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CLINICAL REVIEW

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Acute care of cyclic vomiting syndrome and cannabinoid hyperemesis syndrome in the home and emergency department

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Abstract

Background: Cyclic vomiting syndrome (CVS) and cannabinoid hyperemesis syndrome (CHS) are both characterized by episodic, acute transitions from asymptomatic states to highly symptomatic states of nausea, repetitive vomiting, and often severe abdominal pain. Patients with CVS and CHS face significant challenges to abort or mitigate episodes at home and often require emergency department (ED)-based care.

Purpose: This paper reviews the current treatment approach to abort acute CVS and CHS episodes at home and in ED settings. Multiple pharmacologic and nonpharmacologic interventions have been demonstrated to potentially abort CVS or CHS episodes. Systemic pharmacologic agents often used as abortive therapy include triptans, antiemetics, anxiolytics, NK-1 receptor antagonists, antipsychotics, sedatives in general, and various analgesic / anti-inflammatory medications. Nonsystemic, nonpharmacologic approaches include reducing external stimuli (quiet room, dim lights, etc.), and hot water bathing or the application of topical capsaicin cream. More research is needed to develop evidence-based, individualized abortive treatment plans, as well as to determine whether the abortive treatment for CVS requires a fundamentally different approach than for CHS. When home-based approaches fail, all patients with CVS or CHS should receive nonjudgmental, informed, and compassionate care in the ED to abort their episode. Patients with more severe forms of CVS/CHS who require more frequent ED utilization should develop care plans with their ED to assure predictable and effective treatment.

KEYWORDS
acute care, anti-emetics, cannabis hyperemesis syndrome, care plans, cyclic vomiting syndrome, emergency department

1 | INTRODUCTION

Beyond being miserable to experience, protracted bouts of repetitive retching and vomiting put those with cyclic vomiting syndrome (CVS) and cannabinoid hyperemesis syndrome (CHS) at risk for immediate complications such as acute kidney injury from dehydration, arrhythmia from electrolyte disturbances, or hematemesis from Mallory-Weiss tears. The disruption and impact of CVS and CHS on patients' and their families' lives and livelihoods cannot be overstated. CVS and CHS episodes are typically unpredictable, and thus often interfere with work, education, and family activities. Furthermore, the intense nausea and vomiting during a CVS/CHS attack and the frequent need for ED-based care precludes any other activity. CVS and CHS are associated with significant healthcare utilization and both direct and indirect costs on society.[1,2] In the long term, the cycle of repeated attacks can have devasting consequences with loss of work, education opportunities, and strains on relationships, and about a third of CVS patients become disabled by their condition.[1]

Although CVS may be more easily diagnosed by expert clinicians, the more common experience is that the condition is poorly recognized by most physicians. Consequently, it may take years for patients to be given a correct diagnosis. Patients often develop immense frustration and even despondency in failing to gain a clear diagnosis or effective management plan, and patients may seek out multiple EDs in hopes of accessing optimal care.[3,4] A definitive diagnosis of CVS or CHS is often viewed by patients as a relief and validates the patient's suffering.[3,4]

There is wide variation in the clinical presentations of CVS and CHS, which may reflect distinct mechanisms that drive the episodes, and there is no one-size-fits-all treatment. Nonetheless, it is imperative that patients with CVS and CHS have access to effective treatments that can potentially abort or significantly mitigate attacks at home. Abortive therapies are more effective when taken at the earliest detected onset of an episode.[5–7] However, even with the best home management, many patients will still require acute medical care in a hospital emergency department (ED).[4,8–15] This article summarizes best practices and the current paradigm for abortive therapy in patients with CVS and CHS.

1.1 | Abortive therapy in CVS treatment: The importance of anticipatory guidance to patients and families

An effective CVS management program hinges on taking abortive therapy at the first "inkling" of symptom onset—ideally during the prodrome phase before vomiting has started. Most patients with CVS have a discernable prodrome, with symptom onset presenting a median of ~50 min prior to the transition to the emetic phase.[16] Specific prodromic symptoms can vary widely between patients but tend to be stereotypic for a given patient. Parents may be needed to help pediatric patients recognize early, prodrome signs of an attack and arrange for timely therapy.

Key points

- All patients with CVS and CHS should receive abortive therapies that can be implemented at home.
- Multiple pharmacologic and non-pharmacologic interventions can effectively abortive CVS/CHS episodes, particularly when implemented early during the prodromic period.
- Patients with CVS/CHS should access ED-based abortive treatment when home-based therapy fails. Those with frequent ED utilization benefit from developing an ED care plan.

