THE UNIVERSITY OF ARIZONA | MEL AND ENID ZUCKERMAN COLLEGE OF PUBLIC HEALTH

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The Relationship Between Marijuana Use and Cyclical Vomiting Syndrome

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Introduction

This review evaluates the evidence on the link between marijuana use and cyclical vomiting syndrome (CVS). The Arizona Department of Health Services (ADHS) requested this report as part of a series of assessments on the benefits and harms of using marijuana to treat medical conditions.

Background

Cyclical vomiting syndrome, as defined by the Rome III criteria, includes: "(i) stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week), (ii) three or more discrete episodes in the prior year, and (iii) absence of nausea and vomiting between episodes."[1] In 2004 Allen and colleagues published the first case series suggesting that chronic marijuana use may lead to the development of CVS.[2] Since this first published report multiple case reports and a few observational studies have been published addressing this question. Some of these studies address cannabinoid hyperemesis syndrome (CHS), an illness similar to cyclical vomiting syndrome though the diagnostic criteria include a history of regular cannabis use for years.[3] Differing opinions exist on whether or not CHS is a subgrouping of cyclical vomiting syndrome or whether it is its own seperate entity.[4]

The key question this review will attempt to address is whether there is a proven correlation between marijuana use and CVS, and is there evidence that one causes the other?

Conflicts of Interest

The authors of this review have no conflicts of interests to disclose.

Methods

Literature Search and Strategy

A search of the databases MEDLINE (PubMed), The Chocrane Library, CINAHL (EBSCO), psycINFO, and Web of Science for the topics of marijuana use and CVS was conducted during the time period September - November 2012. The Google Scholar database was also used to search the gray literature, including unpublished and electronically published studies. The reference lists from each article found were reviewed for additional studies. Detailed search strategies can be reviewed in Appendix I.

Inclusion and Exclusion Criteria

All studies identified during search were screened using the following criteria:

1. Humans with CVS
2. English Language
3. 1980 – present
4. Study addressed the key questions

Studies were excluded if they were:

1. Animal studies
2. Editorials or opinions
3. Not addressing a key question
4. Not published in English

Data Synthesis

The quality of each of the case control and cohort studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.[5] The quality of each of the case series studies was assessed using methods adapted from Deeks et al and the Agency for Healthcare Research and Quality[6,7]. The quality of each literature review was assessed using the AMSTAR criteria described in Shea, et al.[8] Two investigators (D.C-O. and A.J.) individually assessed the studies according to the criteria previously mentioned, then met to discuss and come to a conclusion on the final quality rating of each study. Overall quality of evidence and causation criteria were determined using the GRADE methodology and the Bradford Hill criteria, respectively.[9-11] (See Appendix V)

Results

A total of 94 articles were identified through The Cochrane Library, PubMed, PsycINFO, CINAHL (EBSCO), and Web of Science and another one was discovered from references cited in key articles, and 37 were found to either address the key questions or contain data pertinent to the question. The study designs of included article were: 1 case-control study[12], 3 cohort studies [13-15], and 28 case series/case reports [2,4,16-41]. There were also 5 reviews of the literature found. [42-46] Table 1 describes the case-control and cohort studies and the four largest case series.

