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PHARMA

Chemotherapy-Induced Nausea and Vomiting and Cannabis-Based Medicinal Products

An introductory overview for healthcare professionals

Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common symptoms feared by patients undergoing cancer treatment, but its occurrence may be prevented and its frequency reduced with appropriate medications (Fernandez-Ortega et al., 2012).

According to the U.S. National Institutes of Health, CINV has a prevalence of up to 80% in patients undergoing chemotherapy (U.S. NIH, National Cancer Institute, 2021) and may be categorised as: Acute, delayed, anticipatory, breakthrough, or refractory (National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology 2015).

The last three decades have seen many advances in cancer treatment management, but nausea and vomiting continue to be two of the most debilitating side-effects associated with chemotherapy treatment in cancer patients (Coates et al., 1983; Griffin et al., 1993; Lindley et al., 1989; Roscoe et al., 2000).
Despite development of new antiemetic agents, CINV remains an issue for many patients with numerous unmet needs, such as optimising control of non-acute forms of CINV, identifying and managing patients prone to CINV, and increasing adherence to guidelines.

There also remains a significant difference between medical professionals' perceptions and patients' experience of chemotherapy side-effects, bringing about poor control of the condition (Grunberg et al., 2004). In one study, 300 European oncologists reported that the main reason for antiemetic treatment failure was underestimating the emetogenicity of chemotherapy (Aapro et al., 2018).

In this regard, prescription cannabis-based medicinal products (CBMPs) hold promise in addressing the unmet clinical needs of those patients for whom other first line treatments have not worked.
This booklet outlines the case for using CBMPs for better symptom management of CINV in cancer patients for whom other first-line treatment options have been unsuccessful.

Mechanism of CINV

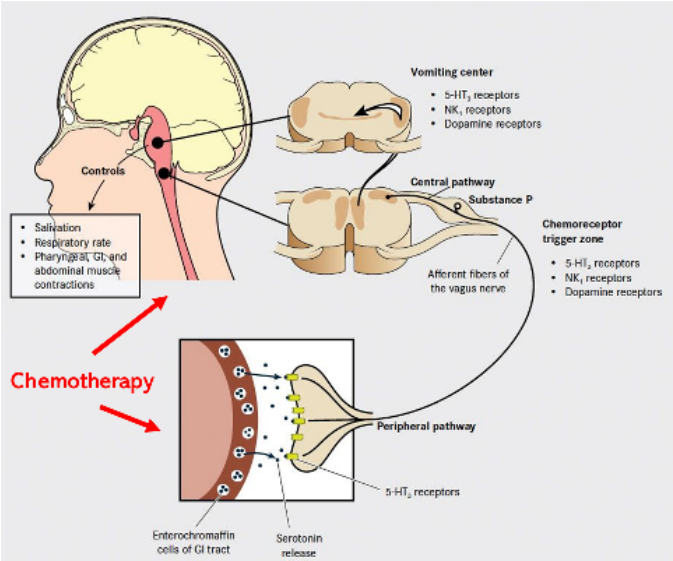

Figure 1 – Mechanism of chemotherapy-induced nausea and vomiting (CINV).

Pathophysiology of CINV

The vomiting (emetic) response is coordinated by the vomiting centre (VC) of the brain, located in the medulla oblongata (Hesketh 2008, Shankar et al., 2015). The VC integrates a variety of peripheral and central inputs known as the peripheral and central pathways, respectively, and elicits the emetic reflex as a response.

The peripheral pathway originates in the gastrointestinal tract, where stimuli such as pharyngeal stimulation or gastric/duodenal distension are transmitted via the abdominal vagal afferents (Aapro et al., 2018). Abdominal vagal afferent fibres express a variety of receptors (e.g., 5-HT3, neurokinin (NK) 1, and cholecystokinin-1) that are able to trigger the emetic response when stimulated (Andrews et al., 2002), with 5-HT3 being the main mediator (Aapro et al., 2018).

These fibres terminate on the dorsal vagal complex, comprised of the nucleus tractus solitarius (NTS), area postrema, and dorsal motor nucleus. The NTS and,

to a lesser extent, the area postrema (also known as the "chemoreceptor trigger zone"), subsequently relay input to the VC (Hesketh 2008). This pathway is primarily associated with acute emesis (Aapro et al., 2018). In contrast, the central emesis pathway describes brain input to the VC eliciting an emetic response.

