Cyclic Vomiting Syndrome:
An Update Illustrated by a Case Report

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ABSTRACT

Objective: This article presents an update on cyclic vomiting syndrome, a potentially exhausting disorder that can occur in children, adolescents, and adults and and has a huge impact on the quality of life. A structured literature search was conducted to explore the current knowledge about antipsychotics in the treatment of cyclic vomiting syndrome. A case report is presented of a 15-year-old boy with refractory cyclic vomiting syndrome (*ICD-10* criteria), who finally responded to a unique combination of risperidone and amitriptyline.

Data Sources: A literature search of English articles was performed in November 2015 using PubMed and the Cochrane Library with *cyclic vomiting syndrome*, *cyclic vomiting*, *risperidone*, and *antipsychotics* as key words. All types of publications were included. The publication period covered a span from 1976 to 2014.

Study Selection and Data Extraction: In total, 13 articles were found. After screening the title and abstract, only 2 were selected.

Results: In the current literature, only the use of chlorpromazine in the treatment of cyclic vomiting syndrome is mentioned. The possible underlying working mechanism of chlorpromazine is not clarified.

Conclusions: Antipsychotics are hardly mentioned in the literature with regard to their antiemetic properties. Antipsychotics like risperidone, and its unique combination with amitriptyline, might be an important alternative to achieve a satisfactory treatment result in refractory cases of cyclic vomiting syndrome.

Prim Care Companion CNS Disord
2016;18(3):doi:10.4088/PCC.15br01912

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Cyclic vomiting syndrome is a disorder characterized by episodes of idiopathic vomiting alternated with periods of no symptoms. This syndrome mostly affects children but can occur in adults as well.[1] The *DSM-IV* and *DSM-5* do not acknowledge this specific syndrome, but the *ICD-10* does. Cyclic vomiting syndrome is defined as a functional gastrointestinal disorder according to the Rome III criteria[2] (created by the Rome Foundation, an independent nonprofit scientific and internationally operating organization that supports research, diagnosis, and treatment of functional gastrointestinal disorders). These diagnostic criteria contain the following items: (1) stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week), (2) 3 or more discrete episodes in the prior year, and (3) absence of nausea and vomiting between episodes. According to the Rome III criteria, all 3 criteria must be met. A supportive criterion is a history or family history of migraine headaches, as cyclic vomiting syndrome may be considered a migraine variant.[3] However, Moses et al[4] state that "the diagnosis of cyclic vomiting syndrome continues to be a clinical one based on exclusion of other conditions and expert consensus with the aid of diagnostic criteria."(p571) Other researchers[5] share this opinion. Kaul and Kaul[6] report a frequency of "2 or more periods (cycles) of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-month period."(p225) The age at onset covers a broad span, with a range from the toddler or preschool years in most cases up to late adulthood (age at onset up to 73 years).[1] The gender ratio shows that the syndrome is slightly more common in females than in males in all age groups (55:45 or 60:40).[7,8] The prevalence ranges from 1.9% to 2.3% in the pediatric population, while the prevalence in adults is not known.[8]

While the exact pathogenesis remains unknown, there seems to be an association between cyclic vomiting syndrome and migraine headaches and abdominal migraine.[1,6] There also may be a link between cyclic vomiting syndrome and food allergy, mitochondrial disorders (eg, defects in fatty acid oxidation or respiratory chains associated with metabolic crises and vomiting), and metabolic and endocrine disorders (defects of the hypothalamic-pituitary-adrenal axis).[1,6] An underlying autonomic neuropathy (impairment of the sympathetic nervous system) has been suggested.[6] Cyclic vomiting syndrome has a big impact on several important domains (eg, emotional, physical, social, and school) and can therefore severely diminish quality of life.[9]

CASE REPORT

To illustrate clinical decision making and treatment for cyclic vomiting syndrome, we present a short case report. In our tertiary university hospital outpatient clinic, we met a 15-year-old boy

Clinical Points

- Cyclic vomiting syndrome can be a serious condition.
- Cyclic vomiting has to be considered in the case of recurrent episodes of vomiting in absence of other explanatory conditions.
- While dopamine seems to be the central neurotransmitter in vomiting, the use of antipsychotics for the treatment of cyclic vomiting syndrome is not well known.

with a second episode of acute refractory vomiting with no preceding factors or stressors. The patient achieved his developmental milestones at normal ages and grew up in a stable, middle-class family consisting of his parents and a younger sister. His medical history includes gastroesophageal reflux as an infant and unilateral congenital blindness in his left eye. The first episode of (retrospectively: cyclic) vomiting started in 2012 after an episode of gastroenteritis and continued for several months. A gastroscopy showed no pathology, except for some irritation of the esophagus, and, thus, lactose intolerance and celiac disease were excluded. Domperidone provided no relief, but after starting pantoprazole, the frequency of vomiting slowly decreased to zero.

