Cannabinoid Regulation of Acute and Anticipatory Nausea

Erin M. Rock,1 Martin A. Sticht,2 Cheryl L. Limebeer1 and Linda A. Parker1,*

Abstract
Chemotherapy-induced nausea is one of the most distressing symptoms reported by patients undergoing treatment, and even with the introduction of newer antiemetics such as ondansetron and aprepitant, nausea remains problematic in the clinic. Indeed, when acute nausea is not properly managed, the cues of the clinic can become associated with this distressing symptom resulting in anticipatory nausea for which no effective treatments are available. Clinical trials exploring the potential of exogenous or endogenous cannabinoids to reduce chemotherapy-induced nausea are sparse; therefore, we must rely on the data from pre-clinical rat models of nausea. In this review, we explore the human and pre-clinical animal literature examining the potential for exogenous and endogenous cannabinoid treatments to regulate chemotherapy-induced nausea. The pre-clinical evidence points to a compelling need to evaluate the antinausea potential of cannabidiol, cannabidiolic acid, and treatments that boost the functioning of the endocannabinoid system in human clinical trials.

Key words: 2-arachidonoylglycerol; acute nausea; anandamide; anticipatory nausea; CB1 receptor; conditioned gaping; endocannabinoid

Introduction
For more than 5000 years, cannabis has been utilized as a medicine (see Ref.1), including for the treatment of nausea and vomiting. In response to their inability to manage patients’ chemotherapy-induced nausea and vomiting with conventional antiemetics, oncologists began to evaluate the antiemetic properties of cannabis in the late 1970s, following anecdotal reports of smoked cannabis alleviating chemotherapy-induced nausea and vomiting. In addition, the synthetic cannabinoid agonists, nabilone (Cesamet®) and dronabinol (Marinol®), were subsequently evaluated and approved for their antiemetic and antinausea properties in chemotherapy patients.2

Currently, vomiting is relatively well managed in the clinic since the advent of the 5-hydroxytryptamine 3 (5-HT3) receptor antagonists (such as ondansetron) and the neurokinin-1 (NK-1) receptor antagonists (such as aprepitant)3; however, nausea and anticipatory nausea (a conditioned response through which simply returning to the treatment clinic causes patients to feel nauseous as a result of their association between the contextual cues of the clinic and the nausea they experience from treatment) are still not properly managed.3 Nausea remains as one of the most distressing symptoms experienced by cancer patients undergoing chemotherapy treatment,4 highlighting the need for alternative pharmacotherapies to be explored.

Pre-clinical animal models of nausea are necessary to evaluate putative antinausea compounds. One such selective and reliable rodent model is nausea-induced conditioned gaping. Although rodents are incapable of vomiting, they display conditioned gaping reactions in response to a flavor previously paired with an illness-inducing agent such as lithium chloride (LiCl).5 They also avoid drinking this flavor as a measure of taste...
avoidance. However, conditioned gaping reactions are indicative of nausea in rodents, because, unlike taste avoidance, only emetic drugs produce conditioned gaping in rats, and antiemetic treatments (including cannabinoids) block conditioned gaping. Rats avoid drinking a flavor paired even with a rewarding drug.

**Cannabinoids in Human Patients**

**Exogenous cannabinoids and chemotherapy-induced acute nausea**

Delta-9-tetrahydrocannabinol (THC), the major psychoactive component of cannabis, is a high-affinity agonist for both the cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors and it has been shown to be effective in reducing chemotherapy-induced vomiting and/or nausea when smoked or orally administered.

Dronabinol (Marinol), an orally administered synthetic THC, has been shown to be effective in reducing chemotherapy-induced nausea and/or vomiting. In 1985, nabilone (Cesamet), another orally administered synthetic THC, was approved for nausea and vomiting only in patients who were unresponsive to conventional treatments. Nabilone has also been shown to reduce chemotherapy-induced nausea and/or vomiting. Please refer to Table 1 for more specific details of these findings. These findings highlight the potential of CB1 receptor agonism to reduce chemotherapy-induced nausea and/or vomiting, over that of classic antiemetic treatments.

