs 2. Topiramate 3. Zonisamide Levetiracetam 4. Aprepitant 5. Mitochondrial supplements CoQ10 L-Carnitine Riboflavin	Placebo or Usual Care	1. Complete Response or Partial Response or Subjective Improvement (reduction in frequency or duration or severity of CVS symptoms) 2. Decrease in frequency or duration or severity of CVS attacks (if reported separately) 3. Reduction in numbers of hospitalizations of ED visits per year 4. Adverse Effects - % of patients discontinuing treatment	GRADE
Abortive Therapy				
Adults with CVS	6. Triptans 7. 5HT3 antagonists Ondansetron 8. Aprepitant	Placebo or Usual Care	1. Complete Response or Partial Response or Subjective Improvement (reduction in frequency or duration or severity of CVS symptoms) 2. Decrease in frequency or duration or severity of CVS attacks (if reported separately) 3. Reduction in numbers of hospitalizations of ED visits per year 4. Adverse Effects - % of patients discontinuing treatment	GRADE and Narrative review

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Table 1: PICO Questions

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Table 3. Should TCAs be used as prophylactic therapy in adults with CVS?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TCAs**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete/Partial Response or Symptom Improvement (variably defined in each study; follow up range 5 months to 5 years)												
14	observational studies [a]	serious [b]	serious [c]	serious[d]	not serious	none	413/600 (70%; range 61-77%) of patients had complete or partial response to treatment or symptom improvement across 14 studies				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in duration or severity of CVS symptoms; follow up 2 years												
1 Hejazi 2010	observational study, n=41	not serious	not serious	not serious	serious[e]	none	Reduction in duration of CVS episodes from baseline 6.7 +/- 6.1 (days) to 2.2 +/- 2.4 (days).				⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in number of episodes; follow up 2 years												
1 Hejazi 2010	observational study, n=41	not serious	not serious	not serious	serious[e]	none	Reduction in number of episodes from baseline (mean) 17.8 +/- 8.3 to 3.3 +/- 2.8.				⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in hospitalizations/ED visits												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	placebo	Relative (95% CI)	Absolute (95% CI)		
1 Hejazi 2010	observational study, n=41	not serious	not serious	not serious	serious[e]	none	Reduction in number of hospitalizations reported: baseline 15 +/-13.4 down to 3.3 +/-3.6.				⊕○○○ VERY LOW	IMPORTANT
Adverse Effects Leading to Treatment Discontinuation[†]												
							See narrative.				⊕○○○ VERY LOW	IMPORTANT

a. Overall, 14 studies (Including the intervention arm from 2 RCTs were included in this analysis.

b. There were issues around selection bias, no intention to treat analysis, confounding, co-interventions with mitochondrial supplements, and variable follow up. The outcomes were variably reported across the different studies: from complete response (no attacks), partial response (50% reduction in frequency and duration) to "good response, fair response, poor response", to the use of a visual analog scale to "subjective improvement".

c. We rated down for inconsistency (high I-squared).

d. We rated down for indirectness as 6 studies were conducted in the pediatric population.

e. There were few events and the sample size was small.

f. Variably reported across studies. See narrative

Table 4. Should topiramate be used as prophylactic therapy in adults with CVS?

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Quality assessment							№ of patients	Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproic acid	Relative (95% CI)	Absolute (95% CI)		
Complete Response (free from attack for at least 1 year)											
1 Sezer 2016	observational study, N=16	not serious[a]	not serious	serious[b]	serious[c]	none	81% were free from attacks at 12 months			⊕◯◯◯ VERY LOW	CRITICAL
Partial Response (50% reduction in both frequency and intensity of CVS symptoms); follow up 12 months											
1	observational study, N=16	not serious[a]	not serious	serious[b]	serious[c]	none	13% achieved a partial response (50% reduction in symptoms)			⊕◯◯◯ VERY LOW	CRITICAL
Reduction in duration or severity of CVS symptoms; follow up 12 months											
1	observational study, N=16	not serious[a]	not serious	serious[b]	serious[c]	none	Reduction in median duration of cycles from baseline 17.0 $\pm$ 5.1 to 11.0 $\pm$ 2.2 hours. Reduction in episodes of vomiting per cycle from baseline 14.0 $\pm$ 2.3 to 12.0 $\pm$ 1.4			⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in number of episodes; follow up 12 months											
1	observational study, N=16	not serious[a]	not serious	serious[b]	serious[c]	none	Decrease in number of attacks per year from 5.0 $\pm$ 0.1 to 1.0 $\pm$ 0.4			⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in hospitalizations/ED visits – NOT REPORTED											

