An Essay on the Management of Adult Cyclic Vomiting Syndrome,
Including the Use of Opiates:
questions posed and lessons learned
from clinical management of 216 patients

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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 relative wellness lasting weeks or months. Samuel Gee first described the condition in the English language literature in 1882 [1]. 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 [2] 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. [3-6]   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 thought and clinical investigation that will lead 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 [7, 8]. 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 patient's 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 [3, 8]

The Vomiting Phase: where should patients be treated?

Treatment of patients whose episodes last days rather than 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 long-term 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 re-hydration and anti-emetic medication, after which the patient may be 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. The hours patients may 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 [9-12]. The majority of children [7] and adults [3] have migraine diathesis as evidenced by the occurrence of migraine headaches in themselves and/or in their first or second degree relatives.[9] This has lead to the 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* [13]

Pediatric patients are more prone to anxiety. [14, 15] Anxiety disorders affect 84% of adults. [16]. Anxiety disorders may be complicated by panic attacks in adult patients. [17, 18] Panic attacks trigger cyclic vomiting episodes in the majority of adult patients. [3] Our experience with adult CVS patients suggested the hypothesis that they occupy a spectrum regarding their predispositions 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 which trigger their cyclic vomiting episodes. Most adults occupy neither end of the spectrum, but have various degrees of both migraine and pathologic anxiety [3].

In contrast to adults, few children with clinically significant anxiety develop panic. [17, 18] Li's analysis of a cohort of 214 children with CVS [9] 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.

Li's non-migranous category of pediatric CVS patients (those with poor responses to anti-migraine agents) might be triggered by acute anxiety, but without the dramatic presentation typical of the panic state.[17] Therefore, the "spectrum" hypothesized for adults[3] 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, in part, on the appropriateness of the match-up between the factors that predispose to cyclic vomiting attacks (e.g. migraine, panic or both) and the pharmacologic agents employed (e.g. anti-migraine, anxiolytics or both).   Patients correctly report that many factors other than anxiety trigger episodes, e.g. fatigue, menstrual periods, infections. [2, 3] However, many are unaware that they are anxious. Failure by the patient or physician to recognize significant anxiety misses an opportunity to treat this important aspect of the disorder when it exists.

The roles of physician and mental health professional

Medical clinicians and mental health professionals need to consider their respective tasks in the collaborative treatment of the anxious CVS patient. This becomes clear when one considers three sources of anxiety. 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 standard, "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 a cohort of 41 adults could not keep their jobs and were receiving disability support. [3]

The second source of anxiety is the *anticipation of the next episode* [3, 19]. Patients' anticipatory anxiety lowers the threshold for the next episode and contributes to a coalescent pattern of attacks [3]. (A similar phenomenon complicates the course of panic disorder in which fear of the unpredictable, uncontrollable onsets of panic attacks contributes to the development of agoraphobia.) [17, 18]

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. [3]

The third category of anxiety originates in the past and 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 [13]. 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 make the episodes less frequent, shorter and less agonizing. 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 has at least 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, analgesics and sedatives [8]; 3) there must be *a rational plan* for the deployment of effective medications [8]; 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 is powerfully therapeutic in that it 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.

The "default" procedure I have used most often consists of therapeutic 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 between attacks and reverses the trend toward a coalescent pattern of episodes. I prefer sedation with non-addictive agents, e.g. a mixture of chlorpromazine plus diphenhydramine [8]. 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 [3, 8]. Feeling 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 the *timing* and *efficacy* of abortive agents. The prodromal phase may last minutes or a day or more; it may not occur at all in patients who are wakened from sleep by the onset of 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 specific symptoms each patient experiences

during their prodromes, for example, ondansetron and/or promethazine for nausea, alprazolam or

lorazapam for anxiety and nausea, an opiate for abdominal pain. Patients may then take a nap,

helped by the sedative effects of promethazine or lorazapam. If they awaken later feeling well, they

would have successfully aborted their episode.

Psychiatric Considerations

Because the majority of adults' cyclic vomiting attacks are triggered by the sudden onset of panic [3],

the diagnostic criteria of panic, consisting of 4 or more of 13 symptoms [3, 17], should be looked for. A

psychiatric discussion of panic in a current textbook states the following: [20]

> "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 during the inter-

episodic phase of their illness that does not trigger a cyclic vomiting episode. However, the panic that

does trigger cyclic vomiting episodes is not brief. The panic-like state that initiates and becomes part of

the cyclic vomiting episode 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. Nevertheless, 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 associated with cyclic vomiting episodes require vigorous intervention. Many of the adult patients with panic-triggered cyclic vomiting episodes 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 - that patient 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 [21-23] are almost always effective in ameliorating ongoing panic, usually within minutes. For example, if a patient with cyclic vomiting episodes triggered by panic is able to administer butorphanol nasal spray at the onset of prodromal symptoms, the episode may be aborted, provided it is taken early enough. 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 relieved. 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

present 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 [22].

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, addiction and pseudo-addiction. [23] *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 unlikely. 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* [22, 23]. Dependency and addiction are not clinically equivalent. Unfounded fear of causing opiate addiction in patients with no history of drug abuse too often results in inadequate treatment of pain.[22-23] The intolerable pain and distress of panic-induced cyclic vomiting episodes are no less excruciating than that suffered by many patients with cancer 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. The author has prescribed opiates to 18.6% of his cohort of 216 adult CVS patients.