Table 1

Article and Citation	Description and Study Design	Results	Quality Assessment
Choung RS, Locke GR,3rd, Lee RM, Schleck CD, Zinsmeister AR, Talley NJ. Cyclical vomiting syndrome and functional vomiting in adults: Association with cannabinoid use in males. *Neurogastroenterol Motil*. 2012;24(1):20-6, e1.	Case Control [n=226 (82 CVS, 62 FV, 82 IBS)] Mayo Clinic Rochester The study retrospectively evaluates whether clinical and gastric emptying data distinguish CVS from FV and IBS.	Cannabis use increased the odds for CVS relative to non-users and those with FV [OR = 2.9, 95% CI (1.2,7.2), P = 0.02] but gender was a confounding variable and it was found that cannabis use in males increased the odds for CVS relative to non-users (OR = 3.9, P < 0.05) but not in females (OR = 1.2, P = 0.77); the study also found cannabis use to be higher in CVS than in IBS [OR = 7.0, 95% CI (2.1,23.5), P < 0.001].	Poor quality– cannabis use was extracted from a self-reported questionnaire completed by all clinic patients with a large potential for under-reporting; confounding variables were not controlled for.
Hejazi RA, Lavenbarg TH, Foran P, McCallum RW. Who are the nonresponders to standard treatment with tricyclical antidepressant agents for cyclical vomiting syndrome in adults? *Aliment Pharmacol Ther*. 2010;31(2):295-301.	Prospective Cohort (n=132) Texas Tech The study analyzed a cohort of patients with CVS to uncover clinical features that distinguish TCA responders from nonresponders.	The study does not directly address the key question but did find that 53% of the nonresponders reported chronic marijuana use and only 22% of the responder group reported chronic marijuana use.	Poor quality – patients all from one author's clinic with potential for sampling bias; no definition/methods /protocol for TCA exposure; marijuana use was self-reported allowing potential for recall bias and underreporting; unclear follow-up length.
Lee LY, Abbott L, Moodie S, Anderson S. Cyclical vomiting syndrome in 28 patients: Demographics, features and outcomes. *Eur J Gastroenterol Hepatol*. 2012;24(8):939-943.	Retrospective Cohort (n=29) London The study analyzes the clinical features of a cohort of patients with CVS. It also explores treatments for attacks and prognosis of patients treated conservatively.	28.6% of patients with CVS reported previous cannabis abuse.	Poor quality – self-reported marijuana use with potential for recall bias and underreporting; subjective scale used to assess clinical outcomes following diagnosis
Namin F, Patel J, Lin Z, et al. Clinical, psychiatric and manometric profile of cyclical vomiting syndrome in adults and response to tricyclical therapy. *Neurogastroenterol*	Prospective Cohort (n=31) Kansas University The study explores the clinical features, psychiatric status, and gastric motility of	The study secondarily addressed the key question and found 13 (42%) patients admitted to at least weekly marijuana use;	Poor quality– high loss to follow-up (45%) with no description of those lost; self-reported marijuana use with potential for

Motil. 2007;19:196-202.	a cohort of patients with CVS along with therapeutic outcomes of TCA therapy in this group.	7 found the marijuana therapeutic for symptoms of CVS; 2 with heavy use dating back to teenage years found resolution of symptoms upon ceasing marijuana use; 4 did not see a relationship between their marijuana use and their CVS.	recall bias and underreporting.
Hejazi RA, Lavenbarg TH, McCallum RW. Spectrum of gastric emptying patterns in adult patients with cyclical vomiting syndrome. *Neurogastroenterol Motil*. 2010;22(12):1298-302, e338.	Case Series (n=92) Texas Tech The study investigates gastric emptying patterns in patients with CVS and explores clinical characteristics associated with the different patterns.	The study does not directly address the key question. 30 (32%) patients reported marijuana use and 11/13 with delayed gastric emptying time reported marijuana use. The authors conclude that CVS patients can have delayed emptying time if they are chronic marijuana smokers.	Poor quality– patients all from one author's clinic with potential for sampling bias; marijuana use is self-reported with the potential for underreporting.
Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: A case series of 98 patients. *Mayo Clin Proc*. 2012;87(2):114-119.	Case Series (n=98) Mayo Clinic, Rochester, though the patients represented 28 states and Canada The study analyzes 98 adult cases of cannabinoid hyperemesis.	The study explores CH and not CVS. Inclusion criteria included long-term cannabis use before onset of CH symptoms. 10 patients were followed up and 6 ceased cannabis resulting in resolution of CH symptoms. 1 patient abstained from cannabis for one month and did not experience resolution of symptoms.	Poor quality– self-reported marijuana use with potential for recall bias and underreporting; low rate of follow-up (10/98).
Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: Cyclicalal hyperemesis in association with chronic cannabis abuse. *Gut*. 2004;53(11):1566-1570.	Case Series (n=9) South Australia The study analyzed a series of cases of a cyclical vomiting illness in association with chronic marijuana use.	In all 9 cases chronic cannabis use preceded the development of the cyclical vomiting illness; 7 patients ceased cannabis use and the illness resolved; 3 of these relapsed and developed the illness again; 2 of these 3 again ceased cannabis use and again their illness resolved. 3	Poor quality – sample was not representative (small n, 2 self-referrals) with potential for sampling bias; frequency of cannabis use was self-reported with the potential for underreporting and recall bias.

