

# **An Essay on the Management of Adult Cyclic Vomiting Syndrome, Including the Use of Opiates: questions posed and lessons learned from 191 patients.**

## ***Introduction***

Cyclic Vomiting Syndrome is a functional vomiting disorder characterized by recurrent, stereotypic episodes of overwhelming nausea and vomiting lasting hours or days, separated by intervals of wellness lasting weeks or months. Samuel Gee first described the condition in the English language literature in 1882<sup>(1)</sup>. He reported a series of 9 children ranging in age from 4 to 8 years. For more than a century thereafter, CVS was viewed as a pediatric disorder<sup>(2)</sup> with the result that it was nearly unknown by physicians practicing adult medicine. The fact that CVS is prevalent in adults has been recognized only in the past few years<sup>(3-6)</sup>. There are no evidence-based guidelines for the management of CVS in children or adults and it is my hope that this essay might contribute to further thinking and clinical investigation leading to a way out of a therapeutic wilderness.

## ***Management of Cyclic Vomiting Syndrome in adults***

Recognition of the four phases of CVS provides a framework for thinking about diagnosis and management<sup>(7)</sup>. The four phases are: The *inter-episodic phase*, during which the patient is relatively symptom free; the *prodromal phase*, which begins when the patient senses the approach of an episode, has nausea of varying intensity, but is still able to retain oral medications; the *vomiting phase*, characterized by intense, persistent nausea, vomiting, and other symptoms; and the *recovery phase*, which begins when nausea subsides and ends when the patients appetite, tolerance of oral intake, and vigor return to normal. Each phase has therapeutic goals. The goal of the inter-episodic phase is *prevention* of episodes. The goal of the prodromal phase is *to abort* the vomiting phase. The therapeutic goal during the vomiting phase is *termination* of the nausea and vomiting or, if this

cannot be achieved, *sedating* the patient until the episode passes; deep sleep makes the vomiting cease and makes the patient insensible to the misery of the attack. The goal of the recovery phase is *resumption of oral intake* without causing a relapse of nausea and vomiting <sup>(3, 8)</sup>

### ***The Vomiting Phase: where should patients be treated?***

Treatment of patients whose episodes last days rather than several hours is best done by direct admission to an in-patient setting. The experiences of sick cyclic vomiting patients in crowded, noisy emergency departments are generally unsatisfactory. There is little or no continuity of care.

Emergency department physicians know the formidable differential diagnosis of vomiting, but if they are unfamiliar with the patient's history or with CVS, they are likely to order redundant diagnostic tests, further delaying relief of the patient's symptoms. Typical treatment consists of rehydration and anti-emetic medication, after which the patient is sent home *before the attack has run its course*.

Many are forced to return to the Emergency Department where they may encounter personnel who are busy caring for the critically ill or injured and may be less responsive to the cyclic vomiting patient's misery. In general, ongoing management of functional disorders is an unwarranted imposition on emergency departments. In particular, the hours patients spend in Emergency Department waiting rooms delay or prevent effective care for those in the vomiting phase of CVS.

### ***Etiology and pathogenesis of CVS***

CVS is considered to be a manifestation of migraine diathesis <sup>(9-12)</sup>. The majority of children <sup>(7)</sup> and adults <sup>(3)</sup> have migraine diathesis as evidenced by the occurrence of migraine headaches in themselves and/or in their first or second degree relatives.<sup>(9)</sup> This has led to the biomedical attitude that CVS is

a disease treatable with anti-migraine and anti-emetic medications. *The central importance of anxiety in the pathogenesis and course of CVS has largely been missed.*

Li's analysis of a cohort of 214 children with CVS<sup>(9)</sup> sub-divided patients into two categories: 82% had migraine-associated CVS and 18% had non-migraine-associated CVS. Patients with migraine-associated CVS were more likely to benefit from migraine prophylaxis. Children with no migraine features responded poorly to anti-migraine drugs. The implication that could be drawn from this study is that there are two kinds of CVS and that they might differ with respect to pathogenesis and management.

