

Nausea

ISSUE BRIEF ON NAUSEA

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Nausea refers to a subjective, unpleasant feeling emerging from the stomach that individuals experience as an urge to vomit. Nausea may or may not be accompanied by vomiting (emesis). Causes of nausea are many and quite variable, including morning sickness due to pregnancy, infections (i.e., viral gastroenteritis), medications (e.g., chemotherapy drugs), labyrinthine causes (e.g., motion sickness), post-operative nausea, and many more (see Quigley et al., 2001 for list of causes). Due to the varied causes of nausea, emphasis on this brief concerns more common causes of nausea listed on the Mayo Clinic website including morning sickness in pregnancy, motion sickness, and viral gastroenteritis. Nausea is also commonly caused by chemotherapy treatment. However, discussion of chemotherapy-induced nausea will be excluded from this brief as nausea associated with cancer or its treatment (e.g., chemotherapy) is already a qualifying condition for MN's medical cannabis program. This

consequently severely limits the literature pool to draw on for this issue brief, as treatment for chemotherapy-induced nausea has been most extensively studied out of all nausea-inducing conditions found in the literature.

Diagnosis

Some acute cases of nausea may go away on their own and do not always warrant medical intervention (i.e., viral gastroenteritis). A patient presenting himself/herself to a health care practitioner will typically undergo a review of medical history and a physical exam to eliminate nausea of non-gastrointestinal origin. If the cause of nausea is found, treatment is targeted to treat the cause. However, in the case that a cause cannot be found, health care practitioners target treatment to ameliorating nausea and vomiting symptoms (Hasler & Chey, 2003).

Prevalence

Estimating nausea prevalence is difficult because the cause of nausea is varied. In addition, data on nausea prevalence is somewhat complicated by the fact that nausea can occur with vomiting—a separation of the two symptoms is not always clear in the literature. Nevertheless, some estimations of nausea exist. For example, a large population based study found that 12.5% of people experienced nausea that they found bothersome in the last 12 months (Haug et al., 2002). There are also some estimations of nausea prevalence for some conditions. For example, morning sickness is estimated to occur in roughly 70% of pregnant women, the majority of which occurs in the first trimester of pregnancy (Quigley et al., 2001). The prevalence of nausea in motion sickness is estimated to be anywhere between 3-60% depending on the study (Shupak & Gordon, 2006; Murrin et al., 2011; Golding, 2006). Postoperative nausea involving general anesthesia has been estimated at just under 40% (Quinn et al., 1994), although a broader range of sources indicate a wider range.

Current Therapies

Anti-emetics (anti-vomiting drugs) are typically administered for nausea regardless of whether it is accompanied by vomiting or not, and the overall consensus is that these treatments are more inconsistent in treating nausea than vomiting (Singh et al., 2016; Sanger & Andrews, 2006). The fact that anti-emetics do not ameliorate nausea and vomiting symptoms in a consistent fashion suggests differences in neural circuitry in the manifestation of these symptoms (Quigley et al., 2001; Singh et al., 2016). These drugs include antihistamines, phenothiazines, scopolamine (a cholinergic antagonist), serotonin (5-HT) antagonists (particularly 5-HT₃ receptor antagonists), benzamides, benzodiazepines, and corticosteroids.

While cannabinoids are discussed as current therapies in the nausea and vomiting literature, they are not discussed here as these cannabinoid treatments are currently indicated for chemotherapy-induced nausea and vomiting in cancer patients (dronabinol (Marinol), liquid dronabinol (Syndros), and nabilone (Cesamet)), which is a group of patients that already qualify for MN's medical cannabis program.

Preclinical Studies

Preclinical evidence suggests that the endocannabinoid system may be involved in non-chemotherapy related nausea and vomiting symptoms. For example, use of the anti-obesity drug rimonabant in humans – a CB₁-receptor antagonist – is associated with an increased incidence of nausea and vomiting as adverse side effects in patients (Despres et al., 2005). While there are a handful of animal models of nausea and vomiting, this brief will focus on a particular animal model which is the rat model of nausea. While there are a handful of different animal models for studying nausea and vomiting, many of them – like the ferret and shrew models – display both nausea-like behaviors and vomiting. Therefore, the delineation between nausea and vomiting is not always clear in studying a species that cannot verbally communicate. Rats, unlike ferrets and shrews, cannot vomit (non-emetic species) but still display behaviors that are associated with the same neuronal circuitry involved in vomiting that is found in emetic species. Below are a couple representative studies investigating the effects of cannabinoids in a rat model of nausea.

Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *NeuroReport*. 2002; 13(5): 1-4.

Preclinical research has previously shown that conditioned rejection reactions in a taste reactivity (TR) test (Grill & Norgren, 1978) may be a model of nausea in rats. Conditioned rejection reactions in rats consist of stereotyped orofacial and somatic responses that occur as a result of pairing an appetitive stimulus (i.e., sugary solution) with a drug that produces illness. These rejection reactions include gaping (example shown at 40-second mark at <https://youtu.be/NdyMEvTSyE>), chin rubbing, and paw treading. In this study, lithium chloride (LiCl)-induced conditioned rejection reactions were measured as a function of prior treatment with the cannabinoid cannabidiol (CBD) or vehicle solution (control). The authors hypothesized the following: If CBD can attenuate conditioned rejection reactions to LiCl, this would demonstrate CBD's anti-nausea properties. In other words, rats pretreated with CBD (Experiment 1) or the synthetic CBD dimethylheptyl homolog (CBD-DMH—a synthetic derivative of CBD; Experiment 2) should display fewer LiCl-induced conditioned rejection reactions than rats pretreated with a vehicle solution (control).

For the *conditioning* phase of the study, the delivery of a sugary solution in half of the rats was paired with LiCl and the other with saline solution. And within each of those two groups of rats, half of them received the CBD pretreatment while the other half received the vehicle pretreatment, effectively creating 4 experimental groups of rats (CBD-LiCl, vehicle-LiCl, CBD-saline, vehicle-saline).

In the *test* phase, each rat underwent two trials of the taste reactivity test upon delivery of the sugary solution alone – once preceded by CBD administration (or CBD homolog in Expt. 2) and the other preceded by vehicle administration. Results overall showed that pretreatment with CBD (Expt. 1) and CBD homolog (Expt 2) significantly reduced conditioned rejection reactions in LiCl-conditioned rats compared to those pretreated with the vehicle solution.

Parker LA, Mechoulam R, Schlievert C, Abbott L, Fudge ML, Burton P. Effects of cannabinoids on lithium-induced conditioned rejection reactions in a rat model of nausea.

***Psychopharmacology*. 2003; 166: 156-162.**

Unlike the previous study discussed above, which explored the role of the cannabinoid CBD (and a CBD homolog) on attenuating lithium chloride-induced nausea in rats, this study explored the role of the cannabinoid delta-9-tetrahydrocannabinol (THC) and a cannabinoid receptor agonist 11-hydroxy-delta-8-tetrahydrocannabinol-dimethyleptyl (HU-210) in conditioned rejection reactions in LiCl-conditioned rats. Similar to Parker et al. 2002, authors hypothesized that pretreatment with THC (Expt. 1) and HU-210 (Expt. 2) would attenuate conditioned rejection reactions in LiCl-conditioned rats. This study also investigated whether a CB₁-receptor antagonist (SR-141716A) could reverse conditioned rejection reactions in LiCl-conditioned rats pretreated with HU-210 (Expt. 3) or potentiate these rejection reactions with SR-141716A pretreatment (Expt. 4).

During conditioning trials, delivery of a sugary solution was paired with LiCl in half of the rats and saline solution in the other half. For those two groups of rats, half received THC pretreatment (Expt. 1) or HU-210 pretreatment (Expt. 2) and the other half received vehicle pretreatment (THC-LiCl, vehicle-LiCl, THC-saline, vehicle-saline in Expt. 1; HU-LiCl, vehicle-LiCl, HU-saline, vehicle-saline in Expt 2).

In the test phase, each rat underwent two trials of the taste reactivity test upon delivery of the sugary solution alone – once preceded by THC administration (or HU-210 in Expt. 2) and the other preceded by vehicle administration.

Results showed that LiCl-conditioned rats who received vehicle pretreatment during the conditioning phase displayed significantly more rejection reactions when given vehicle solution in the test phase than THC in the test phase. Results with HU-210, a cannabinoid receptor agonist, showed similar results as THC but only partially blocked the effects in LiCl-conditioned rats suggesting the THC may be more effective in blocking the expression of LiCl-induced nausea. Pretreatment of CB₁-receptor antagonist SR-141716A with HU-210 reversed some of HU-210's nausea reducing effects observed in Experiment 2, suggesting that nausea may be mediated by CB₁ receptors. Lastly, LiCl-condition rats pretreated with SR-141716A displayed more rejection reactions than any other group, further reinforcing CB₁-receptor involvement in nausea.