Most recently, the oromucosal cannabis-based medicine, Sativex, (1:1, THC:cannabidiol [CBD]), when combined with the standard treatment of a 5-HT3 antagonist and a corticosteroid, reduced delayed nausea (and vomiting). Because Sativex contains both THC and CBD, it is unknown which compound (or both) contributed to its antinausea effects. Moreover, recent findings in our laboratory indicate that subthreshold doses of THC and cannabidiolic acid (CBD), the acidic precursor of CBD, when combined, effectively reduce acute nausea and anticipatory nausea in rats; however, we have not investigated whether these effects are mediated by the action of THC at the CB1 receptor, CBDA at the 5-HT1A receptor, or both.

These findings highlight the therapeutic potential of exogenously administered cannabinoids such as THC to reduce chemotherapy-induced nausea. It is important to note here, the unique ability of cannabinoids, to effectively manage nausea, a symptom that current antiemetic treatments cannot control.

**Endocannabinoid levels during the experience of nausea in humans**

To date, there have been no published clinical trials investigating whether endocannabinoid manipulations (such as increased action of anandamide [AEA] and 2-arachidonoylglycerol [2-AG] through enzyme inhibition of fatty acid amide hydrolase [FAAH] or monoa-cylglycerol lipase [MAGL]) reduce nausea; however, changes in endocannabinoid levels have been measured due to nausea-inducing manipulations. For example, decreases in AEA levels have been reported with administration of the anesthesia sevoflurane, which results in postoperative nausea. In addition, reduced levels of AEA and 2-AG have been shown in those experiencing motion sickness. Therefore, it seems that endogenous cannabinoids may be important neuromodulators involved in the experience of nausea, with decreased levels of AEA and/or 2-AG evident with nausea-inducing manipulations. Further research needs to clarify how the endogenous cannabinoid system is involved in the experience of nausea, and more specifically, how manipulations of this system could attenuate chemotherapy-induced nausea.

**Exogenous cannabinoids and chemotherapy-induced anticipatory nausea**

Anticipatory nausea is a conditional association between the chemotherapy clinic cues and the nausea-inducing chemotherapeutic treatment such that patients experience nausea upon returning to the clinic where illness-inducing treatment was administered. Anticipatory nausea develops in 25–59% of chemotherapy patients, if acute nausea has not been properly managed. Once established, anticipatory nausea is refractive to treatment with the classic 5-HT3 receptor antagonists such as ondansetron, and patients are currently prescribed sedating antianxiety drugs (benzodiazepines). Clearly, there is a great need for alternative therapeutics for anticipatory nausea as current medicines are insufficient.

In the only published clinical trial to date assessing cannabinoids and anticipatory nausea, Lane et al. showed that dronabinol was ineffective in reducing anticipatory nausea, but it is important to note that 86% of the patients included in the study were being given highly emetogenic chemotherapeutic treatments. Although dronabinol may not be as effective for anticipatory nausea resulting from highly emetogenic agents, it may be effective in less emetogenic chemotherapy regimens.
| Compound | References | Efficacy | Dose | Nausea-evoking agent | Sample details |
|----------|------------|----------|------|----------------------|----------------|
| THC      | Chang et al. | Compared to placebo: More effective | Smoked THC (1.93% THC ~ 17.4 mg), oral THC (10 mg/m²) | Methotrexate (250 mg/kg) | 15 patients (10 males, 5 females; 15–49 years old) |
|          | Ekert et al. | Compared to D₂ receptor antagonists: More effective | Oral THC (10 mg/m²) | Various chemotherapy agents | 33 patients (22 males, 11 females; 5–19 years old) |
|          | Frytak et al. | Compared to placebo: More effective | Oral THC (15 mg) | Various chemotherapy agents | 116 patients (70 males, 46 females; 21–70 + years old) |
|          | Kluin-Nelemans et al. | Compared to placebo: More effective | Oral THC (10 mg/m²), Chlormethine (6 mg/m²) and vincristine (1.4 mg/m²) with procarbazine (100 mg/m²) and prednisone (40 mg/m²) | Various chemotherapy agents | 11 patients (10 males, 1 female; 21–53 years old) |
|          | Lucas and Laszlo | Compared to D₂ receptor antagonist: More effective | Oral THC (15 mg/m², or 4 mg/m²) | Details not provided | 53 patients |
|          | McCabe et al. | Compared to D₂ receptor antagonist: More effective | Oral THC (15 mg/m²) | Various chemotherapy agents | 36 patients (9 males, 27 females; 18–69 years old) refractive to antiemetics |
|          | Neidhart et al. | Compared to D₂ receptor antagonist: More effective | Oral THC (10 mg) | Cisplatin, nitrogen mustard, or doxorubicin | 73 patients (42 males, 31 females) |
|          | Orr et al. | Compared to placebo: More effective | Oral THC (7 mg/m²) | Various chemotherapy agents | 55 patients (28 males, 51 females; 22–71 years old) refractive to antiemetics |
|          | Orr and McKernan | Compared to placebo: More effective | Oral THC (7 mg/m²), | Various chemotherapy agents | 79 patients (22–71 years old) refractive to anti-emetics |
|          | Lane et al. | Compared to D₂ receptor antagonist: More effective | Oral dronabinol (10 mg) | Various chemotherapy agents | 62 patients (29 males, 33 females; 20–68 years old) |
|          | Meiri et al. | Compared to placebo: More effective | Oral dronabinol (2.5, 5 mg) | Various chemotherapy agents | 61 patients (24 males, 37 females; 24–81 years old) |