Our experience with adult CVS patients prompted the hypothesis that they occupy a spectrum regarding their predisposition to cyclic vomiting attacks. At one end of the spectrum are those with migraine diathesis, but little or no pathologic anxiety; at the other end are patients devoid of migraine diathesis but afflicted with anxiety disorders complicated by panic attacks. The majority of adults occupy neither end of the spectrum, but have various degrees of both migraine and pathologic anxiety<sup>(3)</sup>. Therefore, it could be that Li's non-migraine children were predominantly anxious and that this could account for their low rate of response to anti-migraine medications. Few children with clinically significant anxiety develop panic attacks before early adolescence.<sup>(13,14)</sup> Therefore, the spectrum seen in adults may be less discernable in children, but may exist, nevertheless. The implication of the "spectrum" hypothesis for management is that the chances of success in individual patients depends on the appropriateness of the match-up between the pharmacologic agents used (e.g. anti-migraine, anti-anxiety or both) and the predisposing factors to attacks in individual patients (e.g. migraine, panic, or both)<sup>(3)</sup>.

Anxiety is one of many stresses that cause nausea and vomiting.<sup>(2-4)</sup> CVS patients, as a group, are more anxiety-prone<sup>(15)</sup>. Tarbell's prospective survey of children and adolescents with CVS revealed that they were at increased risk for internalizing psychiatric disorders, especially anxiety disorders<sup>(16)</sup>. Our review of a cohort of 41 adults<sup>(3)</sup> revealed that 68% had symptoms necessary for the diagnosis of panic attacks<sup>(13)</sup> during the prodromal and emetic phases of most or all of the cyclic vomiting episodes.

### ***The roles of physician and mental health professional***

Management of anxiety is a key factor in treating anxious CVS patients. In order to engage in this aspect of management, medical clinicians and mental health professionals need to consider their respective tasks as their basis for collaboration. This becomes clear when one considers three sources of anxiety in CVS patients.

One source of anxiety is the burden of illness, e.g., fragmented care, encounters with physicians who haven't heard of, or don't believe in the existence of CVS, the unavailability of a "quick and easy" treatment, patient's fears of losing their jobs and medical insurance because of absences from work, the unpredictability of episodes, and the financial burdens and damage done to family life caused by their illness. One-third of 41 adults surveyed were receiving disability support<sup>(3)</sup>.

The second source of anxiety is the anticipation of the next episode<sup>(3, 17)</sup>. Patients' anticipatory anxiety lowers the threshold for the next episode and contributes to a coalescent pattern of attacks<sup>(3)</sup>. (A similar phenomenon complicates the course of panic disorder in which fear of the unpredictable, uncontrollable onset of panic attacks contributes to the development of agoraphobia.<sup>(13)</sup>)

The third source of anxiety is neurotic or post-traumatic anxiety caused by past psychological traumas. All three categories of anxiety are present in a large number of anxious adults with CVS.<sup>(3)</sup>

The third category of anxiety is best treated by mental health professionals or, if that is not practicable, by the patients' personal physician to the best of his or her ability<sup>(18)</sup>. By contrast, the first two categories are based on current reality. The mental health professionals' contribution to the care of the anxious, panicky adult with CVS attacks can only succeed if the physician is able to bring the cyclic vomiting episodes under control. Referral of a patient to a mental health professional does little or no good if the first two sources of anxiety (the burden of illness and anticipatory anxiety) aren't being dealt with by the physician. The overwhelming power of the dysautonomic storms of CVS is hardly amenable to behavioral or psychotherapeutic measures alone.

Effective medical care of CVS patients seems to have five elements: 1) *continuity of care* by a caring physician who is familiar with CVS and who is accessible and responsive to the patient, especially during attacks; 2) the availability of *effective medications*, e.g. prophylactic agents, anti-emetics, anxiolytics and sedatives<sup>(8)</sup>; 3) there must be a *rational plan* for the deployment of effective medications<sup>(8)</sup>; 4) *promptness* in the clinician's response to the acutely suffering patient is itself therapeutic; long waits in treatment facilities are counter-therapeutic for patients in severe distress; 5) a "*default*" *procedure* of sedation is needed to relieve the misery of an episode that has failed attempts to prevent, abort, or terminate the attack. Clinical care that embodies these five elements creates a change in patients' attitudes, from feeling out of control of an illness that no one seems to understand or is willing or able to help, to a feeling of hope and having some control.