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Quality assessment							№ of patients	Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproic acid	Relative (95% CI)	Absolute (95% CI)		
Adverse Effects leading to treatment discontinuation; follow up 12 months											
1	observational study, N=13	not serious[a]	not serious	serious[b]	serious[c]	none	None observed			⨁◯◯◯ VERY LOW	IMPORTANT

a. This was a retrospective study based on chart review

b. The study (Sezer 2016) included16 pediatric patients. Overall responders (≥ 50% reduction) =**94%** (partial or complete response). In one additional study, (Kumar 2012), 17/76 adult patients received topiramate but there was not enough detail provided for the analysis (as patients may also have been treated with amitriptyline and mitochondrial supplements. In this study, overall response was 86% (≥ 50% reduction in frequency of CVS episodes).

c. There were few events and small numbers of patients

Table 5. Should aprepitant be used as prophylactic therapy in adults with CVS?

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Complete response (no episodes) (follow up: 12 months)									

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Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
1 Cristofori 2014	observational study, n=16	serious [a]	not serious	serious [b]	not serious	none	3/16 (19%) of patients had no further episodes at 12 months	⨁◯◯◯ VERY LOW	CRITICAL
Partial response: ≥50% decrease in both frequency (# episodes/year) and intensity (episode duration in days); follow up: 12 months									
1	observational study, n=16	serious [a]	not serious	serious [b]	not serious	none	10/16 (62%) had a partial response	⨁◯◯◯ VERY LOW	IMPORTANT
CVS episode duration (follow up: 12 months)									
1	observational study, n=16	serious [a]	not serious	serious [b]	not serious	none	Reduction in the duration of episodes (days): Baseline 5 (4-7) to 3 (1-3). Reduction in number vomits/episode: Baseline 9 (7-10) to 6 (5-8).	⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in number of CVS episodes/year (follow up: 12 months)									
1	observational study, n=16	serious [a]	not serious	serious [b]	not serious	none	CVS episodes/year: Baseline 12 (9-14) to 3 (2-6) at 12 months	⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in hospitalizations/year (follow up: 12 months)									

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Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
1	observational study, n=16	serious [a]	not serious	serious [b]	not serious	none	Reduction in number of hospital admissions/year from baseline 8 (6-12) to 2 (1-4) at 12 months	⊕◯◯◯ VERY LOW	IMPORTANT
Symptom-free interval length (days) (follow up: 12 months)									
1	observational study, n=16	serious [a]	not serious	serious [b]	not serious	none	Duration of interspersed period (days): Baseline 30 (21-40) to 120 (60-180) at 12 months	⊕◯◯◯ VERY LOW	IMPORTANT
School attendance (follow up: 12 months)									
1	observational study, n=16	serious [a]	not serious	serious [b]	not serious	none	Increase in school attendance: 67% (58-72) to 81% (78-85) at 12 months	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse Effects (follow up: 12 months)[c]									
1	observational study, n=16	serious [a]	not serious	serious [b]	not serious	none	Only one child with migraine stopped the medication (1/16)	⊕◯◯◯ VERY LOW	IMPORTANT

a. This was a retrospective cohort study with no control population and concerns about possible selection bias. The study included cohorts who received prophylaxis and abortive treatment. Only the patients who received prophylaxis are presented here.

b. The patient population included pediatric patients that failed prior CVS treatments and were on several concomitant medications.

c. Side effects were reported only in the prophylactic group affecting 5/16, 31%: Hiccup (3/16, 19%), Asthenia/fatigue (2/16, 12.5%), Increased appetite (2/16, 12.5%), Mild headache (1/16, 6%), Severe migraine (1/16, 6%)

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Table 6. Should (antiepileptics) zonisamide or levetiracetam be used as prophylactic therapy in adults with CVS?