(continued)
Table 1. Continued

| Compound (Cesamet<sup>9</sup>) | Ahmedzai et al.<sup>24</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (2 mg) | Cyclophosphamide (1g/m<sup>2</sup>), adriamycin (40 mg/m<sup>2</sup>), and etoposide (100 mg/m<sup>2</sup>) | 34 patients (19 males, 15 females; 27–72 years old) |
|---------------------------------|-----------------------------|---------------------------------------------|-----------------|---------------------------------------------------------------------------------|--------------------------------------------------|
|                                | Dalzell et al.<sup>26</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (1–3 mg) | Various chemotherapy agents | 18 patients (14 males, 4 females; 0–17 years old) |
|                                | Einhorn et al.<sup>27</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (2 mg) | Various chemotherapy agents | 80 patients (15–74 years old) |
|                                | Herman et al.<sup>30</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (2 mg) | Various chemotherapy agents | 152 patients (126 men, 26 women; 15–70 years old) |
|                                | Johansson et al.<sup>31</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (2 mg) | Cisplatinum (50 mg/m<sup>2</sup>), adriamycin (40 mg/m<sup>2</sup>), cyclophosphamide (500 mg/m<sup>2</sup>) | 26 patients (18–70 years old) refractive to antiemetics |
|                                | Jones et al.<sup>32</sup> | Compared to placebo: | Nabilone (2 mg) | Various chemotherapy agents | 54 patients (35 men, 19 women; 38–57 years old) |
|                                | Levitt<sup>28</sup> | Compared to placebo: | Nabilone (2 mg) | Various chemotherapy agents | 36 patients (12 men, 24 women; 17–78 years old) |
|                                | Niederle et al.<sup>34</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (2 mg) | Cisplatin (20mg/m<sup>2</sup>) and adriamycin (600 mg/m<sup>2</sup>) | 20 patients (male; 19–45) |
|                                | Niiranen and Mattson<sup>35</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (1 mg) | Various chemotherapy agents | 24 patients (20 males, 4 females; 48–78 years old) |
|                                | Pomeroy et al.<sup>36</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (1 mg) | Various chemotherapy agents | 38 patients (23 males, 15 females; 21–66 years old) |
|                                | Steele et al.<sup>37</sup> | Compared to D<sub>2</sub> receptor antagonist: | Nabilone (2 mg) | Various chemotherapy agents | 37 patients (19–65 years old) |
|                                | Wada et al.<sup>38</sup> | Compared to placebo: | Nabilone (2 mg) | Various chemotherapy agents | 114 patients (47 males, 67 females; 18–81 years old) |
|                                | Sativex<sup>30</sup> | Compared to standard antiemetic treatment (corticosteroid/5-HT<sub>3</sub> receptor antagonist or D<sub>2</sub> receptor antagonist: | Oromucosal spray (2.7 mg THC + 2.5 mg CBD/spray) | | 16 patients (1 male, 15 females; 34–76 years old) refractive to antiemetics |