The VC receives direct cholinergic and histaminic input to induce vomiting in response to pain, vestibular perturbation, or emotional factors. The VC also receives inputs from the chemoreceptor trigger zone or area postrema, located on the floor of the fourth ventricle, in response to endogenous toxins and other chemical stimuli (e.g., chemotherapy or other medications) (Shankar et al., 2015). Neurochemical mediators of the latter pathway include the neurotransmitter serotonin (5-HT) and its receptors; substance P and the NK1 receptor; and dopamine and its receptors (Aapro 2018; Navari and Aapro 2016), specifically D2 and D3 located in the NTS, dorsal motor nucleus, and area postrema (Bashashati M, McCallum 2014; Darmani and Ray 2009). Certain medications, such as opioids and dopamine agonists, act directly on receptors in the area postrema due to the absence of a blood-brain barrier surrounding this sensory circumventricular organ (Aapro 2018). Fig. 1 illustrates the interplay of the central and peripheral pathways for triggering emesis (Navari and Aapro 2016).

The pathophysiology of nausea is less well understood and remains difficult to describe, due it being a subjective sensation and usually perceived as being in the stomach and preceding emesis (Stern et al., 2011). It remains unclear whether the same neurotransmitters and receptors responsible for emesis, such as serotonin and substance P, are related to nausea, but dopaminergic, histaminic, and muscarinic receptors may possibly be involved (Navari 2009).

Chemotherapy and the emetic response

Chemotherapeutic drugs can activate neurotransmitter receptors in the area postrema of the brain or stimulate vagal afferents near the enterochromaffin cells in the intestine (Navari and Aapro, 2017). The peripheral pathway is activated within 24 hours after initiation of chemotherapy by the oxidative action of free radicals generated by chemotherapeutic agents, which stimulate enterochromaffin cells in the gastrointestinal tract to release serotonin (Janelsins et al., 2013,). Serotonin subsequently stimulates abdominal afferent vagal fibers as part of the peripheral emesis pathway and activates the emetic response via the VC (Hesketh, 2008; Janelsins et al., 2013; Rapoport, 2017). Accordingly, activation of the peripheral pathway is primarily associated with acute CINV (Navari and Aapro, 2016).

Chemotherapy drugs can also elicit the release of substance P in both the central and peripheral nervous systems, resulting in NK1-mediated vomiting (Janelsins et al., 2013, Rapoport 2017). A majority of findings indicate that centrally expressed NK1 receptors, particularly those expressed in the NTS and area postrema, are

responsible for nausea as the result of chemotherapy-induced substance P release (Scatliff et al., 1959; Girish and Manikandan 2007; Herrstedt, 2008). The results of clinical trials for 5HT3 and NK1 receptor antagonists further support a principal role for central NK1 activation in delayed CINV (Hesketh et al., 2003).

It should be noted that cancer patients are prone to nausea and vomiting for reasons other than the chemotherapy itself, for example due to radiation therapy; non-chemotherapy medications; cancer related metabolic effects, impaired gastric emptying, gastrointestinal obstruction, and brain or spinal metastases; and other causes such as pain or anxiety (Warr, 2008).

Chemotherapy drugs that are emetogenic

There are four levels of emetogenic drugs, categorized by risk of causing CINV: minimal (<10%), low (10–30%), moderate (31–90%), and high (>90%) (Grunberg et al., 2011). Table 1 (Berger et al., 2017; Hesketh et al., 2017; Roila et al., 2015) lists the drugs that fall into each of these categories and stratifies them by mode of administration. Currently, no clear explanation has been found for why some agents are more emetogenic than others. It should be noted that, more often, regimens are stratified by emetogenicity rather than individual agents (Razvi et al., 2019). For example, highly emetogenic chemotherapy (HEC) regimens typically include high-dose cisplatin, carmustine, cyclophosphamide at doses greater than 1500 g/m2, dacarbazine, mechlorethamine, streptozocin, and combinations of anthracyclines and phosphamide (AC) (Razvi et al., 2019). Moderately emetogenic chemotherapy (MEC) regimens are more variable but may include carboplatin, doxorubicin, irinotecan, oxaliplatin, and cyclophosphamide (Razvi et al., 2019).

Clinical Presentation of CINV

CINV symptoms can manifest at various points in chemotherapy treatment. Acute CINV occurs within 24 hours of initial administration of chemotherapy, with acute vomiting primarily mediated by 5-HT3 (Aapro, 2018). With antiemetic prophylaxis, acute nausea occurs in up to 35% of patients and acute vomiting in approximately 13% (Grunberg 2004; Escobar et al., 2015).

Delayed CINV occurs 24 hours to 5 days after chemotherapy and is predominantly mediated by substance P binding to NK1 receptors in the central nervous system (Aapro, 2018). The incidence of delayed nausea and vomiting after antiemetic prophylaxis is 20–50% (Grunberg, 2004; Escobar et al., 2015). Anticipatory CINV describes nausea and vomiting occurring before chemotherapy treatment as a conditioned response due to the occurrence of CINV in previous cycles (Morrow et al., 1998) and is likely mediated by a combination of physiological and psychological mechanisms (Janelsins et al., 2013).