Fully aborting a CVS or CHS episode means that patients recover quickly and resume normal functioning without further treatment. However, partially successful abortive therapy may still be clinically useful if it mitigates episodes—either by substantially shortening the length of the episode or the severity of symptoms during an episode. In general, patients and families are encouraged to have a low threshold to deliver abortive treatment, as the benefits of aborting an attack most often outweigh harms in "overtreating." For many patients, simply having access to an effective abortive regimen (i.e., a regimen that can successfully abort 75% or more of episodes) is inherently therapeutic by reducing anticipatory anxiety and dampening neurohormonal stress responses that may trigger episodes. In some cases, simply reducing anxiety and stress may secondarily reduce the frequency of CVS/CHS episodes in pediatric and adult patients.[17–19]

1.2 | Home-based abortive therapy protocols

There are several approaches to home-based abortive therapy for both CVS and CHS. The medications that have been used to abort CVS and CHS attacks are presented in Table 1. Several nonpharmacologic measures may play an adjunctive role, but in general, most patients will require more than one pharmacologic agent to abort an episode. Systemic pharmacologic agents often used as abortive therapy include triptans, antiemetics, anxiolytics, NK-1 receptor antagonists, anti-inflammatory agents such as NSAIDs, antipsychotics, sedatives in general, and in some cases cannabis.

Nonsystemic, nonpharmacologic approaches include reducing external stimuli (quiet room, dim lights, etc.), relaxation therapies (i.e., deep breathing, meditation), or hot water bathing. The application of topical capsaicin cream has some limited evidence for efficacy in CHS and mostly in ED settings, but in theory capsaicin could be applied at home, and potentially could work in CVS.

The relative efficacy of various abortive therapies is summarized in Table 2. More research is needed to develop evidence-based, individualized abortive treatment plans, as well as to determine whether abortive treatment for CVS requires a fundamentally different approach

TABLE 1 Abortive medication therapies in CVS and CHS.

Abortive therapy	Setting	Medication	Mechanism of action	Dosage	Common side effects	Clinical considerations
Triptans	Home	Sumatriptan	$5HT_{1B/1D/1F}$ receptor agonist	Single intranasal 20 mg dose, repeated once after 2 h if needed, not to exceed 40 mg in a 24- hour period	Chest discomfort Fatigue Dizziness Paresthesia Unpleasant taste	Should not be used in pregnancy Contraindicated in patients with ischemic heart disease, stroke, PVD, or uncontrolled hypertension
Anti-emetics	Home or ED	Ondansetron	$5\text{-}HT_3$ receptor antagonist	8 mg (sublingual or IV) every 4–6 h during episode	Headache Malaise Drowsiness Constipation with frequent doses	Baseline EKG is advised; associated with prolonged QTc
	Home or ED	Promethazine	Dopamine receptor antagonist with anti-histaminergic and anti-cholinergic effects	12.5–25 mg PO, PR, or IV every 4–6 h during episode	CNS depression, anticholinergic effects, extrapyramidal symptoms	Peripheral IV administration can cause tissue injury including gangrene or thrombophlebitis
	Home or ED	Prochlorperazine	Dopamine receptor antagonist	5–10 mg PO or IV every 6–8 h 25 mg PR every 12 h	CNS depression, anticholinergic effects, extrapyramidal symptoms, drug-induced leukopenia or neutropenia, rare cause of neuroleptic malignant syndrome.	Caution in patients with history of leukopenia or neutropenia, dementia, glaucoma, or seizure disorder
Neurokinin-1 System	Home or ED	Aprepitant/Fosaprepitant	Neurokinin-1 receptor antagonist	125 mg PO or 150 IV once	Neutropenia Fatigue	Potential interference with oral contraceptive pills Safer in pregnancy Challenging to obtain insurance coverage for "off-label" use in CVS; expensive
Sedatives	Home or ED	Alprazolam Lorazepam	GABA receptor agonist	0.5–2 mg PO every 4–6 h 5 mg PO or PR every 4–6 h	CNS depression, anterograde amnesia, paradoxical aggression in the elderly	Caution in pregnancy and those with history of substance abuse
	Home or ED	Diphenhydramine	H1 receptor antagonist with anticholinergic effects	12.5–25 mg PO or IV every 4–6 h during episode	Anticholinergic effects, over sedation, confusion	Caution in elderly patients, those with glaucoma, BPH, ischemic heart disease, or hypertension
Antipsychotics	ED	Haloperidol Droperidol	D2 receptor antagonist	2.5–5.0 mg IV 0.5–2.5 mg IV	Dystonia	Not for use in prolonged QT
Topical therapy	ED	Capsaicin	TRPV1 channel agonist	0.025%–0.1% topical cream	Skin irritation Skin photosensitivity	Caution handling (avoid eye/mouth exposure)