CBD, cannabidiol; 5-HT<sub>3</sub>, 5-hydroxytryptamine 3; THC, delta-9-tetrahydrocannabinol.
As proper management of acute nausea is the best prevention for the development of anticipatory nausea, the efficacy of THC and its synthetic derivatives in reducing acute nausea (as discussed in the section “Exogenous cannabinoids and chemotherapy-induced acute nausea”) should reduce the risk of anticipatory nausea developing. Clinical trials are necessary to evaluate THC, as well as other phytocannabinoids such as CBD, for their ability to reduce acute and/or anticipatory nausea, especially in comparison to the current first-line treatment (5-HT3 receptor antagonist/dexamethasone/NK-1 receptor antagonist).

Endogenous cannabinoids and chemotherapy-induced anticipatory nausea
Cannabinoid compounds are effective in reducing acute nausea in human patients (as discussed in the section “Exogenous cannabinoids and chemotherapy-induced acute nausea”) and anticipatory nausea in animal models (as discussed in the section “Exogenous cannabinoids reduce anticipatory nausea in rats”), but no published clinical trials have evaluated enzyme inhibitors in anticipatory nausea patients. Such investigations have relied solely on animal models, highlighting the need for clinical trials.

Table 2. Efficacy of Various Exogenous and Endogenous Cannabinoids to Alleviate Nausea-Induced Conditioned Gaping and Contextually Elicited Conditioned Gaping in Rats

| Compound                    | Dose details                     | Efficacy in acute nausea-induced gaping | Efficacy in contextually elicited gaping |
|-----------------------------|----------------------------------|----------------------------------------|----------------------------------------|
| CB1 receptor agonists       |                                  | Compared to VEH:                       | Compared to VEH:                       |
| THC                         | 0.5 mg/kg, i.p., 30 min pretreatment | ● More effective (Limebeer and Parker69; Parker and Mechoulam60; Parker et al.61) | ● More effective (Limebeer et al.78; Rock et al.79) |
| Endocannabinoid manipulations |                                  |                                        |                                        |
| Anandamide                  |                                  | Not evaluated                          | Not evaluated                          |
| 2-AG                        | 1.5, 2 mg/kg, i.p., 15 min pretreatment, 0.5, 1 µg, bilaterally, after acute nausea test | Compared to VEH:                       | Compared to VEH:                       |
|                            |                                  | ● More effective (Sticht et al.57) Administration to the IC, compared to VEH: | ● More effective (Sticht et al.57) Administration to the IC, compared to VEH: |
| FAAH inhibition             |                                  | Compared to VEH:                       | Compared to VEH:                       |
| PF-3845                     | 10 mg/kg, i.p., 120 min pretreatment, 2 µg, bilaterally, 30 or 70 min pretreatment | ● More effective (Rock et al.64) Administration to the IC, compared to VEH: | ● More effective (Rock et al.64) Administration to the IC, compared to VEH, 5-HT3 receptor antagonist: |
| MAGL inhibition             |                                  | Compared to VEH:                       | Compared to VEH:                       |
| MJN110                      | 10, 20 mg/kg, i.p., 120 min pretreatment, 2 ug, bilaterally, 30 or 70 min pretreatment | ● More effective (Parker et al.66) Administration to the IC, compared to VEH: | ● More effective (Parker et al.66) Administration to the IC, compared to VEH, 5-HT3 receptor antagonist: |
| Dual FAAH/MAGL inhibition   |                                  | Compared to VEH:                       | Compared to VEH:                       |
| JZL195                      | 10 mg/kg, i.p., 120 min pretreatment |● More effective (Sticht et al.57) Administration to the IC, compared to VEH: | ● More effective (Limebeer et al.80) |

CB1, cannabinoid 1; 2-AG, 2-arachidonylglycerol; FAAH, fatty acid amide hydrolase; IC, insular cortex; MAGL, monoacylglycerol lipase.
through a CB1 receptor-mediated effect. Thus, as demonstrated in humans, THC (through CB1 receptor agonism) has an antinausea effect in the rat conditioned gaping model (acute nausea).