Current management of CINV

A number of antiemetic agents with different mechanisms of action have been developed for CINV, a majority of which are typically given as prophylactic medications. The most commonly used medications with anti-emetic and anti-nausea properties are:

1. *5-HT3 antagonists* (such as, ondansetron, granisetron, dolasetron and palonosetron), which inhibit the activation of serotonin receptors expressed both peripherally in the intestine and centrally in the area postrema (Rao and Faso, 2012) corticosteroids, and NK1 receptor antagonists (Adel, 2017; Rao and Faso, 2012). These drugs are considered to be well tolerated and have minimal side effects such as headache, constipation, elevated liver enzymes, and QT interval prolongation on electrocardiogram (Rao and Faso, 2012).

2. *Corticosteroids* (such as dexamethasone) have been used for CINV for several decades (Rao and Faso, 2012) and are a mainstay treatment for both acute and delayed CINV (Shankar et al., 2015), despite the precise mechanism of action for this class of medicines being unknown – some hypotheses include direct action on the NTS and interactions with serotonin and neurokinin receptors (Chu et al., 2014) that may provide a "booster effect" for other antiemetics. Common adverse effects of corticosteroid therapy include insomnia, epigastric discomfort, agitation, weight gain, and hyperglycemia (Vardy et al., 2006).

3. *NK1 receptor antagonists* act peripherally and centrally by blocking the binding of substance P at the NK1 receptor (Rao and Faso 2012). Approved NK1 antagonists in the United States include aprepitant, fosaprepitant, and rolapitant (Adel, 2017). As aforementioned, these agents are typically administered in combination with a 5-HT3 antagonist and dexamethasone; however, another regimen for delayed CINV is aprepitant with or without dexamethasone (Basch et al., 2011; Berger et al., 2017; Roila et al., 2016). The most common adverse effects include fatigue, headache, anorexia, diarrhea, hiccups, and increased liver enzymes (Rao and Faso 2012)

4. *Dopamine receptor antagonists*, such as metoclopramide and prochlorperazine, act by inhibiting D2 receptors in the NTS, dorsal motor nucleus, and area postrema (Darmani and Ray, 2009). Antiemetic effects are mediated by inhibiting the central emesis pathway and via prokinetic effects on the motor function of the esophagus and small intestine (through cholinergic effects and the 5-HT4 receptors) (Bashashati and McCallum, 2014). Unfortunately, these agents have an unfavorable

side-effect profile including extrapyramidal symptoms, dystonia, and drowsiness (Rao and Faso 2012), and are thus less commonly used.

5. *Benzodiazepines*, a type of anxiolytic medication, have been used for anticipatory nausea and vomiting but can also be included in regimens to treat breakthrough or refractory CINV (Bassch et al., 2011; Berger et al., 2017; Roila et al., 2016). Sedation is the most common side effect (Rao and Faso 2012).

6. *CBMPs* can be used as an adjunctive treatment in the setting of breakthrough CINV (Berger et al., 2017). Some research suggests that the mechanism of delayed nausea and vomiting may involve CB1 receptors (Frame, 2010). The increasing availability of THC/CBD extracts, as well as synthetic cannabinoids (e.g. nabilone) and analogues (e.g. dronabinol) make CBMPs a promising therapeutic option for CINV.

Cannabis use in patients with unmet needs for whom first-line medications have failed

Due to the significant proportion of chemotherapy patients experiencing CINV, efforts continue to search for better treatment options whilst optimising current antiemetic treatments (Dranitsaris et al., 2017).

Studies make use of metrics to assess quality of life, such as the Functional Living Index-Emesis (FLIE), which assesses interference with activity due to CINV, suggest that CINV has profound negative effects on patient quality of life (Cohen et al., 2007; Kottschade et al., 2016; Haiderali et al., 2010). A substantial financial burden is also associated with CINV due to the substantial costs of antiemetic medications that have been listed above, such as use of intravenous palonosetron.

The main feature of this booklet focusses on the promising prescription-based approach of using medical cannabis for the symptom management of CINV. Indeed, some research suggests that the mechanism of delayed nausea and vomiting may directly involve CB1 receptors (Darmani, 2010). Additionally, a small pilot double-blind randomized trial of nabiximols for CINV, refractory to first-line treatment after moderately emetogenic chemotherapy, showed substantial efficacy and good tolerability (Duran et al., 2010). However, common side effects include drowsiness, fatigue, and confusion. Prospective clinical studies are being drafted and are necessary to support the development of a guideline for the use of cannabinoid agents in CINV.

Table 1 – Emetogenic category risk for different chemotherapeutic agents.