The “default” procedure I have used most often consists of intravenous sedation in an in-patient setting. Sedation has two benefits: first, deep sleep makes the centrally-generated vomiting cease immediately. Second, it makes the patient insensible to his or her nausea, abdominal pain and emotional distress. Being protected from the experience of misery by this procedure lessens patients’ anticipatory anxiety during the inter-episodic phase and reverses the trend toward a coalescent pattern of attacks. I prefer sedation with non-addictive agents, e.g. a mixture of chlorpromazine plus diphenhydramine <sup>(8)</sup>. Such a procedure, repeated until spontaneous clearing of the vomiting phase, gives the patient an “escape,” a way of coping with insufferable symptoms and a sense of having some control over their illness, rather than no alternative to unrelieved suffering <sup>(3, 8)</sup>. This sense of being in control, rather than helpless, is an indispensable therapeutic achievement necessary for progress towards improvement. The patient’s ability to abort the onset of the vomiting phase is one key element in achieving that sense of being in control.

### ***Practical considerations in the management of prodromal panic***

The two most important elements for success in aborting the vomiting phase during the prodrome are *timing* and the *efficacy* of abortive agents. The prodromal phase may last seconds or a day or more; it may not occur at all when the patient wakes from sleep already vomiting. The prodromal phase is important because patients may still be able to take medications by mouth and keep them down long enough for them to take effect. The chances of success are greater the earlier the abortive medications are used. Delay allows prodromal symptoms to gain momentum and become less stoppable. Therefore, many patients are advised to carry their abortive medications on their person. Abortive medications are directed at the typical symptoms each patient experiences during their prodrome, for example, ondansetron and/or promethazine for nausea, alprazolam or lorazepam for anxiety and nausea. The patient may then take a nap, helped by the sedative effects

of promethazine or lorazepam. If they awaken later feeling well, they would have successfully aborted their episode.

### *Psychiatric Considerations*

Because the majority of adults' attacks are triggered by the sudden onset of panic<sup>(3)</sup>, the diagnostic criteria of panic, consisting of 4 or more of 13 symptoms<sup>(13)</sup>, should be looked for. A psychiatric discussion of panic in a current textbook states the following:<sup>(19)</sup>

“Attacks usually last from 5 to 20 minutes and rarely last as long as an hour. Patients who claim they have attacks that last a whole day may fall into one of four categories. Some patients continue to feel agitated and fatigued after the main portion of the attack has subsided. At times, attacks occur, subside, and occur again in a wave-like manner. Alternatively, the patient with so-called long panic attacks is often suffering from some other form of pathologic anxiety, such as severe generalized anxiety, agitated depression, or obsessional tension states. In some cases, such severe anticipatory anxiety may develop with time in expectation of future panic attacks so that the two may blend together in the patient's description and be difficult to distinguish.”

Any adult CVS patient prone to panic attacks may have an ordinary, brief panic attack that does not trigger a CVS episode during the inter-episodic phase of their illness. However, the panic that triggers their cyclic vomiting episodes is not brief. Along with the CVS episode it leads to and becomes part of, the panic of CVS typically lasts hours or days. A valid question worthy of psychiatric research is whether such patients have any of the prolonged panic-like attacks mentioned in the section quoted above. However, such distinctions are not much help to the clinician managing a panicky patient who is in the throes of the vomiting phase of CVS.

Conventional prescriptions for psychotropic medications prescribed for patients with panic attacks are aimed at lowering the level of anxiety that predisposes to panic. In other words, standard pharmacotherapy for panic attacks aims at prevention of the attacks, not relief of an attack in progress. This approach is appropriate for ambulatory patients experiencing ordinary panic attacks that often resolve before orally-administered medications can have much effect. By contrast, the long lasting panic symptoms that occur during cyclic vomiting episodes require vigorous intervention. Many of the adult patients with panic-triggered cyclic vomiting episodes seen in my practice are already being treated with conventional agents, but haven't responded sufficiently. The patient who moans, writhes, vomits, sweats profusely, trembles, hyper-ventilates, has paresthesias, tachycardia, hypertension and cannot think clearly, can't wait for the episode to pass. Their dysautonomic "storm" is not likely to be quieted by SSRI's or even intravenous benzodiazepines. They need immediate relief.

### ***Opiates: a blessing and a problem.***

Opiates with anxiolytic properties are almost always effective in terminating ongoing panic, usually within minutes. If a patient with cyclic vomiting episodes triggered by panic is able, for example, to administer butorphanol nasal spray at the onset of prodromal symptoms, the episode may be aborted. However, it must be taken early enough during the prodrome because delays seem to lessen its efficacy. If a CVS patient who is vomiting and experiencing other symptoms of panic is given parenteral hydromorphone, the abdominal pain and nausea may subside as the panic attack is terminated. Therefore, anxiolytic opiates can be powerful tools in the management of panic-triggered CVS. It is reasonable to hypothesize that these calming effects involve opiate receptors in the amygdala, locus ceruleus and paraventricular nucleus of the hypothalamus, parts of the brain that are essential for the emotional and autonomic components of fear and panic <sup>(20)</sup>.