It is interesting to note that two nonpsychoactive cannabinoids found in cannabis, CBD60 and its precursor CBDA,41 also interfere with acute nausea-induced conditioned gaping in rats without impairing the locomotor activity. CBDA was 1000 times more potent than CBD in reducing acute nausea.62 Unlike THC, however, the antinausea effect of CBD63 and CBDA41 was mediated by agonism of 5-HT1A receptors, not CB1 receptors. Furthermore, subthreshold doses of CBDA potentiated the antinausea effect of the 5-HT3 receptor antagonist, ondansetron.62 These findings suggest that CBDA, in particular, may be a highly effective treatment for acute nausea alone or in combination with conventional treatments, although it has not yet been evaluated in clinical trials.

Endogenous cannabinoids reduce acute nausea-induced conditioned gaping

Recent studies in our laboratory have investigated the role of the endogenous cannabinoid system in acute nausea-induced conditioned gaping, utilizing enzyme inhibitors that increase AEA and 2-AG levels (through inhibition of FAAH or MAGL, respectively). PF-3845, a novel FAAH inhibitor, reduces acute nausea-induced conditioned gaping; however, this effect was reversed by a peroxisome proliferator-activated receptor alpha (PPARα) receptor antagonist, not a CB1 receptor antagonist.64 It is likely that this antinausea effect is due to increases in oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) following PF-3845 administration.65 Further investigation of the effect of fatty acids other than AEA on acute nausea is thus warranted. However, AEA may also be involved in the antinausea effect of FAAH inhibition, because the FAAH inhibitor, URB597, potentiated the antinausea effect of systemic AEA administration and this effect was reversed by CB1 receptor antagonism.66

Exogenous 2-AG administration (which is rapidly deactivated by MAGL) reduces acute nausea-induced conditioned gaping.67 MJN110, a MAGL inhibitor, also reduces acute nausea-induced conditioned gaping, a CB1 receptor-mediated effect.68 The aforementioned results, pertaining to systemic administration of enzyme inhibitors, suggest a role of the endogenous cannabinoid system in the suppression of nausea, but the specific brain region(s) critical for nausea are still not completely clear.

A brain region of interest for nausea is the interoceptive insular cortex (IC), an area shown to be involved in nausea,69 as stimulation of the IC70-72 and functional neuroimaging studies in humans73,74 pinpoint the IC as a critical region for nausea.

Our laboratory has begun to investigate how the endogenous cannabinoid system mediates nausea, with a specific focus on the rat interoceptive IC. Indeed, administration of the synthetic cannabinoid, HU-210, into the interoceptive IC reduces conditioned gaping through a CB1 receptor-mediated effect.75 Furthermore, administration of 2-AG to the interoceptive IC reduces conditioned gaping,57 and administration of the MAGL inhibitor MJN110 into the interoceptive IC (but not the FAAH inhibitors URB597 or PF-3845) reduces conditioned gaping, a CB1 receptor-mediated effect.76 These results suggest that the effects of the endocannabinoid system during an experience of acute nausea may be mediated by 2-AG (and not AEA) in the interoceptive IC.

Exogenous cannabinoids reduce anticipatory nausea in rats

In addition to displaying conditioned gaping to a nausea-paired flavor, rats also display conditioned gaping when returned to a nausea-paired context; a phenomenon analogous to human anticipatory nausea.77 Furthermore, much like with human anticipatory nausea, ondansetron does not reduce contextually elicited conditioned gaping in rats.78,79 Also, similar to human anticipatory nausea, administration of benzodiazepine does reduce contextually elicited conditioned gaping in rats, but also impairs locomotor activity.79 In contrast, low doses of THC reduce contextually elicited gaping in the absence of impaired locomotion,78,79 indicating that THC may be a superior therapeutic, over sedating benzodiazepines, in treating anticipatory nausea.