Soriano-Co M, Batke M, Cappell MS. The cannabis hyperemesis syndrome characterized by persistent nausea and vomiting, abdominal pain, and compulsive bathing associated with chronic marijuana use: A report of eight cases in the united states. *Dig Dis Sci*. 2010;55(11):3113-3119.	Case Series (n=8) Missouri The study analyzes 8 adult cases of cannabinoid hyperemesis syndrome.	The study explores CH (not CVS), 5 patients ceased cannabis use and 4 had resolution of CH. 1 of these 4 resumed cannabis use and symptoms of CH recurred.	Poor quality – unrepresentative sample (small n, patients all pulled from investigators' clinics) with potential for sampling bias; self-reported marijuana age of onset and frequency of use with potential for recall bias and underreporting.
CVS, cyclical vomiting syndrome; FV, functional vomiting; IBS, irritable bowel syndrome; MCR, Mayo Clinic Rochester; CH, cannabinoid hyperemesis; TCA, tricyclic antidepressant			

The four observational studies included one case-control study of patients with GI problems, 1 prospective cohort and 2 small retrospective cohort studies. All were of poor quality and none were designed to determine if CVS occurs more frequently in cannabis users than in nonusers. The four case series described 207 cases in total and included patients with CVS or cannabinoid hyperemesis syndrome; 115 of the cases reported chronic cannabis use that preceded cyclical vomiting or cannabinoid hyperemesis symptoms. Eighteen of the 207 (9%) ceased cannabis use and 16 of those 18 (89%) had resolution of their vomiting symptoms. Two of these 13 (13%) patients re-challenged themselves with marijuana and both found that the vomiting symptoms recurred.

The remaining 24 original articles were all case reports that included a total of 34 cases. They described patients with CVS who reported chronic cannabis use that preceded their illness or had cannabinoid hyperemesis syndrome; 21 of these 34 ceased cannabis use when informed that it may be the cause of their symptoms and 19 of those 21 (90%) had resolution of their vomiting symptoms. Nine of these 19 (47%) patients re-challenged themselves with marijuana use and all 9 found that the vomiting symptoms recurred. No cases reported spontaneous resolution of vomiting symptoms.

The 5 literature reviews described the cases and studies previously mentioned in this report. These articles were all poor quality general literature reviews with none providing a systematic assessment of the quality of the studies they discussed. They simply summarized what had been found in the above observational studies and case reports.

Overall Evidence Quality

The overall quality of the evidence on the key questions is very low. There are a limited number of observational studies of poor quality and that do not directly address the key questions. As observational studies they start at a GRADE level of "low" and are downgraded to "very low" because of serious threats to validity and probable publication bias, although we did not directly test this last criterion.

The body of evidence met only two of the nine Bradford Hill criteria for causation; temporality and plausibility. There is not enough evidence available at this time to determine strength of association, consistency, specificity, biological gradient, coherence, experiment, analogy.

Discussion

At this time the evidence is insufficient to know whether chronic cannabis use causes CVS or not. There is no information at this time that indicates that CVS occurs in chronic marijuana users at higher rates than non-users. The case reports published indicate that there might be some patients with CVS whose symptoms improve with cessation of marijuana use but in the absence of higher quality evidence this should be considered every preliminary and suggestive, and not as proof of a relationship.