(Continues)

TABLE 1 (Continued)

Abortive therapy	Setting	Medication	Mechanism of action	Dosage	Common side effects	Clinical considerations
Analgesics/ Anti-inflammatories						
NSAIDS	Home or ED	Ibuprofen Ketorolac	COX 1 / 2 inhibitor	400–800 mg PO IV 30 mg; may repeat 15 mg q6 h ×2	GI upset/ulcers Renal insufficiency	Caution in those with known renal disease
Opiates	ED	Morphine Hydromorphone	Mu-opiate receptor agonist	5–10 mg IV 0.2–1 mg IV	Sedation Respiratory depression	Caution against frequent use to reduce dependency
Dissociative anesthetic	ED	Ketamine	NMDA glutamate receptor antagonist	10–25 mg IV (~0.2 mg/kg)	Dissociation Agitation Hypertension	Caution with use in patients with cardiac conditions

Abbreviations: IV, intravenous; PO, per oral; PR, per rectum.

than for CHS or other subtypes of CVS. It is also uncertain to what extent abortive therapy for CVS subtypes of pediatric patients should differ from adults with CVS. For example, NSAIDs may be particularly helpful as abortive therapy for pediatric patients with a migraine-like presentation or in adults with catamenial CVS attacks. Finally, some adult patients find that acute cannabis use can help abort CVS attacks. Such use patterns may be reasonable to continue if truly limited in scope, but any cannabis use runs some risk of escalation to more chronic cannabis exposure. Cannabis use is particularly problematic in pediatric patients and young adults, where exposures exert negative impacts on brain development and have inherent risks for dependence.

The ANMS-CVSA guidelines for the management of CVS in adults emphasizes pharmacologic therapy using triptans as particularly effective agents to abort CVS/CHS attacks.[20] Triptans such as sumatriptan may be administered either by nasal, oral, or parenteral administration.[20–30] If nasal administration is elected, it is important to draw attention to the package insert which recommends a "face forward" technique rather than head backward posture used for sinus medication administration.

The ANMS-CVSA guidelines and general clinical experience have also focused on the use of ondansetron as a useful abortive medication.[20] This is available in sublingual formulations that may expedite absorption. Often, a third medication, to induce some degree of sedation, is needed as a component of a successful abortive regimen. Many patients find that diphenhydramine can be helpful. Alternatively, some patients require an anxiolytic/hypnotic medication such as a benzodiazepine. In this instance, short acting benzodiazepines such as alprazolam (available in pill or sublingual forms) can be effective. Thus, a typical home-based medication regimen may include intranasal sumatriptan, sublingual ondansetron, and a diphenhydramine tablet.

More recently, the NK-1 inhibitor aprepitant has been identified as especially effective in refractory CVS in both adults and children.[31–33] Although the medication is expensive, by avoiding the ED and hospitalization and/or shortening lengths of stay, the choice of aprepitant may be arguably cost effective for selective patents.[33] For adults, a single oral dose of 80 or 125 mg can effectively abort an episode, whereas children require lower doses.

1.3 | Emergency department issues in CVS and CHS: The patient experience

Despite the best attempts to abort episodes at home, most CVS and CHS patients will seek ED treatment at some point. Repeated ED visits can be frustrating for patients and providers. Stigmatization and the perceived patient-blaming of those in a vulnerable state can amplify an already frustrating and complex patient experience. It is worth considering the treatment environment and the processes of care that occur in the ED. There are certainly some Emergency or Urgent Care Centers that offer a calm, reassuring environment in which staff acknowledge a CVS/CHS diagnosis and initiate effective treatments. However, this is not always what the patient or families experience.[4] Despite the best

TABLE 2 Synthesized evidence of pharmacologic intervention for acute attacks of CVS. Adapted from.[10]