Clinical Trials

As of early September 2017, one clinical trial was identified on ClinicalTrials.gov relating to cannabis/cannabinoids as treatment for nausea unrelated to chemotherapy treatment. This particular study's main objective is to measure changes in postoperative pain with cannabinoids, but it is also measuring post-operative nausea and vomiting (PONV) as a secondary outcome. One other clinical trial had been identified on PONV and cannabis; however, this study was terminated due to a lack of a treatment effect, meaning that cannabis was not associated with any changes to PONV ([NCT00695487: Does Intravenous Cannabis Reduce Postoperative Nausea and Vomiting \(PONV\)?](#)).

NCT02283281: Anesthetic Premedication With a Cannabis Extract (Cannapremed)
(Cannapremed). <https://clinicaltrials.gov/show/NCT02283281>

This clinical trial examines how well cannabinoids may help with the management of acute post-operative pain as well as nausea and vomiting. Patients undergoing an operation are given a treatment dose before anesthetic induction. Treatment arms are 1) low dose nabiximols (balanced THC:CBD product) which is 10.8 mg THC and 10 mg CBD as an oromucosal spray, 2) high dose nabiximols (21.6 mg THC and 20 mg CBD), 3) an active treatment comparator which consists of acetaminophen (1 g/50 ml vial) + midazolam (2 mg/2 ml prefilled syringe), and 4) control. The primary outcome measures are collected at multiple time points and are 1) self-reported pain ratings on a visual analog scale and 2) post-operative pain measures (number of patient-controlled morphine pushes at various time points, and total dose of morphine received in 24 hours). Secondary outcome measures are also collected at multiple time points and are 1) post-operative nausea and vomiting scores, 2) anxiety ratings on a visual analog scale, and 3) cannabinoid blood levels. Principal investigator is Dr. Elyad Davidson of Hadassah Medical Organization (Israel). Estimated study completion date is listed as February 2017; no results have yet been posted to ClinicalTrials.gov, nor have any publications have been found relating to this study.

Observational Studies

A search for observational studies examining the role of cannabinoids/endocannabinoids in nausea yielded very few studies when eliminating chemotherapy-induced nausea. The two that were found do not involve the same patient population and examined nausea induced from different conditions – one examining motion sickness in male participants (Chouker et al., 2010) and the other morning sickness in pregnancy, as well as nausea unrelated to chemotherapy (Westfall et al., 2006).

Chouker A, Kaufmann I, Kreth S, Hauer D, Feuerecker M, Thieme D. Motion sickness, stress and the endocannabinoid system. *PLOS One*. 2010; 5(5): e10752.

This was a prospective study where participants (n = 21) who took scopolamine (anti-motion sickness drug) underwent multiple, in-flight parabolic maneuvers (PMs) in an aircraft (quick cycles of ascents and descents in the shape of an inverted-U) and observed for any developments of motion sickness. [While scopolamine was administered to all participants, please keep in mind while reading through the summary that that drug was not a treatment focus for this study. It administered to all participants on compassionate grounds to lessen motion sickness severity, as the study may have been difficult to execute otherwise]. The researchers hypothesized that participants with lower endocannabinoid signaling (as measured by peripheral endocannabinoids and cannabinoid receptor expression) would experience heightened motion sickness and stress (as measured by self-report and cortisol levels in saliva).

Blood samples were collected during the study to eventually detect for differences in endocannabinoid levels (anandamide and 2-AG) between participants who experienced motion sickness from those who did not. CB₁ and CB₂ receptor expression was also analyzed in blood samples taken before and after the in-flight experiment. Participants rated the severity of their

stress level and nausea at various time points in the study (in-flight before start of PMs, after the 10th PM, after 20th PM, after 30th PM, in-flight after the end of the PM cycles, and 24-hours after the study). Videotaping also occurred on the flight to observe for vomiting in participants. Cortisol measures were taken from saliva samples as a stress indicator.

Of all participants (n = 21), 7 (33%) subjects developed motion sickness. These 7 participants rated their stress levels significantly higher than those not experiencing motion sickness. In addition, nausea ratings were significantly higher by the 20th PM in participants with motion sickness than those who did not experience it. Most importantly, participants experiencing motion sickness had lower concentrations of circulating endocannabinoids (anandamide and 2-AG) than those not experiencing motion sickness. Pearson *r* correlations showed that nausea severity was inversely related to anandamide levels after the 30th PM but not at other time points or with 2-AG concentrations. Stress scores were inversely related to both anandamide and 2-AG by the 30th PM but not at other time points. Lastly, when comparing cannabinoid receptor expression pre- and post- flight, CB₁ receptor expression had decreased post-flight in participants who had developed motion sickness but not in participants who didn't experience it. CB₂ receptor expression did not change between the motion sickness group and the non-motion sickness group (possibly indicative of CB₂ receptors not playing a significant role in the development of motion sickness and associated nausea).