As with acute nausea, both CBD80 and CBDA41,79 reduce anticipatory nausea in this pre-clinical model by a 5-HT1A receptor mechanism of action, with CBDA about 1000 times more potent than CBD.79 Neither CBD nor CBDA interfered with motor activity. Given that these compounds are nonpsychoactive, future clinical trials with human patients are greatly needed as there are currently no specific treatments for anticipatory nausea in humans.
Endogenous cannabinoids reduce anticipatory nausea in rats

The endogenous cannabinoid system has also been implicated in the control of anticipatory nausea (for review). The FAAH inhibitors URB597 or PF-3845 reduce contextually elicited conditioned gaping; unlike acute nausea, the antinausea effect of FAAH inhibition on anticipatory nausea was reversed by a CB1 receptor antagonist, presumably through AEA elevation. The MAGL inhibitor, MJN110, also reduces contextually elicited gaping in rats, a CB1 receptor-mediated effect. Finally, dual FAAH-MAGL inhibition with JZL195 reduces contextually elicited gaping by elevated AEA, PEA, and OEA, a CB1 receptor-mediated effect. Recent findings in our laboratory indicate that infusion of the MAGL inhibitor, MJN110 (but not the FAAH inhibitor PF-3845 or ondansetron), into the interoceptive IC suppressed contextually elicited conditioned gaping, a CB1 receptor-mediated effect. These results suggest that the interoceptive IC may be a critical region for AN (in addition to acute nausea), mediated by 2-AG activity at the CB1 receptor.

Conclusions

The endocannabinoid system clearly plays an important role in the regulation of nausea. The pre-clinical findings suggest that CB1 receptor agonists, as well as FAAH and MAGL inhibitors, which elevate levels of AEA and 2-AG, respectively, reduce acute nausea and anticipatory nausea. As well, by a noncannabinoid mechanism of action, both CBD and CBDA are highly effective antiemesis treatments in these animal models without producing sedation or psychoactive effects. Nausea remains an elusive, difficult to control symptom in human chemotherapy patients and there are currently no selective treatments for anticipatory nausea. Clinical trials with FAAH inhibitors, MAGL inhibitors, CBD, and CBDA are warranted to improve the quality of life of patients undergoing cancer treatment by reducing the side effects of nausea and anticipatory nausea when it develops.

Acknowledgments

The authors gratefully acknowledge research support from the Natural Sciences and Engineering Research Council of Canada (NSERC: 92057) to LAP and Canadian Institutes of Health Research (CIHR: 334086) to LAP and Keith Sharkey.

Author Disclosure Statement

No competing financial interests exist.
27. Einhorn LH, Nagy C, Fumas B, et al. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. J Clin Pharmacol. 1981;21:645–695.

28. Levitt M. Nabilone vs. placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Cancer Treat Rev. 1982;9:49–53.

29. Herman TS, Jones SE, Dean J. Nabilone: a potent antiemetic cannabinoïd with minimal euphoria. Biomedicine. 1977;27:331–334.

30. Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. N Engl J Med. 1979;300:1295–1297.

31. Johansson R, Klikku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. Cancer Treat Rev. 1982;9:25–33.

32. Jones SE, Durant JR, Greco A, et al. A multi-institutional phase III study of nabilone vs. placebo in chemotherapy-induced nausea and vomiting. Cancer Treat Rev. 1982;9:45–48.

33. Niiranen A, Mattsson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. Am J Oncol. 1985;8:336–340.

34. Pomeroy M, Fennelly JJ, Towers M. Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic induced emesis. Cancer Chemother Pharmacol. 1986;17:285–288.

35. Steele N, Gralla RJ, Braun DW Jr, et al. Double-blind, placebo-controlled study of nabilone vs. placebo in chemotherapy-induced nausea and vomiting. J Pain Symptom Manage. 2001;22:843–850.

36. Zocher L, Delavaux N, Farvaques C, et al. Prevention of adjustment disorders and anticipatory nausea secondary to adjuvant chemotherapy: a double-blind, placebo-controlled study assessing the usefulness of alprazolam. J Clin Oncol. 1993;11:1384–1390.

37. Rock EM, Limebeer CL, Parker LA. Effect of low doses of cannabidiolic acid and cannabidiolic acid CBDA on acute and anticipatory nausea using rat (Sprague-Dawley) models of conditioned gaping. Psychopharmacology (Berl). 2015;232:4445–4454.

38. Bolognini D, Rock EM, Clapp WE, et al. Cannabinoid acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation. Br J Pharmacol. 2013;168:1456–1470.