Treatment	No. of Studies	No. of PTS	Response rate		
			100%	50%–100%	Total responders
Sumatriptan (Subcutaneous)	3	51	4/51 (8%)	31/51 (61%)	35/51 (69%)
Sumatriptan (Nasal spray)	2	40	1/5 (20%)	23/40 (58%)	24/40 (60%)
Ondansetron (Intravenous)	3	97	NR	57/97 (59%)	57/97 (59%)
Ondansetron (Oral)	1	85	NR	56/85 (66%)	56/85 (66%)
Dextrose (Intravenous)	2	60	NR	35/60 (58%)	35/60 (58%)
Phenothiazine (e.g., Promethazine)	3	63	NR	13/63 (21%)	13/63 (21%)
Prokinetic agents (Cisapride)	1	40	NR	8/40 (20%)	8/40 (20%)
Isometheptene	1	13	NR	4/13 (31%)	4/13 (31%)
Aprepitant	1	25	3/25 (12%)	16/25 (64%)	19/25 (76%)

efforts of staff, Emergency Departments are the last resort for many of the ills of the healthcare system. The typical ED may be harshly lit, noisy, frightening, unresponsive, or impersonal. Care may not occur for many hours after an initial assessment. Patients who are judged to have non-life-threatening status simply are given a lower priority than those with active bleeding, trauma, or other more dramatic presentations due to the nature of limited resources and the need for triage. The consequence is that patients and families often find the ED experience frustrating, and this may delay presentation to the ED well into the course of their episode when symptoms may have become more refractory to simpler interventions.[4,7,8,11] Lastly, patients with CVS may use cannabis intermittently, many times even specifically to abort an episode, whereas CHS patients have patterns of more chronic and/or heavy use of cannabis.[34] Unfortunately, in many cases, patients suspected of CHS (often in error, based on the patient's admission of occasional cannabis use) do not receive appropriate care and are informed that "nothing can be done" other than to quit cannabis. Current efforts are underway to educate physicians about CVS and CHS. All patients, whether CVS or CHS, deserve to be treated with abortive therapy in the ED.

1.4 | ED Management of CVS and CHS

In the best cases, a patient with an established CVS or CHS diagnosis should be identified and treated using order sets which are commonly used in many other chronic medical conditions.[35,36] Children and other patients with a migraine-like pattern will often respond well to existing ED migraine order sets / care plans. An example of a CVS-specific ED order set is shown in Table 3. While CVS patients tend to have stereotypical attacks, the challenge for the ED is that different subsets of CVS and CHS patients (i.e., those with migraines, or anxiety predominant presentations, or hyperadrenergic variants) may require individualized programs. One patient may respond to ondansetron and intravenous ketorolac, whereas another may have a history of a superior response to triptans. Anxiolytic medications may be more important for older adolescent and adult patients than in children. Special considerations for the patient with CHS are discussed below. Providing care which has *previously proven effective* for a particular patient is especially challenging in an environment in which there is no "continuity of care" due to rotating shifts of ED physicians and staff who have variable degrees of familiarity of with CVS and CHS.

Several of the abortive medical therapies listed in Table 1 are reserved for intravenous administration in a monitored, ED setting. A sequence of escalating interventions, as needed, is the typical paradigm for ED management as shown in Table 3. Intravenous ondansetron is often used as first line therapy for both pediatric and adult CVS/CHS patients who are actively vomiting.[10,20] If ondansetron has failed to quell vomiting, other elements of the treatment program are offered. For example, intravenous 150 mg fosaprepitant (intravenous prodrug of aprepitant) can be quite effective.[37] Most adult patients have favorable responses to sedating medications such as benzodiazepines.

Finally, most patients with CVS or CHS attacks experience significant abdominal pain with their episodes. Some form of analgesic is often needed as a part of the ED abortive care plan, and best practice is to avoid narcotics, if possible, to reduce the likelihood of dependency. In addition to their analgesic effects, NSAIDs may have a particular ability to abort CVS attacks in those with migraine-like presentations. If vomiting precludes taking oral NSAID doses, intravenous doses of NSAIDs such as ketorolac are standard practice.[20] Finally, there is an emerging role of opiate-sparing approaches such as ketamine to help treat pain and abort CVS/CHS episodes.[38,39]

The use of opiates as a component of ED-based abortive therapeutic regimens can be quite problematic. On one hand, these medications not only offer pain relief but also can abort an attack in a subset of patients. On the other hand, the frequent reliance on opiate medications in recurrent ED-based CVS/CHS care is a setup for psychological and physical dependence and may even ultimately confound the clinical presentation in cases of opiate withdrawal. Opiate administration should be considered only for those patients with extremely severe cases; it is not recommended for most CVS/CHS patients that are seen in the ED. It is imperative that if opiates are used in an ED-based abortive regimen that such use occurs in a comprehensive care model in which opiate exposures are tracked and patients are connected to psychological and/or addiction resources.