In October 2014, the boy suddenly started vomiting again after another episode of gastroenteritis. Pantoprazole provided no relief. Because of the lack of pathology during his previous presentation, he was sent to our department of child and adolescent psychiatry with a suspicion of somatic and psychiatric comorbidity. At that time, he had lost 11 lb (5 kg) and weighed 123 lb (56 kg, height: 1.78 m). He was very exhausted and had stopped going to school and his sports clubs. After admission and exclusion of acute stressors, we first sent him to a pediatric gastroenterologist and a child neurologist to ensure that there was no underlying pathology. Organic causes were excluded, and a trial with a hypoallergenic diet made no difference. His cytochrome P450 (CYP) status was also checked, and he appeared to be a slow metabolizer of CYP2D6, CYP2C9, and CYP2C19. The patient was suspected to have cyclic vomiting (*ICD-10* criteria). He vomited several times a day at that time, mostly in the morning and without being nauseous.

Starting in January 2015, he was treated initially with risperidone liquid 1 mg/mL in a daily dose up to 0.4 mg. He responded very well at first. The vomiting stopped for 4 weeks. However, the daily vomiting started again when the medication administration time was changed from evening to morning (because he sometimes forgot to take the medication in the evenings). The dose of risperidone was slowly increased to a daily dose of 1.6 mg. After every dose increase, the vomiting stopped for 4 or 5 days and then reappeared again. Because of the lack of effect, risperidone was phased out in May 2015 and replaced with amitriptyline in a daily dose up to 30 mg (initially in the morning and later changed to the evening because of vomiting in the morning). The vomiting continued. A lifestyle diary was no help in discovering a possible trigger. Nevertheless, we referred the boy to a psychologist for additional cognitive-behavioral therapy in an attempt to control his vomiting. In June 2015, we decided—also at the request of the patient and his family due to lack of therapeutic response—to add risperidone liquid 1 mg/mL again in a daily dose of 0.4 mg before bed. The vomiting abruptly stopped, and at the time of article submission, the boy had experienced no vomiting episodes for almost 7 months.

LITERATURE REVIEW

Because of the unique response of our patient to risperidone (and its combination with amitriptyline), a structured literature search of English-language articles was conducted in November 2015 to explore the current knowledge about antipsychotics in the treatment of cyclic vomiting syndrome. PubMed and the Cochrane Library were searched using the key words *cyclic vomiting syndrome*, *cyclic vomiting*, *risperidone*, and *antipsychotics*. There were no other search limitations. All types of publications were included. The publication period covered a span from 1976 to 2014.

Study Selection and Data Extraction

In PubMed, the combination of search terms revealed 9 publications. Five were excluded after screening the title (subject other than cyclic vomiting syndrome). Three were excluded after screening the abstract (use of therapeutic interventions other than antipsychotics). The remaining article by Özdemir et al[10] on the use of chlorpromazine in cyclic vomiting syndrome was selected. This article referred to an important article by Forbes and Fairbrother,[3] which was also selected after full screening.

In the Cochrane Library, the combination of search terms revealed 4 publications. Three were excluded after screening the title (subject other than cyclic vomiting syndrome) and 1 was excluded after screening the abstract (use of therapeutic interventions other than antipsychotics).

Results

In total, only 2 articles were selected.[3,10] The first identified article by Özdemir et al[10] describes the case of a 19-year-old woman with cyclic vomiting syndrome that finally responds to chlorpromazine. The article[10] mentions that, although the antiemetic effect of chlorpromazine is known, the effectiveness in cyclic vomiting syndrome is only described in a few publications. Possible underlying working mechanisms are not clarified.

Forbes and Fairbrother[3] state in the second identified article that "sedation and anxiolysis with agents such as chlorpromazine or lorazepam is important as sleep decreases vomiting frequency."(p36) Also in this article, possible underlying working mechanisms are not clarified. No other antipsychotics are mentioned in these articles.