Level 1 (minimal risk, <10%)	Level 2 (low risk, 10-30%)	Level 3 (moderate risk, 31-90%)	Level 4 (high risk, >90%)
Intravenous			
Bevacizumab	Asparaginase	Alemtuzumab	Actinomycin D
Bleomycin	Bortezomib	Altretamine	Carmustine
Busulfan	Catumaxomab	Azacitidine	Cisplatin
Chlorambucil	Cetuximab	Bendamustine	Cyclophosphamide (>1.5 g/m²)
Cladribine	Cytaribine (<1 gm/m²)	Clofarabine	Dacarbazine
Cytaribine (<100 mg/m²)	Docetaxel	Carboplatin	Lomustine
Fludarabin	Doxorubicin liposomal	Cyclophosphamide (≤1.5 g/m²)	Mechlorethamine
Hormones	Etoposide	Cytarabine (>1 g/m²)	Pentostatin
Hydroxyurea	5-Fluorouracil	Daunorubicin	Streptozocin
Interferon	Gemcitabine	Doxorubicin	
Mercaptopurine	Ixabepilone	Epirubicin	
Methotrexate (<100 mg/m²)	Methotrexate (>100 mg/m²)	Idarubicin	
Thioguanine	5-Mitoxantrone (<12 mg/m²)	Ifosfamide	
Vinblastine	Paclitaxel	Irinotecan	
Vincristine	Panitumumab	Melphelan	
Vinorelbine	Pegasparaginase	Mitoxantrone (>12 mg/m²)	
	Pemetrexed	Oxaliplatin	
	Teniposide	Temozolamide	
	Thiotepa	Treosulphan	
	Topotecan	Trabectedin	
	Trastuzumab		
*Percentages indicate the risk of vomiting with intravenously administred antineoplastic agents in the absence of antiemetic prophylaxis; Data from Jordan et al. (2007), Kris et al.(2006), Roila et al. (2006,2010).			
Oral			
Chlorambucil	Capecitabine	Cyclophosphamide	Hexamethylmelanine
Erlotinib	Etoposide	Imatinib	Procarbazine
Gefitinib	Everolimus	Temozolamide	
Hydroxyurea	Fludarabine	Vinorelbine	
Melphalan	Lapatinib		
Methotrexate	Lenalidomide		
Sorafenib	Sunitinib		
6-Thioguanine	Thalidomide		
*Percentages indicate the risk of vomiting with orally administered antineoplastic agents in the absence of antiemetic prophylaxis; Data from Jordan et al. (2007), Roila et al. (2006,2010).			

A retrospective cohort study in the United States of 19,139 patients found the estimated mean costs of CINV visits, including inpatient, outpatient, and emergency room visits to be $5299 for the first chemotherapy cycle (a period up to 30 days) and mean per-patient CINV-associated costs to be $731 (Burke et al., 2011). Such high costs are likely to be replicated in principle in all developed nations. For some patients, the cost of managing CINV is greater than the actual cost of the regimen of chemotherapy cycles (Gyawali et al., 2016). With this consideration, it is necessary to optimize CINV treatment with respect to cost-benefit ratios and consider alternative symptom management options that may clinically benefit patients, whilst providing cost savings in healthcare over the long term.

Increasing preclinical evidence suggests that the endocannabinoid system plays a significant role in the regulation of both nausea and vomiting (Parker et al., 2011). Cannabinoid receptors CB1 and CB2, located within the brainstem and the GI tract, are associated with emetogenic control in mammals such as the rat, mouse, ferret, and shrew (Van Sickle et al., 2005; Malik et al., 2015, Darmani, 2001) indicating that this mechanism has been evolutionarily conserved. For example, THC reduced the emetic effects of cisplatin chemotherapy induced in the least shrew (Darmani, 2001). In addition, CBD-induced suppression of vomiting was reversed by systemic pre-treatment with a 5-HT1A antagonist (Darmani, 2001), suggesting that the anti-emetic effect of CBD may be mediated by activation of 5-HT autoreceptors. In a parallel mechanism, substance P may be a key neurotransmitter in chemotherapy-induced nausea and vomiting (Saito et al., 2003; Tyers and Freeman 1992) and cannabinoids modulated release of substance P in several preclinical studies (Lever and Malcangio, 2002; Oshita et al., 2005; Mailleux and Vanderhaeghen, 1994). For example, THC was shown to increase substance P release in adult rat brain (Mailleux and Vanderhaeghen, 1994). In addition, CB1 receptor stimulation promoted its release in adult mouse spinal cord (Lever and Malcangio, 2002) and in cultured rat dorsal root ganglion cells (Oshita et al., 2005).

Patient claims that cannabis relieves chemotherapy- induced nausea and vomiting are widely recognised in the scientific community and by clinicians, and increasing clinical evidence supports these anecdotes (Malik et al., 2015; Amato et al., 2016; Musty and Rossi, 2001). For example, in 2001, Musty and colleagues published a review of previously unpublished technical reports from six U.S. states that conducted trials of smoked cannabis; they reported that 70–100% of subjects experienced relief from nausea and vomiting, while those taking oral THC experienced a 76–88% reduction (Musty and Rossi, 2001). In one of the few studies carried out in the 21st century, Duran and colleagues recruited 16 patients on chemotherapy who experienced chemotherapy-induced nausea or vomiting despite standard anti-emetic treatment (Duran et al., 2010). Patients were randomized to either an oromucosal cannabis-based spray containing THC and CBD or a placebo. Those in the treatment group experienced less nausea and

vomiting than those on the placebo.