The obvious problem with the use of opiates is their potential for the development of tolerance and dependency as well as the possibility of addiction in addiction-prone patients.

At this point, it might be useful to review the distinctions between tolerance, dependency and addiction

<sup>(20)</sup>. *Tolerance* occurs over time as increased doses are required to produce the same physiologic response. *Dependence* means that, in addition to tolerance, the patient experiences withdrawal symptoms when the opiate is abruptly discontinued. By contrast, *addiction* is a behavioral syndrome characterized not only by tolerance and dependence, but, in addition, a behavioral pattern which includes compulsive use of opiates, an overwhelming preoccupation with their procurement, and a tendency to relapse after achieving abstinence. If opiates are self-administered during infrequent, panic-induced cyclic vomiting episodes, the development of tolerance and dependence is not likely. However, patients who treat themselves for almost daily prodromal panic are likely to develop tolerance and, in time, dependence. Nevertheless, *tolerance and dependence are not predictors of addiction* <sup>(20)</sup>. Fear of causing opiate addiction too often results in inadequate treatment of pain.<sup>(21)</sup> The intolerable pain and distress of panic-induced cyclic vomiting episodes are no less excruciating than that suffered by many patients with cancer, acute trauma, diabetic neuropathy or myocardial infarction. The indications for relief of pain are similar. If nothing less than opiates are required for adequate relief, then opiates should be administered.

Most non-addicted, opiate-dependent patients prefer to not use opiates. However, they are reluctant to give up access to opiates because they fear that, should they have another CVS attack, there would be no defense against the suffering it would cause.

The prognosis for improvement in CVS in children and adults is generally good <sup>(2, 3)</sup> and the hope of becoming opiate-free is realistic in non-addict patients. (Addicted patients are extremely difficult to treat as long as they use their doctor as a source of drugs rather than a source of help.) It is important to remember, however, that the course of any individual's CVS and the prospect of becoming drug-free are determined by the severity of the patient's co-morbid anxiety. The therapeutic goal in patients who use opiates on a daily basis should be to bring their anxiety disorder and CVS under control, and then withdraw them from opiates. It is almost impossible to discontinue opiates in a patient with panic-triggered CVS episodes before at least the first two of the three sources of anxiety (the burden of illness and anticipatory anxiety) have been managed successfully by attentive, responsive medical care.

Deterioration in panic disorder patients may take the form of agoraphobia <sup>(19)</sup>. Similarly, in panic-induced cyclic vomiting patients, deterioration takes the form of a coalescent pattern of attacks in which the episodes become more frequent and the level of autonomic hyperactivity during the interval between attacks approaches that of the prodromal phase of CVS.<sup>(3)</sup> In such cases, patients feel prodromal most of the time and the distinction between cyclic vomiting episodes and inter-episodic periods of wellbeing becomes unclear. Anxiolytic opiates taken at the onset of the prodrome are important because they relieve panic-induced pain and vomiting more effectively than any other drug available at this time.

A challenging problem that the opiate-dependent patient and the clinician share has to do with withdrawal symptoms that may occur as soon as a few hours after a missed dose. Withdrawal symptoms are easily confused with panic and with the prodrome of a CVS episode. The patient may not be able to distinguish panic from withdrawal and use opiates indiscriminately to gain relief. By so doing, opiate dependency is reinforced. Such patients are more challenging to manage because they need

more surveillance and responsiveness by their physicians. When a patient is sedated with substantial doses of non-narcotic sedatives, e.g., chlorpromazine and diphenhydramine, but sleeps for only about an hour, consider the possibility that opiate withdrawal may be interfering with sedation.