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Symptomatic Improvement assessed by Likert Scale: 0 (no significant improvement/worse) to 3 (clinical remission and complete satisfaction); follow up ~9 months[a]									
1 Clouse 2007	observational study, n=20	serious [a]	not serious	serious [b]	serious [c]	none	"Favorable outcome" 15/20 (chart review); "Better" 18/20 patients (patient interviews); 12/16 had less severe vomiting (4: no change); 7/16 had shorter episodes (9: no change)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in number of episodes/episode frequency (per month); median follow up ~9 months									
1	observational study, n=20	serious [a]	not serious	serious [b]	serious [c]	none	Reduction in the number of episodes per month: Baseline: 1.3 +/- 0.3 to 0.5 +/- 0.2 episodes/month	⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in hospitalizations/ED visits-NOT REPORTED									

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Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Adverse Effects (AEs); follow up ~9 months[e]									
1	observational study, n=20	serious [a]	not serious	serious [b]	serious [c]	none	**Severe** AEs: 4/20 (20%). One subject on levetiracetam developed angioedema, which resolved when switched to zonisamide One subject discontinued therapy in spite of switching drugs and dosages	⨁◯◯◯ VERY LOW	IMPORTANT

a. A score ≥ 2 was required for a "favorable" clinical response. "Better" as a clinical response was not defined. Likert scale: 0= no significant improvement or worse; 1= slight improvement, requiring treatment changes; 2 =moderate improvement, regimen stable but symptoms not completely resolved; 3= clinical remission and complete patient satisfaction with therapy. Of the 20 patients with a "favorable" clinical response,12/16 received zonisamide and 3/4 received levetiracetam

b. This retrospective study was based on chart review and patient interviews with no control group and concerns for possible selection bias, baseline confounding, and awareness of treatment when measuring outcome (no blinding).

c. This patient population was adults who were unresponsive to TCAs.

d. We rated down for imprecision due to the small sample size and few events.

e. Severe side effects: fatigue, confusion, headache, and dizziness (4/20) which were eliminated in 3 of 4 patients once antiepileptic was switched to the other. Moderate side effects: depression, muscle weakness, dizziness, difficulty sleeping, poor concentration/memory, confusion, or tiredness/fatigue (5/20).

Table 7. Should mitochondrial supplements be used as prophylactic therapy in adults with CVS?

Quality assessment	№ of patients	Effect	Quality	Importance

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mitochondrial supplements*	Relative (95% CI)	Absolute (95% CI)		
Complete/Partial Response –NOT REPORTED											
Reduction in duration or severity of CVS symptoms											
1 Boles 2010	observational study, N=32	not serious[a]	not serious	serious[b]	serious[c]	none	Using varying doses of CoQ10, 68% of subjects had improvement in symptoms.			⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in number of episodes –NOT REPORTED											
											IMPORTANT
Adverse Effects leading to treatment discontinuation											
1 Boles 2010	observational study, N=28	not serious[a]	not serious	serious[b]	serious[c]	none	Out of 28 participants on CoQ10, 0 side effects were reported.			⊕◯◯◯ VERY LOW	IMPORTANT

a. This was a retrospective study based on chart review

b. The studies included adult and pediatric patients.

c. There were few events and small numbers of patients

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Table 8. Should triptans be used as abortive therapy in adults with CVS?