TABLE 3 Cyclic vomiting ED order set—Adapted from.[20]

Sample ED ADULT CVS Protocol
Operational definition
* A recurring pattern of discrete episodes of severe vomiting, accompanied by profound nausea and/or severe abdominal pain * Patient returns to usual health status between episodes (may have interepisodic nausea and or dyspepsia) * In some patients, CVS episodes resemble a migraine attack * Patients may be restless, anxious, and distressed * Patients are not customarily dehydrated until late in the episode
Therapeutic goal
Rapid recognition and intervention may decrease severity of the attack and promote prompt resolution of symptoms
ED management
1. Clinical assessment: Pulse/Temp/BP/Weight, consciousness, and hydration 2. Laboratories/evaluation: CBC, urea, creatinine, LFT's, lipase, glucose, and electrolytes EKG Urine analysis Diagnostic imaging at discretion of attending physician
Treatment
1. Intravenous fluids a. IV saline bolus if clinically dehydrated b. IV D5NS at 100%–150% maintenance (suggested rate is 200 cc/h for a 70 kg adult.) 2. For vomiting and nausea a. IV ondansetron 8 mg IV × 1—may repeat q 4–6 h if ondansetron is ineffective b. Consider diphenhydramine 50 mg IV and metoclopramide 10 mg IV c. Consider IV fosaprepitant 150 mg if available 3. For sedation a. IV lorazepam 1–2 mg and b. IV diphenhydramine 50 mg for additional sedation 4. For migraine-like presentation a. Sumatriptan nasal 20 mg (head forward technique) or b. Sumatriptan subcutaneous injection 6 mg/0.5 mL 5. For pain a. IV ketorolac 30 mg if >60 min from onset; may repeat 15 mg q 6 h × 2 (maximum 60 mg/d) b. Opioids may be considered as part of an ongoing treatment plan only in the most refractory patients
Reassess
1. Treatment failure—intensify treatment as indicated above or admit patient 2. Positive treatment response—discharge a. Continue ondansetron (soluble tablets) q 6–8 h × 24–48 h if initially effective b. Continue lorazepam × 24–48 h if initially effective c. Continue NSAIDs for pain as needed

1.5 | Developing an individualized ED care plan

An individualized care plan should be developed for patients who have frequent utilization of the ED to abort CVS or CHS attacks. For some patients, care could be provided with standing orders at an outpatient infusion center or even in a home care setting. For most patients, however, it is more feasible to organize a predictable care plan at a community or academic hospital ED. The ideal time to discuss and implement such a plan is during the interepisodic phase, informed by past responses to specific medical therapies. Process discussions to implement a care plan most often occur with the responsible medical administrator, who likely is the ED nurse manager. Hospitals adopting computerized medical records can increasingly trigger individualized treatment protocols for conditions such as CVS. These care plans relieve the patient of the effort to educate medical and nursing staff at every visit, as well as reassure ED staff against the idea of drug seeking behavior when requesting medications such as benzodiazepines. Ideally, these care plans should be developed by a patient's primary care physician or specialist and ED representatives, with the final care plan approved by the patient. An example of an individualized ED care plan for CVS is shown in Table 4. Physicians often find that the care plan simplifies decision-making and patients particularly find relief in experiencing predictable, effective care. Although data is lacking, anecdotal experience has shown that admission rates are lower in CVS or CHS patients whose care adheres to the ED care plans. This may reflect the fact that the care plan is informed by previously effective regimens, rather than reliant on a trial-and-error approach.

1.6 | Cannabinoid hyperemesis (CHS)

Unlike in CVS, the management of cannabinoid hyperemesis may be complicated by the implicit assumption that the patient has brought their misfortune on themselves. Most adult patients with CHS use cannabis in the belief that it is an effective antiemetic.[40] In an ED setting, the admission to previous use of cannabis tends to translate into overgeneralizations that any bout of protracted vomiting is the result of conscious overconsumption of a recreational psychoactive drug. This attitude becomes problematic as care can become compromised by moral judgment on the part of providers. Thus, it is incumbent on caregivers to be particularly careful in taking the medical history of the nature of cannabis exposure. The true nature of CHS is still murky due to factors which include stigma of nonmedical use, uncertainty of the concentration of THC in unregulated products and drug level achieved through different routes of drug ingestion.[41–47]