The majority of adults experience severe abdominal pain during CVS episodes.<sup>(3)</sup> The clinician should bear in mind that long-term escalation of opiate intake may lead to Narcotic Bowel Syndrome, characterized by worsening bouts of abdominal pain caused by opiate-induced bowel dysfunction.<sup>(22)</sup>

Another problem associated with the use of opiates is “drug seeking behavior.” Addicts use any manipulation in their all-consuming quest for the drug they need to achieve a “high” and relieve symptoms of withdrawal. By contrast, non-addicted opiate-dependent patients with panic-triggered CVS may also seek opiate medication, but for a legitimate therapeutic need. Many clinicians fear that preventing withdrawals by supplying a schedule of regular opiate medication will lead to addiction. In withholding or limiting opiate sufficient to prevent withdrawal symptoms, they induce drug-seeking in those CVS patients who need the drug, but do not escalate their intake or take it for a “high.” The problem such patients have when encountering physicians unfamiliar with the patient or the disorder, is that legitimate “drug-seeking” prompts the false assumption that the patient is an addict. Too often, this causes judgmental “rejection behavior” by the clinician which is a very damaging experience for the patient. The physician may also insist that the patient enter drug rehabilitation. Unfortunately, drug rehabilitation personnel, like many physicians, may not recognize or understand panic-triggered CVS and may be unable to deal with recurrences of the patient’s cyclic vomiting attacks. In my opinion, treatment for dependency can only be successful in clinical settings in which CVS episodes can be effectively treated, i.e. settings in which the five elements of care are provided. Only then, may the patient be willing to try giving up the medication that he or she has relied upon for relief of cyclic

vomiting attacks. Dependency and addiction are not clinically equivalent. Whereas management of dependent, but non-addicted patients should start with controlling their CVS followed by weaning of opiates, management of addicted individuals should start with detoxification before other non-emergent medical and psychiatric problems are addressed. The collaboration of a sub-specialist in Addiction Medicine is optimal for this purpose.

Prescribing opiates causes qualms about their legal and moral implications which inhibit their use by many clinicians. Irresponsible or self-serving prescribers of opiates behave immorally and illegally, but prescribing opiates for therapeutic benefits that cannot be achieved by any other means should not be viewed as such. There's another moral dilemma for the physician confronted with a CVS patient in distress: he or she has to choose whether to give the patient the agent that gives relief or choose to not get involved and just walk away.

The high level of care required for management of CVS patients is difficult for individual clinicians to provide. What is needed, therefore, are CVS "centers," each consisting of a small group of clinicians experienced in treating CVS patients who work together and cover each other in providing "24/7" access and prompt, effective treatment. That is what all CVS patients need, but it is especially important for CVS patients with psychiatric co-morbidities, such as anxiety disorders complicated by panic attacks and/or opiate dependency.

I look forward to the availability of anxiolytic agents that are powerful enough to relieve panic attacks but have no potential for tolerance or dependence. Neuropharmacologic agents that antagonize corticotrophin-releasing factor (CRF) may prove to be helpful in this regard.<sup>(23, 24)</sup> CRF is a neuropeptide secreted by the paraventricular nucleus of the hypothalamus. Under normal conditions, CRF regulates

the cyclical secretion of ACTH. It also coordinates the endocrinologic, autonomic and behavioral responses during stress<sup>(24)</sup>. It may play a key role in the pathogenesis of CVS<sup>(23)</sup>, including its nauseogenic suppression of gastric motility and its action on the locus cerueles that is probably involved in the hyper-adrenergic features of many CVS patients' episodes<sup>(3)</sup>. Other neuropeptides participate in the response of the CNS to stress and further research in the pharmacology of neuropeptide receptors may provide alternative agents to opiates for the management of panic.<sup>(25, 26)</sup>

## Summary

A large number of adults with CVS experience episodes that are triggered by panic attacks.<sup>(3)</sup> Unlike the ordinary brief panic attacks in patients with anxiety disorders, the panic experienced by many CVS patients persists during the prodromal and vomiting phases of their cyclic vomiting episodes. The psychopharmacologic agents used to treat typical panic are essentially prophylactic and are not effective in quelling the psychologic and dysautonomic aberrations that occur during the prolonged panic of CVS. Opiates that are anxiolytic seem to be the only agents capable of lysing this panic. The first step toward overcoming panic-induced CVS requires that patients' attitudes change from feeling out of control to feeling in control by having something they can do to protect them from the onslaught of a CVS episode. Having the ability to promptly relieve the panicky feelings associated with CVS attacks is therefore a crucial element in their management. Failure to quell prolonged panic results in ongoing suffering which, in turn, promotes anticipatory anxiety and coalescence of CVS episodes. Therefore, notwithstanding the problems of tolerance and dependency inherent in the use of opiates, the author recommends the administration of anxiolytic opiates in selected patients for whom no other pharmacologic agents are effective.

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