Quality assessment							№ of patients	Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**triptans**	**Relative (95% CI)**	**Absolute (95% CI)**		
Treatment Response (variably defined in each study)											
3 Kumar 2012 Hikita 2011 Li1999	observational studies	serious [a,b]	not serious	serious [c]	serious [d]	none	The range of effects was 36-82% response (across the 3 studies) in aborting an episode or preventing an attack			⊕◯◯◯ VERY LOW	CRITICAL
INDIRECT EVIDENCE-Relief of (or improvement in) nausea within 2 hours in migraine headache patients[e]											

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Quality assessment							№ of patients	Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	triptans	Relative (95% CI)	Absolute (95% CI)		
8	randomised trials (overview of SRs)	not serious	not serious	serious [e]	not serious	none	The range of effects for reduction in nausea symptoms within 2 hours was 45% to 76% (across 8 RCTs); higher rates of symptom improvement were seen with intranasal (50-60% range) and subcutaneous medication (76%).			⊕⊕⊕◯ MODERATE	CRITICAL
Reduction in number of CVS episodes											
1 Hikita 2011	observational study, n=12	serious [a]	not serious	serious [f]	serious [d]	none	In 11 patients with 35 attacks, response was seen in 19 attacks (subcutaneous). In 5 patients with 6 attacks, response was seen in 2 attacks (nasal spray).			⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in hospitalizations/ED visits- NOT REPORTED											
Adverse effects leading to treatment discontinuation[g]											

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Quality assessment							№ of patients	Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	triptans	Relative (95% CI)	Absolute (95% CI)		
3	observational studies	serious[a]	not serious	serious [c]	serious[d]	none	No adverse events observed across the three studies in CVS patients.			⊕◯◯◯ VERY LOW	IMPORTANT

a. The observational studies were at risk for selection bias.

b. The outcome was variably defined across studies: “medication response” or “benefit” which may represent complete/partial response or symptom improvement. Li et al. found that 69% of kids (24/35) had improvement in nausea symptoms (defined as a >50% reduction in vomiting episodes with subcutaneous sumatriptan. Hikita et al. found 54% of attacks in 11 kids/1adult were responsive to sumatriptan therapy (defined as complete improvement or at least a 50% reduction in vomiting frequency.

c. Some studies were conducted in pediatric populations and some data comes from a CVS-migraine associated phenotype.

d. We rated down for imprecision due to the small sample size and few events.

e. An overview of SRs was used to provide indirect evidence to support the use of triptans for nausea and vomiting. These 8 studies were conducted in individuals with migraine headaches and nausea relief was a secondary outcome. This estimate was derived from the Cochrane overview of SRs by *Derry et al. Sumatriptan (all routes of administration) for acute migraine attacks in adults-overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2014, Issue5, Art. No. CD009108.*

f. The Hikita 2011 study included 1 adult and 11 pediatric patients.

g. No data on adverse events leading to treatment discontinuation were provided in the Derry et al. SR. AE were generally described as mild or moderate and self-limited. No cardiovascular problems were noted.

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Table 9. Should aprepitant be used as abortive therapy in adults with CVS?

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Complete response (no episodes) (follow up: 12 months)									

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Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1 Cristofori 2014	observational studies, n=25	serious [a]	not serious	serious [b]	not serious	none	3/25 (12%) of patients had no further episodes	⨁◯◯◯ VERY LOW	CRITICAL
Partial response: (≥50% decrease in both frequency (# episodes/year) and intensity (episode duration in days)) (follow up: 12 months)									
1	observational studies, n=25	serious [a]	not serious	serious [b]	not serious	none	16/25 (64%) of patients had partial response	⨁◯◯◯ VERY LOW	CRITICAL
CVS episode duration (follow up: 12 months)									
1	observational studies, n=25	serious [a]	not serious	serious [b]	not serious	none	Reduction in duration of episodes: Baseline 5 (3.5-7) to 1 (0.75-2). Reduction in number vomits/episode: Baseline 9 (7-10) to 4 (2-4.5).	⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in number of CVS episodes/year (follow up: 12 months)									
1	observational studies, n=25	serious [a]	not serious	serious [b]	not serious	none	CVS episodes/year: Baseline 12 (9.5-16.5) to 6 (2-8.5) at 12 months	⨁◯◯◯ VERY LOW	IMPORTANT