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Appendix 1 – Search Protocol

CINAHL (EBSCO)

September 11, 1-2pm

Search Number	Search Terms	Results Yielded
1	MH "Cannabis"	2853
2	MH "Vomiting"	1517
3	MH "Anticipatory Nausea and Vomiting"	45
4	MH "Anticipatory Nausea and Vomiting"	45
5	MH "Nausea and Vomiting"	2086
6	MH "Emetics"	37
7	"cyclical vomiting syndrome"	24
8	"cyclical vomiting syndrome" AND (1 AND 7)	0
9	1 AND 2	14
10	(1 AND 2) AND (1 AND 3)	0
11	1 AND 5	37
12	(1 AND 5) AND (1 AND 6)	0
13	1 AND 6	0
14	1 AND 7	0

Medline (PubMed)

September 10, 2-4pm

Search Number	Search Terms	Results Yielded
2	"Cannabis"[Mesh]	6340
3	"Marijuana Abuse"[Mesh]	3750
4	"Marijuana Smoking"[Mesh]	2107
5	"Receptors, Cannabinoid"[Mesh]	6076
7	"Vomiting"[Mesh]	23768
8	"Vomiting, Anticipatory"[Mesh]	216
9	"Familial cyclical vomiting syndrome" [Supplemental concept]	21
12	2 AND 7	42
13	2 AND 8	0
14	2 AND 8 Schema: all	0
15	2 AND 9	1
16	3 AND 7	41
17	3 AND 8	0
18	3 AND 8 Schema: all	0
19	3 AND 9	2
21	4 AND 7	22

22	4 AND 8	0
23	4 AND 8 Schema: all	0
24	4 AND 9	1
25	5 AND 7	28
26	5 AND 8	0
27	5 AND 8 Schema: all	0
28	5 AND 9	0
29	5 AND 9 Schema: all	0

October 18, 4:30-6pm

Search Number	**Search Terms**	**Results Yielded**
2	"Cannabis"[Mesh]	6377
4	"Marijuana Abuse"[Mesh]	3828
5	"Marijuana Smoking"[Mesh]	2152
7	"Receptors, Cannabinoid"[Mesh]	5923
9	"Tetrahydrocannabinol"[Mesh]	5328
11	"Vomiting"[Mesh]	23960
12	"Vomiting, anticipatory"[Mesh]	217
13	"Familial cyclical vomiting syndrome"[Supplementary concept]	24
15	"Emetics"[Mesh]	659
16	Cyclical vomiting syndrome	184
17	Marijuana	18007
18	Vomiting	56503
19	2 AND 11	42
20	2 AND 12	0
21	2 AND 12 Schema: all	0
22	2 AND 13	1
23	2 AND 15	0
24	2 AND 15 Schema: all	0
25	2 AND 16	1
26	2 AND 18	62
27	4 AND 11	42
29	4 AND 12 Schema: all	0
28	4 AND 12	0
30	4 AND 13	2
31	4 AND 15	0
32	4 AND 15 Schema: all	0
33	4 AND 16	5
34	4 AND 18	49
35	5 AND 11	22

36	5 AND 12	0
37	5 AND 13	1
38	5 AND 15	1
39	5 AND 16	1
40	5 AND 18	27
41	7 AND 11	28
42	7 AND 12	0
43	7 AND 13	0
44	7 AND 15	4
45	7 AND 16	0
46	7 AND 18	51
47	9 AND 11	134
48	9 AND 12	2
49	9 AND 13	0
50	9 AND 15	2
51	9 AND 16	0
52	9 AND 18	169
53	11 AND 17	136
54	12 AND 17	1
55	13 AND 17	5
56	15 AND 17	1
57	16 AND 17	13
58	17 AND 18	202