In addition, in 2007, Meiri and colleagues carried out a randomized, double-blind, placebo-controlled, parallel-group, 5-day study evaluating the antiemetic efficacy (on days 2–5) and safety of oral dronabinol (synthetic delta-9 THC). N= 64 randomized patients received moderately to highly emetogenic chemotherapy to dronabinol, ondansetron, both, or a placebo in addition to standard anti-emetic treatments (Meiri et al., 2007). The results showed that dronabinol's performance was equal to that of ondansetron to prevent CINV, with no additive effects on the combination, and all treatment groups were more effective than the placebo (Fig. 3, Fig. 4 and Fig.5). All active treatments significantly reduced the intensity of nausea versus placebo ($p< 0.05$) (Fig. 5), and nausea intensity and vomiting/retching were lowest in patients treated with dronabinol; however, no statistically significant differences between active treatment groups were observed. No statistically significant difference was observed among groups for mean number of episodes of vomiting and/or retching. Active treatment reduced the number of episodes of vomiting to 0 by days 4 and 5, with the ondansetron group showing an increase at day 5. Active treatment reduced the duration of vomiting/retching to 0 hours in all groups by days 4 and 5; duration of nausea was comparable among groups. Results additionally showed that complete responder rate was 62% with dronabinol, 60% with combination therapy, 58% with ondansetron, and 20% with placebo.

Dronabinol or ondansetron was similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone. Active treatments were also well tolerated.

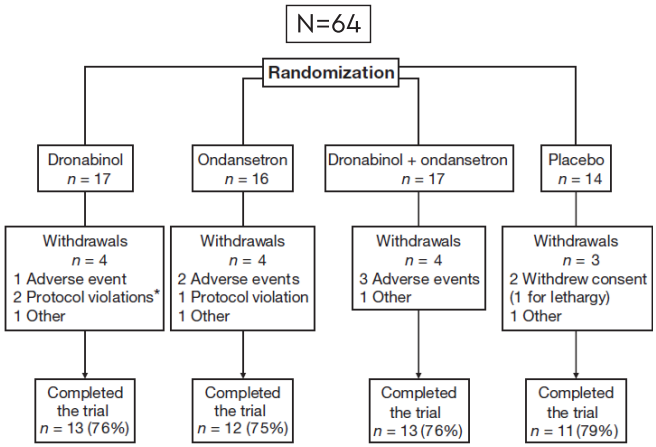

Figure 2 – Trial Flow of patients: Intention-to-treat population, N=64

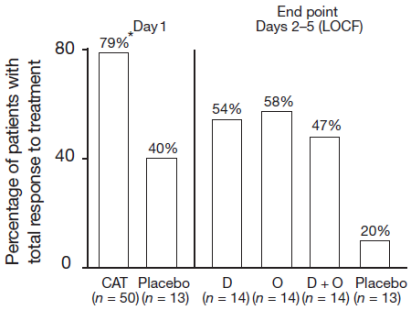

Figure 3 – Total response during active treatment.

Day 1 results are separated from days 2–5 with the vertical line. *p < 0.05 vs. placebo

CAT = combined active treatment; D = dronabinol; D + O = combination; LOCF = last observation carried forward; O = ondansetron; P = placebo

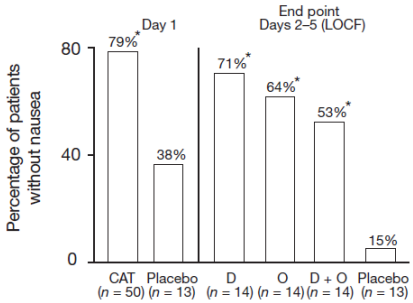

Figure 4 – Absence of nausea during active treatment.

Day 1 results are separated from days 2–5 with the vertical line.

64% of patients receiving ondansetron, 53% of those receiving combination therapt, and 15% of placebo-treated patients responded to treatment.

*p < 0.05 vs. placebo

CAT = combined active treatment; D = dronabinol; D + O = combination; LOCF = last observation carried forward; O = ondansetron; P = placebo

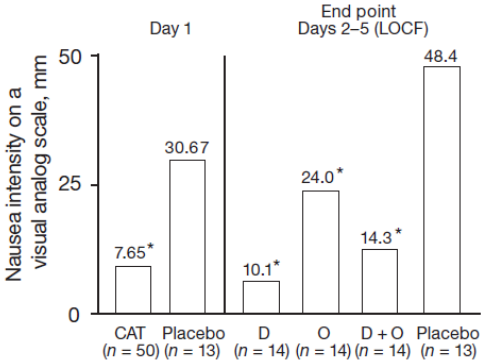

Figure 5 – Mean nausea intensity during active treatment

Day 1 results are separated from days 2–5 with the vertical line.