Most non-addicted, opiate-dependent patients prefer to not use opiates. However, they may be 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 [2, 3] 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. The collaboration of a specialist in addiction medicine is optimal for this purpose. It is important to remember, however, that the course of any individual's CVS and the chances of becoming drug-free are determined by the severity and tractability of the patient's co-morbid anxiety. The therapeutic goal for patients who use opiates on a daily basis should be to bring their anxiety and CVS under control. Only then are they willing to pursue withdrawal from opiates and often do so on their own. It is almost impossible to discontinue opiates in a patient with panic-triggered CVS episodes before the first two of the three sources of anxiety (the burden of illness and anticipatory anxiety) have been brought under control by attentive, responsive medical care.

Deterioration in panic disorder patients may take the form of agoraphobia [17, 18]. By analogy, deterioration in adult CVS patients 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. [3] In such cases, patients feel prodromal most of the time and the distinction between episodes and inter-episodic periods of wellbeing becomes unclear. The use of anxiolytic opiates taken at the onset of the prodrome can be a valuable therapeutic adjunct 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 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 from their physicians. When a patient requires sedation 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 functional abdominal pain during CVS episodes.[3, 16] Three kinds of functional abdominal pain may affect CVS patients: Irritable Bowel Syndrome[2, 16], abdominal migraine [10] and the abdominal pain that is a symptom of panic.[17] Administration of hydromorphone, for example, dramatically relieves the abdominal pain that afflicts the majority of patients[3] To what extent the relief of pain is due to opiate's analgesic effect or anxiolytic effect, both, or some other mechanism is worthy of further research.

The clinician should also bear in mind that long-term escalation of opiate intake may occasionally lead to Narcotic Bowel Syndrome, characterized by worsening bouts of abdominal pain caused by opiate-induced bowel dysfunction. [24]

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 withdrawal symptoms. By contrast, non-addicted opiate-dependent patients with panic-triggered CVS

may also seek opiate medication, <u>but for a legitimate therapeutic need</u>. "Pseudo-addiction" to opiates is

a syndrome that resembles true addiction in that both are characterized by "drug-seeking behaviors."[25, 26] (See Table 1.) Differentiating the pseudo-addict from the true addict may not be easy at first

encounter. Some of the contrasting features of the two syndromes are indicated in Table 2.

Table 1

Drug Seeking Behaviors
- **Aggressive complaining about the need for more drug that may seem excessive**
- **Drug hoarding during periods of decreased symptoms**
- **Requests for specific drugs**
- **Requesting parenteral, rather than oral administration**
- **Interactions with medical staff have a manipulative quality**
- **Patient is unusually sophisticated about opioids and opioid treatment**
- **Patient presents a posture of negotiation about treatment**

Adapted from Portenoy RK, Payne R, Passik, SD *Acute and Chronic Pain,* Lowinson JH, Ruiz P, Millman RB, Langrod JG, *Substance Abuse,* Chapter 55, 4th Edition, Philadelphia, Lippincott Williams & Wilkins, 2005

Table 2
Comparative Features of Opiate Addiction & Pseudo-Addiction [25]

Addiction	*Pseudo-Addiction*
Drugs are acquired and used outside of the medical context	**Drugs are acquired within a clinical relationship for medically indicated purposes**
Drug seeking to satisfy addictive cravings and avoidance of withdrawal	**Drug seeking for symptom relief and avoidance of withdrawal**
Seeks unlimited access to opiates	**Declines opiates in excess of the amount needed for symptom control**
Poor control over drug intake despite awareness of harmful effects	**Good control over drug intake and concern about potential harmful effects**
Strong tendency to relapse after successful detoxification	**No tendency to relapse after successful detoxification**
Treatment: detoxification in patients who use opiates for their psychic effects	**Treatment: increase the dose to levels at which the patient is relieved of pain; then wean opiates as the cause of the pain resolves.**

Many clinicians fear that preventing withdrawals by supplying a schedule of regular opiate medication to a non-addict will lead to addiction. Instead, withholding or limiting opiate sufficient to relieve symptoms or prevent withdrawal leads to pseudo-addiction by inducing drug-seeking in those non-addict 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 opiate pseudo-addiction, is that legitimate drug-seeking prompts the false assumption that the patient is an addict. Too often, this causes judgmental rejection by the clinician which is a damaging experience for the patient.   The physician may also insist that the patient enter drug rehabilitation on the assumption that the recurrent vomiting is caused by the use of opiates. I have yet to encounter a cyclic vomiting patient whose nausea was intensified by butorphanol or hydromorphone administered during the prodromal or vomiting phases of an episode. 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 active dependency requires a clinical setting 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 to wean themselves from the medication that he or she has relied upon for relief of cyclic vomiting attacks.

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 provides 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. Neuro-pharmacologic agents that antagonize corticotrophin-releasing factor (CRF) may prove to be helpful in this regard. [27, 28] 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 endocrinologic, autonomic and behavioral responses during stress [28]. It may play a key role in the pathogenesis of CVS [27], 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 [3]. 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 prolonged panic. [29, 30]

Summary

A large number of adults with CVS experience episodes that are triggered by panic attacks. [3,16] Unlike ordinary brief panic attacks experienced by some 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 psychological and dysautonomic aberrations that occur during the prolonged panic of CVS. Opiates that are anxiolytic seem to be the only agents capable of relieving 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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The author declares that he has no competing interest, financial or otherwise, in writing this essay or submitting it for publication.