39. Schelling S, Hauer D, Azad SC, et al. Effects of general anesthesia on anandamide blood levels in humans. Anesthesiology. 2006;104:273–277.

40. Rock EM, Limebeer CL, Parker LA. Effect of combined doses of Δ9-tetrahydrocannabinol (THC) and cannabidiolic acid (CBDA) on acute and anticipatory nausea using rat (Sprague-Dawley) models of conditioned gaping. Psychopharmacology (Berl). 2015;232:4445–4454.

41. Akechi T, Okuwaya T, Endo C, et al. Anticipatory nausea among ambulatory cancer patients undergoing chemotherapy: prevalence, associated factors, and impact on quality of life. Cancer Sci. 2010;101:2596–2600.

42. Stockhorst U, Kosterlitz H, Schellenberg H, et al. Anticipatory nausea in cancer patients receiving chemotherapy: classical conditioning etiology and therapeutic implications. Integr Physiol Behav Sci. 1993;28:177–181.

43. Tyc VL, Mulhern RK, Bieberich AA. Anticipatory nausea and vomiting in pediatric cancer patients: an analysis of conditioning and coping variables. J Dev Behav Pediatr. 1997;18:27–33.

44. Stein CA, Kornblau SM, Inman JK, et al. Localized pain and the endocannabinoid system. PLoS One. 2010;5:1–7.

45. Nesse RM, Carli T, Curtis GC, et al. Pretreatment nausea in cancer chemotherapy: a conditioned response? Psychosom Med. 1980;42:33–36.

46. Zachariae R, Paulsen K, Mehlsen M, et al. Anticipatory nausea: the role of individual differences related to sensory perception and autonomic reactivity. Ann Behav Med. 2007;33:69–79.

47. Stockhorst U, Kosterlitz H, Schellenberg H, et al. Anticipatory nausea and vomiting in cancer patients undergoing chemotherapy: classical conditioning etiology and therapeutic implications. Integr Physiol Behav Sci. 1993;28:177–181.

48. Vogt MV, McCarroll J, Law M. Anticipatory nausea and emesis, and psychological morbidity: assessment of prevalence among out-patients on mild to moderate chemotherapy regimens. Br J Cancer. 1992;66:862–866.

49. Rock, et al. Cannabis and Cannabinoid Research 2016, 1.1

50. Zachariae R, Paulsen K, Mehlsen M, et al. Anticipatory nausea: the role of individual differences related to sensory perception and autonomic reactivity. Ann Behav Med. 2007;33:69–79.

51. Foubert J, Vaessen G. Nausea: the neglected symptom? Eur J Oncol Nurs. 2005;9:21–32.

52. Rock EM, Limebeer CL, Parker LA. Anticipatory nausea in rats by fatty acid amidolipolysolethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Neurosci. 2014;286:338–344.

53. Rock EM, Limebeer CL, Parker LA. Anticipatory nausea in animal models: a review of potential novel therapeutic treatments. Exp Brain Res. 2014;232:2511–2534.

54. Rock EM, Limebeer CL, Ward J, et al. Interference with acute nausea and anticipatory nausea in rats by fatty acid amide hydrolase (FAAH) inhibition through a PPARα and CB1 receptor mechanism, respectively: a double dissociation. Psychopharmacology (Berl). 2015;232:841–848.

55. Rock EM, Limebeer CL, Ward J, et al. Interference with acute nausea and anticipatory nausea in rats by fatty acid amidolipolysolethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Br J Pharmacol. 2013;169:685–692.

56. Rock EM, Bolognini D, Limebeer CL, et al. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT3 receptors. Br J Pharmacol. 2013;168:1566–1576.

57. Rock EM, Limebeer CL, Parker LA. Delta-9-tetrahydrocannabinol interferes with the establishment and the expression of conditioned rejection reactions produced by cyclophosphamide: a rat model of nausea. Neuroreport. 1999;10:3769–3772.

58. Rock EM, Limebeer CL, Parker LA. Anticipatory nausea among ambulatory cancer patients undergoing chemotherapy: prevalence, associated factors, and impact on quality of life. Cancer Sci. 2010;101:2596–2600.

59. Rock EM, Limebeer CL, Ward J, et al. Interference with acute nausea and anticipatory nausea in rats by fatty acid amidolipolysolethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Br J Pharmacol. 2012;165:2620–2634.