Study limitations include the small sample size and the lack of clarity on whether scopolamine – which was administered to all participants prior to the in-flight study – has any interaction with endocannabinoid signaling that wasn't measured in the study.

Westfall RE, Janssen PA, Lucas P, Capier R. Survey of medicinal cannabis use among childbearing women: patterns of its use in pregnancy and retroactive self-assessment of its efficacy against 'morning sickness'. *Complementary Therapies in Clinical Practice*. 2006; 12: 27-33.

This was an anonymous survey study of women in Canada using medical cannabis through a compassion society. The survey asked questions regarding the respondents' medical cannabis use, including for the treatment of nausea and vomiting (not necessarily pregnancy-related) as well as morning sickness during pregnancy.

Questions on the 21-item survey included the type, frequency, and quantity of medical cannabis the patients consumed and the conditions for which they were taking medical cannabis. Respondents were also asked to rate the efficacy of medical cannabis for treating nausea, vomiting, and loss of appetite for the conditions they reported taking medical cannabis for. In addition, respondents were asked if they took cannabis while pregnant for morning sickness and how effective it was for that condition. Lastly, respondents were asked to report the number of children they gave birth to and whether they had taken cannabis while pregnant – either recreationally or medically – and to assess cannabis' effectiveness for treating it.

Of the 142 women who picked up a survey (which was available through the two medical cannabis compassion societies), 84 women had completed the survey (59% response rate). All 84 women indicated they were current users of medical cannabis with 87% of them indicating they used medical cannabis at least once a day (57% of respondents indicated medical cannabis use more than once a day). Smoked form was the most common form of

administration (95% of respondents). Results provided in the paper indicated that none of the respondents had used medical cannabis for cancer. Of all respondents, 77% (n = 65) indicated using cannabis for treating nausea. Of those responding to the question on efficacy of cannabis in nausea treatment (n = 71), 54% (n = 39), 38% (n = 27), and 5% (n = 5) rated that cannabis was respectively extremely effective, effective, and somewhat effective. While not explicitly stated in the paper, the fact that there were more respondents to assessing the efficacy of cannabis as nausea treatment (n = 71) than respondents to using cannabis for nausea (n = 65) indicates that the two questions were independent of each other (one did not have to have experience using cannabis for nausea to answer the question on whether cannabis was effective for treating nausea). Ninety-four percent of total respondents (n = 79) answered questions on cannabis use during pregnancy. Of those respondents, 42% (n = 33) and 46% (n = 36) respectively indicated using cannabis recreationally and medically while pregnant. Of 59 respondents who experienced morning sickness during pregnancy, 92% rated cannabis as extremely effective or effective for treating morning sickness.

Limitations of this study include potential sampling bias and response bias in the survey, as well as the retrospective elements of the survey design.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of non-chemotherapy related nausea were found.

The National Academies of Sciences, Engineering and Medicine published a report on the health effects of cannabis and cannabinoids in 2017. The committee for this report has a statement on chemotherapy-induced nausea and vomiting specifically, which is already a qualifying condition for MN's medical cannabis program. It states that "there is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting" (see Conclusion 4-3; National Academies of Sciences, 2017). Their statement does not extend to nausea more broadly.

Minnesota Medical Cannabis Program Data

Data is routinely collected from patients purchasing medical cannabis through participation in MN's medical cannabis program. Symptom data is collected on the Patient Self-Evaluation (PSE), which is administered prior to each medical cannabis purchase. One of the symptom measures collected on the PSE is nausea, and responses are given using a 0-10 rating scale (0 = symptom not present; 10 = symptom as bad as patient can imagine). In the first program year, 1512 patients made at least a one medical cannabis purchase and had an observation period of at least 4 months at the time of data analysis. Of those patients, 864 of them (57.1%) experienced nausea at moderate to severe levels at baseline. Of those moderate-to-severe sufferers, just over half (55.6%) experienced at least a 30% reduction in nausea. Roughly a third (32.9%) both achieved at least a 30% reduction in nausea and maintained it, on average, for the following 4-month period. While these overall results include patients certified

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for cancer, it is important to note that patients certified for cancer only accounted for a third of all moderate to severe nausea sufferers at baseline (283 out of 864 patients; 32.7%).

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