*p < 0.05 vs. placebo

CAT = combined active treatment; D = dronabinol; D + O = combination; LOCF = last observation carried forward; O = ondansetron; P = placebo, SD = standard deviation

This study demonstrated that the efficacy of dronabinol alone was comparable with ondansetron for the treatment of delayed CINV. This finding is important because standard antiemetic therapy does not relieve symptoms for many patients (Grunberg et al., 2004), and alternative treatments are necessary.

Combining these data with data from the 1970s and 1980s, a 2017 report concluded that there is

conclusive evidence that oral cannabinoids are effective in the treatment of chemotherapy-induced
nausea and vomiting (The National Academies of Sciences, Engineering, and Medicine, 2017).

Since evidence suggested that medicinal cannabis in the form of tetrahydrocannabinol (THC) may reduce CINV, and addition of cannabidiol (CBD) may improve efficacy and tolerance (Chow et al., 2020), an 81 patient, multicentre (10 sites), randomised, double-blind, placebo-controlled, phase II/III trial, was carried out by Grimison and colleagues (Grimison et al., 2020): This aimed to evaluate whether an oral THC: CBD cannabis extract was effective in preventing refractory CINV over multiple chemotherapy cycles.

The baseline characteristics of the 78 participants were as follows: mean age of 55 years (range 29 – 80 years); mainly, female with good ECOG performance status (0 or 1); or typically receiving first-line chemotherapy for breast, colorectal, or lung cancer with either curative or palliative intent (Table 2).

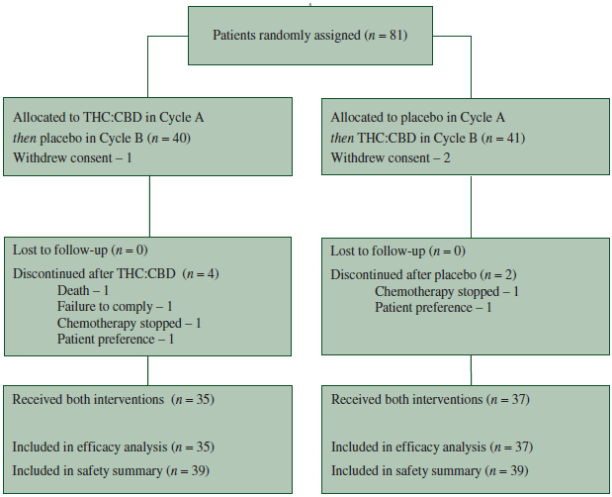

Figure 6 – Trial flow of patients

Characteristic	n (%)
Age (years)	
18–29	1 (1)
30–49	23 (29)
50–69	49 (63)
≥70	5 (6)
Sex	
Female	61 (78)
Male	17 (22)
Previous cannabis use	
No	45 (58)
Yes	33 (42)
Alcohol use (average days per week)	
0	44 (56)
1	16 (21)
>1	18 (23)
History of motion sickness	
No	57 (73)
Yes	21 (27)
History of nausea during pregnancy	
No	22 (41)
Yes	32 (59)
ECOG Performance Status	
0	39 (50)
1	36 (46)
2	3 (4)
Malignancy	
Breast	26 (33)
Colorectal	10 (13)
Lung	9 (12)
Oesophageal/gastric	7 (9)
Gynaecological	7 (9)
Pancreatic	7 (9)
Haematological	3 (4)
Testicular	3 (4)
Other	6 (8)
Treatment intent	
Curative	43 (55)
Palliative	35 (45)
Chemotherapy	
First-line	55 (71)
Second-line	10 (13)
Third-line or greater	13 (16)
Chemotherapy regimen	
Doxorubicin + cyclophosphamide	20 (26)
FOLFOX ± biological	13 (17)
Cisplatin based	12 (15)
FOLFIRINOX	6 (8)
Other	27 (35)
Emetogenic risk	
High	35 (45)
Moderate	43 (55)
Background antiemetic prophylaxis	
Steroid	78 (100)
5-HT_3 antagonist	78 (100)
NK-1 antagonist	62 (79)
Olanzapine	3 (4)

Table 2 – Patient characteristics

72 participants completed both cycles A and B of treatment and were eligible for the efficacy analyses. Of the nine participants excluded from the primary efficacy analyses, three withdrew consent or had no data, five had only completed cycle A, and one had died (Figure 6); 68 participants had complete quality of life data. The typical number of capsules (median (interquartile range)) taken per dose was 2 (1 to 3) for **THC:CBD**, equating to **5 mg THC and 5 mg CBD** three times a day and was 3 (2 to 4) for placebo.