60. Rock EM, Limebeer CL, Parker LA. Anticipatory nausea in rats by fatty acid amidolipolysolethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Br J Pharmacol. 2013;169:685–692.

61. Rock EM, Bolognini D, Limebeer CL, et al. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT3 receptors. Br J Pharmacol. 2013;168:1566–1576.

62. Rock EM, Limebeer CL, Parker LA. Anticipatory nausea in rats by fatty acid amidolipolysolethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Br J Pharmacol. 2013;169:685–692.

63. Rock EM, Limebeer CL, Parker LA. Anticipatory nausea in rats by fatty acid amidolipolysolethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Br J Pharmacol. 2012;165:2620–2634.

64. Rock EM, Limebeer CL, Ward J, et al. Interference with acute nausea and anticipatory nausea in rats by fatty acid amidolipolysolethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Br J Pharmacol. 2013;169:685–692.

65. Rock EM, Bolognini D, Limebeer CL, et al. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT3 receptors. Br J Pharmacol. 2013;168:1566–1576.

66. Rock EM, Limebeer CL, Parker LA. Anticipatory nausea in rats by fatty acid amidolipolysolethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Br J Pharmacol. 2012;165:2620–2634.
74. Scocco R, Kim J, Garcia RG, et al. Brain circuitry supporting multi-organ autonomic outflow in response to nausea. Cereb Cortex. 2014;26:485–497.

75. Limebeer CL, Rock EM, Mechoulam R, et al. The anti-nausea effects of CB1 agonists are mediated by an action at the visceral insular cortex. Br J Pharmacol. 2012;167:1126–1136.

76. Sticht MA, Limebeer C., Rafi B, et al. Endocannabinoid regulation of nausea is mediated by 2-arachidonoylglycerol (2-AG) in the rat visceral insular cortex. Neuropharmacology. 2016;102:92–102.

77. Limebeer CL, Krohn JP, Cross-Mellor S, et al. Exposure to a context previously associated with nausea elicits conditioned gaping in rats: a model of anticipatory nausea. Behav Brain Res. 2008;187:33–40.

78. Limebeer CL, Hall G, Parker LA. Exposure to a lithium-paired context elicits gaping in rats: a model of anticipatory nausea. Physiol Behav. 2006;88:398–403.

79. Rock EM, Limebeer CL, Navaratnam R, et al. A comparison of cannabidiolic acid with other treatments for anticipatory nausea using a rat model of contextually elicited conditioned gaping. Psychopharmacology (Berl). 2014;231:3207–3215.

80. Rock EM, Limebeer CL, Mechoulam R, et al. The effect of cannabidiol and URB597 on conditioned gaping (a model of nausea) elicited by a lithium-paired context in the rat. Psychopharmacology (Berl). 2008;196:389–395.

81. Parker LA, Rock EM, Sticht MA, et al. Cannabinoids suppress acute and anticipatory nausea in pre-clinical rat models of conditioned gaping. Clin Pharmacol Ther. 2015;97:559–561.

82. Limebeer CL, Abdullah RA, Rock EM, et al. Attenuation of anticipatory nausea in a rat model of contextually elicited conditioned gaping by enhancement of the endocannabinoid system. Psychopharmacology (Berl). 2014;231:603–612.

83. Limebeer CL, Rock EM, Puvanenthirarajah N, et al. Elevation of 2-AG by monoacylglycerol lipase inhibition in the visceral insular cortex interferes with anticipatory nausea in a rat model. Behav Neurosci. 2016;130:261–266.

**Abbreviations Used**

- 2-AG = 2-arachidonoylglycerol
- 5-HT3 = 5-hydroxytryptamine 3
- AEA = anandamide
- CB1 = cannabinoid 1
- CBD = cannabidiol
- CBDA = cannabidiolic acid
- FAAH = fatty acid amide hydrolase
- IC = insular cortex
- LiCl = lithium chloride
- MAGL = monoacylglycerol lipase
- NK-1 = neurokinin-1
- OEA = oleoylthanolamide
- PEA = palmitoylethanolamide
- THC = delta-9-tetrahydrocannabinol