CHS may be more resistant to ED treatments than conventional CVS. While most patients will be given ondansetron or even aprepitant, anxiolytic medication or antidopaminergics such as prochlorperazine or haloperidol play a more prominent role in the CHS patient group.[48] Several studies suggest efficacy of topical capsaicin may be particularly helpful, implying a central mechanism dependent on TRPV1 receptor signaling in cutaneous dermal receptors.[49,50] Indeed, CHS was first identified in a cohort of patients reporting the use of habitual hot showers and chronic cannabis use,[51] leading to experimentation with the use of topical capsaicin as agonists for the cutaneous "heat sensor" ion channel. There are several special considerations in the administration of topical capsaicin. It is imperative that the caregiver wear gloves while administering topical capsaicin to prevent the caregiver and patient from inoculating their own eyes

TABLE 4 Example of an individualized ED CVS care plan of a patient with severe CVS.

Patient: John Doe Date: 5/12/24
DOB: 3/23/1983
"This care plan was developed to help improve compliance with treatment and promote better outcomes of care. All patients presenting to the Emergency Department receive a screening medical examination and have their emergency medical condition, if present, stabilized. All care is rendered with respect for patient privacy and dignity. No part of this care plan is intended to interfere with the clinical decision making of the treating physician."
Medical History: Cyclic vomiting syndrome
Emergency Department Care Plan:
If acute problem is exacerbation or recurrence of abdominal pain, nausea, vomiting:
a. Diagnostics per ED.
b. Recommend the regimen below for symptom management:
IV fluids (D5 ½ NS)
Ondansetron 8 mg IV
Diazepam 5–10 mg IV × 1
Toradol 15 mg IV × 1
Pantoprazole 40 mg IV × 1
Diphenhydramine 25 mg PO x1 after cessation of vomiting
Hydromorphone 0.3–0.5 mg IV q30 min prn ×2 if insufficient response from regimen above
c. If no acute pathology found, recommend discharge for outpatient follow up with her regular providers. Prescription for opioid or other controlled medications should not be provided unless extenuating circumstances are present.

Note: ED management is ultimately determined at the discretion of the emergency department physician.

or other sensitive areas.[49,50] Furthermore, capsaicin applied to the patients' trunk and back is more effective than when it is applied to the arms or legs.

Though temporarily effective in reducing anxiety, habitual use of cannabis as a form of self-medication may have unanticipated consequences. These concerns include the development of cannabis use disorder, which may be particularly problematic in the adolescent population. Emergency departments can at most serve to identify and refer patients for appropriate assessment and treatment for cannabis use disorder. The provision of a detailed discharge plan for those suspected of cannabis use disorder and CHS should include patient education, a continuing home medication protocol, specialist referral and referral to a drug counseling program.[20,49,50,52,53]

1.7 | Future directions in abortive therapy for CVS/CHS

The development of abortive therapies for CVS and CHS is limited by a lack of understanding of the pathophysiological basis of these disorders. Thus, there has been a largely empiric, rather than mechanistic, foundation for the abortive therapies discussed in this article. Future research into pathophysiological mechanisms that operate in CVS and CHS will be critical to develop the next generation of abortive therapies. For example, as has been well described in migraine, the calcitonin gene-related peptide (CGRP) system may similarly be important for CVS and/or CHS. If so, then CGRP inhibitors could have great potential use as novel abortive therapy for these conditions.

2 | CONCLUSION

CVS and CHS are highly impactful conditions that severely affect patients' quality of life. Patients can become demoralized by repeated attacks, and the frequent use of emergency department services poses burdens for the healthcare system. Medical treatment plans based on previously effective approaches for the individual patient are essential to abort attacks. In the best situations, patients learn to activate individualized rescue plans in the home, and when required, there is continuity of treatment in a local emergency department.

AUTHOR CONTRIBUTIONS

David J. Levinthal: Literature review, manuscript preparation, approval of final manuscript, agreement to be accountable for all aspects of the work. Blynda Killian: Literature review, manuscript preparation, approval of final manuscript, agreement to be accountable for all aspects of the work. Robert M. Issenman: Literature review, manuscript preparation, approval of final manuscript, agreement to be accountable for all aspects of the work.

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DJL is a consultant for Takeda Pharmaceuticals and Mahana Therapeutics. RMI has served on a Drug Safety Monitoring Board for Takeda Pharmaceuticals. BK has no conflicts to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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