The primary end point for the crossover phase II component of the trial was: difference between cycles A and B in the proportions of participants with complete response: Defined as no vomiting and no rescue medication use during the overall phase of treatment (0 to 120 hours).

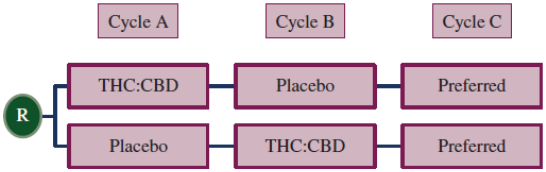

Figure 7 – Study schema for crossover phase II component of trial (planned for N = 80); R, randomised; CBD, cannabidiol; thc, tetrahydrocannabinol.

- Participants were randomised in either trial arm to receive either oral THC:CBD or placebo starting one day before chemotherapy (day -1) and continuing three times per day on the first day of chemotherapy (day 1) through to midday on day 5.

- Participants were able to self-titrate dose of study treatment (up or down, based on experience): 2.5 mg THC and 2.5 mg CBD (or matching placebo) of CINV or side-effects, from an initial dose of 1 capsule 24 h before chemotherapy to a standard dose of 2 capsules, up to a maximum of 4 capsules.

Efficacy Result: Table 3 shows that the addition of THC:CBD to guideline-consistent antiemetics during chemotherapy increased the proportion of participants with complete response during the overall phase of treatment (0 to 120 hours) from 14% to 25% (relative risk 1.77, 90% confidence interval (CI) 1.12 – 2.79, P = 0.041) compared with placebo. There was no evidence of a difference in efficacy for participants who received THC:CBD followed by placebo or the reverse order (P value for carry-over effect = 0.29). Also observed was a statistically significant reduction in the mean and maximum number of vomits per day, and self-reported mean and maximum nausea scores.

Table 3 – Efficacy of THC:CBD versus placebo during 0 to 120 h, within-patient comparisons between cycles A and B (N = 72)

Outcome	THC:CBD	Placebo	Absolute difference (90% CI)	Relative risk (90% CI)	P*
Complete response, *n* (%)	18 (25)	10 (14)	11% (3 to 19)	1.8 (1.1 to 2.8)	0.04
No vomiting, *n* (%)	50 (69)	41 (57)	12.5% (2 to 23)	1.2 (1.0 to 1.4)	0.05
No use of rescue medications, *n* (%)	20 (28)	11 (15)	12.5% (3 to 22)	1.8 (1.1 to 2.8)	0.04
No significant nausea (score <2), *n* (%)	15 (21)	7 (10)	11% (4 to 19)	2.0 (1.2 to 3.4)	0.03
Complete response and no significant nausea, *n* (%)	9 (13)	4 (6)	7% (0.2 to 14)	2.1 (0.96 to 4.8)	0.12
Mean number of vomits per day, mean ± SD	0.2 ± 0.0	0.6 ± 0.2	−0.4 (−0.7 to −0.2)		0.003
Maximum number of vomits per day, mean ± SD	0.5 ± 0.1	1.4 ± 0.3	−0.8 (−1.2 to −0.4)		0.001
Mean nausea score[a], mean ± SD	3.2 ± 0.2	4.7 ± 0.2	−1.4 (−1.8 to −1.0)		<0.001
Maximum nausea score[a], mean ± SD	4.3 ± 0.3	6.1 ± 0.3	−1.8 (−2.3 to −1.2)		<0.001

CBD, cannabidiol; CI, confidence interval; SD, standard deviation; THC, tetrahydrocannabinol.
[a] Scale 0–10. Higher score indicates worse nausea.
* *P* value from a model without the carry-over effect. No significant period effect for comparisons (defined as a change from cycle 1 to cycle 2). No significant carry-over effect for comparisons (defined as no residual effect of the treatment received in the first cycle).

Adverse events(AEs): Grade 3 or 4 AEs occurred in 14 participants while receiving THC:CBD, and 10 participants while receiving placebo during cycles A and B. These were mainly infection, nausea/vomiting, anaemia, decreased neutrophil/platelet count, and in one case hypertension. Serious adverse events (SAEs) occurred in five participants while receiving THC:CBD and seven participants while receiving placebo. All grade 3 or 4 and SAEs were attributed to background chemotherapy, disease, or other medical conditions, but none to the study treatments.

Self-reported cannabinoid-related AEs: Self-reported moderate-to-severe cannabinoid-related AEs occurred in 22 participants (31%) while receiving

THC:CBD, compared with 5 (7%) while receiving placebo. The most common moderate-to-severe cannabinoid-related AEs were sedation, dizziness, and disorientation; anxiety was uncommon, and no moderate or severe hallucinations or palpitations were reported.

Patient preference: After cycle B completion, 60 of the 72 (83%) participants who completed the study reported a preference for THC:CBD, with 11 of 72 participants (15%) reporting a preference for placebo (P < 0.001).