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Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in hospitalizations/year (follow up: 12 months)									
1	observational studies, n=25	serious [a]	not serious	serious [b]	not serious	none	Reduction in number of hospital admissions/year: Baseline 9 (6-12) to 2.5 (1-5.5)	⊕◯◯◯ VERY LOW	IMPORTANT
Symptom-free interval length (days) (follow up: 12 months)									
1	observational studies, n=25	serious [a]	not serious	serious [b]	not serious	none	Duration of interspersed period (days): Baseline 30 (21-35) to 60 (40-180) at 12 months	⊕◯◯◯ VERY LOW	IMPORTANT
School attendance (follow up: 12 months)									
1	observational studies, n=25	serious [a]	not serious	serious [b]	not serious	none	Increase in school attendance: 65% (57.5-74) to 80% (72-87.5) at 12 months	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse Events leading to treatment discontinuation (follow up: 12 months)									
1	observational studies, n=25	serious [a]	not serious	serious [b]	not serious	none	None reported in abortive group	⊕◯◯◯ VERY LOW	IMPORTANT

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a. This was a retrospective cohort study with no control population and concerns about possible selection bias. The study included cohorts who received prophylaxis and abortive treatment. Only the patients who received abortive therapy are presented here.

b. The patient population included pediatric patients that failed prior CVS treatments and were on several concomitant medications.

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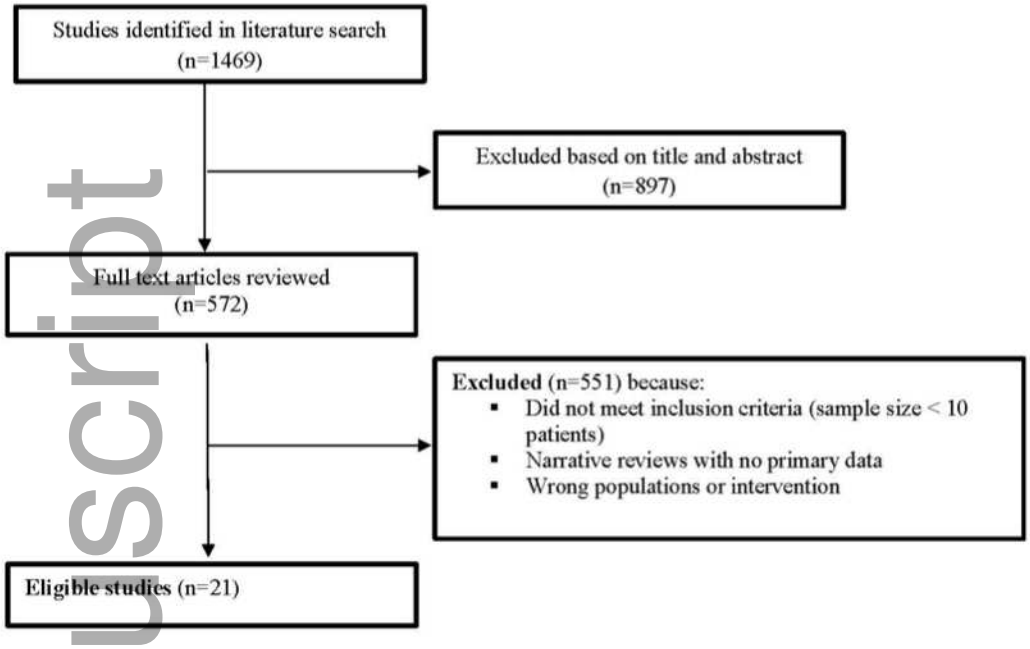

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