DISCUSSION

Cyclic vomiting syndrome is a heterogeneous disease, and its definition differs in the literature.[2,5,6] Our case

shows—like many cases in clinical medicine—an atypical course. The patient does not meet all Rome III criteria for cyclic vomiting syndrome. However, because there is no consensus on the diagnostic criteria of cyclic vomiting syndrome[4–6] and given the fact that organic causes and major stressors were excluded, the diagnosis of cyclic vomiting syndrome therefore still suits our patient. An eating disorder and cannabis hyperemesis syndrome[11] would have been important differential diagnoses. We ruled out an eating disorder because the vomiting was involuntary, the vomiting already existed when the anticipation behavior started, his self-image was not disturbed, and he had no intention to lose weight. Cannabis hyperemesis syndrome was ruled out because he did not use cannabis.

The treatment of cyclic vomiting syndrome includes nonpharmacologic and pharmacologic interventions. The nonpharmacologic interventions consist of avoiding triggers and supportive psychological interventions. In this case, we initially decided to treat the boy with medication because of his worsening condition and progressive weight loss. Because of the patient's heavy anticipation of vomiting, we also referred him to a psychologist for cognitive-behavioral therapy. Pharmacologic interventions are based on influencing the neurotransmitters that are involved with vomiting and the vomiting center in the reticular formation of the medulla oblongata. The most important neurotransmitters in vomiting are dopamine, histamine, acetylcholine, and serotonin.[12,13] In clinical practice, pharmacologic interventions consist of drugs like ondansetron and domperidone in the acute phase and tricyclic antidepressants and beta blockers in the preventive phase.[5,7,12]

Although dopamine is an important neurotransmitter in the treatment of vomiting and cyclic vomiting syndrome, pharmacologic treatment options with antipsychotics are hardly mentioned in the literature. Most antipsychotics, especially haloperidol, have antiemetic properties.[14] Risperidone is comparable to haloperidol in its receptor-binding profile, but we chose risperidone because of (1) a possibly lower risk of side effects like extrapyramidal symptoms and (2) a previous positive experience in another child with the same disorder.

Still, after almost 7 months, the combination of risperidone and amitriptyline remains effective in our patient, but we do not understand why. We wonder if the change in time of medication administration triggered the vomiting again and why increasing the risperidone dose did not stop the vomiting. Maybe the relation between risperidone, its effect on cortisol levels, and, as a result of varying cortisol levels, its effect on nausea could be explanatory. Nevertheless, the maximum daily dose of risperidone 1.6 mg in the morning used during his relapse even exceeds the previous very successful daily dose of 0.4 mg in the evening.

We also do not understand why the unique combination of amitriptyline and risperidone was rapidly successful. Maybe the fact that the boy is a slow metabolizer of CYP2D6, CYP2C9, and CYP2C19 is explanatory. The combination of amitriptyline and risperidone creates a relatively high anticholinergic effect, which may diminish nausea and vomiting. But, clinically, the patient only experienced a dry mouth as a result of this anticholinergic effect. However, it is remarkable that our patient responded to several drugs (pantoprazole, risperidone) initially but not when the drugs were restarted or changed. This reason is also why we have not decreased or stopped the dose of amitriptyline to investigate if the abrupt on-off effect is caused by risperidone only. Given the low quality of life during vomiting, such a medication change would be unethical. The patient's high sensitivity to changes in medication could also be related to the individual development of the pubertal brain (work in progress: pruning in combination with myeliniation) and the development of the vomiting center. Another explanation that the observed effect is a result of a benignant natural course is unlikely, given the slow extinguishing of vomiting in the former episode, in combination with 2 fast on-off medication effects.

In relation to causation, we have applied Hill's criteria[15] to the case history. Six of the 9 criteria apply to this case. The criterion of temporality applies because of the evident relation in time and that of strength applies relatively because of the 2-fold acute medication effects. The criteria of plausibility and coherence apply because of our argumentation and considerations. The criterion of consistency applies because of the current literature about the vomiting center and its neurotransmitters. And, the criterion of alternative explanation has already been addressed as well. So, only the criteria of specificity, dose-relationship, and experiment are not really applicable because of the context of regular common outpatient care.

CONCLUSION

Refractory cyclic vomiting is a perhaps not so rare but potentially exhausting and dangerous disorder with a big impact on quality of life. Remarkably, antipsychotics are, despite their well-known antiemetic properties, hardly mentioned in literature on the treatment of cyclic vomiting syndrome. Risperidone, in its unique combination with amitriptyline, might be an important alternative to achieve a satisfactory treatment result in refractory cases.

Submitted: November 23, 2015; accepted February 18, 2016.
Published online: May 12, 2016.
Drug names: lorazepam (Ativan and others), ondansetron (Zofran and others), pantoprazole (Protonix and others), risperidone (Risperdal and others).
Potential conflicts of interest: None.
Funding/support: None.
Acknowledgment: We are grateful to the patient and his family, who gave their written consent.

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