PsycINFO

September 11, 2-3pm

Search Number	**Search Terms**	**Results Yielded**
1	DE “Marijuana”	1892
2	DE “Cannabis”	2380
3	DE “Vomiting”	839
4	Vomiting	3298
5	DE “Nausea”	587
6	1 AND 3	3
7	(1 AND 3) AND (2 AND 3)	0
8	2 AND 3	2
9	1 AND 5	5
10	(1 AND 5) AND (2 AND 5)	0
11	2 AND 5	2
12	DE “Cyclical vomiting syndrome”	0
13	Nausea	3577

14	Cannabis	4844
15	Marijuana	6656
16	Cyclical vomiting syndrome	21
17	1 AND 13	22
18	1 AND 16	0
19	2 AND 13	13
20	2 AND 16	0
21	3 AND 14	7
22	3 AND 15	10
23	4 AND 14	23
24	4 AND 15	36
25	5 AND 14	6
26	5 AND 15	10
27	14 AND 16	0
28	15 AND 16	0

Web of Science

September 11, 3-5pm

Search Number	**Search Terms**	**Results Yielded**
1	Topic=(vomiting)	29072
2	Topic=(marijuana)	8934
3	Topic=(cannabis)	9445
4	Topic=(cyclical vomiting)	398
5	Topic=(marijuana abuse)	2609
6	Topic=(marijuana smoking)	2233
7	2 AND 1	65
8	3 AND 1	57
9	5 AND 1	18
10	6 AND 1	16
11	4 AND 2	9
12	4 AND 3	14
13	5 AND 4	4
14	6 AND 4	0

Google Scholar

October 18, 5:30 – 6:30pm

Search Number	Search Terms	Results Yielded
1	"cannabis" OR "marijuana" OR "THC" OR "marijuana smoking" OR "marijuana abuse" AND "vomiting" OR "cyclical vomiting syndrome"	>27,000
2	Cyclical vomiting syndrome	22,500
3	"cyclical vomiting syndrome" AND "marijuana" OR "cannabis"	126

Cochrane Library

September 10, 4-5pm

Search Number	Search Terms	Results Yielded
1	MeSH descriptor: [Cannabis] explode all trees	245
2	MeSH descriptor: [Vomiting] explode all trees	3867
3	cyclical vomiting syndrome:ti,ab,kw (Word variations have been searched)	3
4	marijuana:ti,ab,kw (Word variations have been searched)	736
5	vomiting:ti,ab,kw (Word variations have been searched)	11537
6	thc:ti,ab,kw (Word variations have been searched)	358
7	MeSH descriptor: [Tetrahydrocannabinol] explode all trees	374
8	#1 and #2	3
9	#1 and #3	0
10	#1 and #5	3
11	#2 and #4	3
12	#2 and #6	12
13	#2 and #7	35
14	#3 and #4	0
15	#3 and #6	0
16	#3 and #7	0
17	#4 and #5	10
18	#5 and #6	28
19	#5 and #7	42

Appendix 2 – Excluded Studies

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Appendix 3 – Evidence Quality Rating

Table 4 – GRADE Methodology

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or
	Very low	Imprecision -1 Serious -2 Very serious	+1 Would suggest a spurious effect when results show no effect
		Publication bias -1 Likely -2 Very likely	

Bradford Hill Criteria for Causation

1. Strength of association—The difference in the incidence or prevalence of disease in the exposed vs unexposed. For CVS, it would be the prevalence of CVS in chronic marijuana users compared to non-users.
2. Consistency— The same increased prevalence would be found in multiple studies involving different populations and locations.
3. Specificity—The degree to which the exposure causes a specific set of symptoms and the disease is caused by a limited number of agents.
4. Temporality—The exposure should occur before the disease.
5. Biological gradient—Higher levels of exposure should cause higher incidence of disease or worse symptoms.
6. Plausibility—There is a plausible biological explanation for the results.
7. Coherence—The results should not contradict or clash with well- established facts.
8. Experiment—Controlled trials of exposure to an agent compared to a placebo.
9. Analogy—If a similar agent causes a similar response.