Self-reported quality of life: Data for both cycles A and B were available for 68 participants. The addition of THC:CBD to guideline-consistent antiemetics during chemotherapy was associated with reduced impact of CINV on daily life in both the nausea (mean difference 20.9 on a 100-point scale, P < 0.001) and the vomiting domain (mean difference 11.9 on a 100-point scale, P < 0.001), according to the FLIE questionnaire (Table 4). There was a small but significant improvement in AQOL-8D utility-based quality of life (mean difference 0.04, 95% CI 0.01 – 0.07, P = 0.019), and in the Physical Health Super Dimension mean difference 0.06, 95% CI 0.03 – 0.09, P < 0.001, as shown in Table 4.

Table 3 – Efficacy of THC:CBD versus placebo during 0 to 120 h, within-patient comparisons between cycles A and B (N = 72)

	THC:CBD (*N* = 68), mean ± SD	Placebo (*N* = 68), mean ± SD	Mean difference (95% confidence interval)	*P*
FLIE scale analyses[a]				
Nausea domain (scale 0—100)[b]	72 (25)	51 (29)	21 (12 to 29)	<0.001
Vomiting domain (scale 0—100)[c]	91 (15)	79 (29)	12 (6 to 18)	<0.001
AQOL-8D scale analyses[a]				
Independent living[d]	0.72 ± 0.18	0.70 ± 0.18	0.02 (−0.01 to 0.04)	0.13
Happiness	0.71 ± 0.16	0.70 ± 0.18	0.01 (−0.02 to 0.05)	0.50
Mental health	0.66 ± 0.12	0.63 ± 0.12	0.04 (0.01 to 0.06)	0.004
Coping	0.67 ± 0.14	0.66 ± 0.16	0.01 (−0.03 to 0.04)	0.67
Relationships	0.66 ± 0.15	0.65 ± 0.14	0.01 (−0.02 to 0.03)	0.61
Self-worth	0.75 ± 0.16	0.73 ± 0.17	0.03 (−0.00 to 0.06)	0.07
Pain	0.79 ± 0.19	0.71 ± 0.22	0.08 (0.03 to 0.13)	0.003
Senses	0.86 ± 0.11	0.84 ± 0.13	0.02 (−0.01 to 0.05)	0.18
Super Dimension Mental	0.33 ± 0.16	0.31 ± 0.16	0.02 (−0.01 to 0.05)	0.27
Super Dimension Physical	0.63 ± 0.17	0.58 ± 0.18	0.06 (0.03 to 0.09)	<0.001
AQOL-8D utility	0.65 ± 0.17	0.61 ± 0.19	0.04 (0.01 to 0.07)	0.019

CBD, cannabidiol; SD, standard deviation; THC, tetrahydrocannabinol.
[a] Higher score indicates better quality of life.
[b] $n = 67$ (one participant with missing data).
[c] $n = 66$ (two participants with missing data).
[d] Data were imputed for one question for two participants in the Independent Living Dimension.

In conclusion, the oral THC:CBD cannabis extract was active and tolerable in preventing CINV, when combined with guideline-consistent antiemetic prophylaxis for a study population with refractory CINV.

Concluding summary

Since vomiting is mediated by neurotransmitters in the central nervous system, patients receiving therapy with cannabinoids might be expected to have sensorial CNS AEs consistent with those reported in previous trials with THC compounds McCabe et al., 1998; Sallan et al., 1975; Sallan et al., 1980). In the Meiri et al., 2020 study, the highest rate of CNS-related events (dizziness and fatigue) occurred in patients receiving combination therapy and the incidence of CNS-related events in the dronabinol group was low. The CNS-related AEs reported in the previous studies (Sallan et al., 1975; Sallan et al., 1980) may have been dose-related considering that the dosage of THC used was at least 50% greater than in previous studies (30– 45 mg/day) than in the study reported here (median dosage of 20 mg/day,).

Well-tolerated and effective treatment of CINV, particularly for those patients refractory to treatment with standard antiemetics, may lead to improved treatment outcomes through improved compliance with chemotherapy.

In 2017, the U.S. National Academies of Sciences report concluded that there was conclusive evidence that orally administered cannabinoids are effective in the symptom management of CINV (The National Academies of Sciences, Engineering, and Medicine, 2017) and the Grimision study (Grimison et al., 2020) adds further weight to this statement.

More recent advances in the delivery of cannabinoids, using e-cigarettes and vaporiser technology, has led to easier routes for patient administration and dosing. Inhalable medical cannabis for the management of CINV may represent a convenient and efficient means of improving drug bioavailability. Indeed, some medical cannabis companies already specialise in providing vaping technology options for patients, such as Columbia Care Inc., Aurora Inc., Tilray Inc. and Grow Pharma, as well as providing whole extract CBMPs as either capsules or oils

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