MEDICINA HUMANA

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Extracto oral de cannabis con THC:CBD para las náuseas y los vómitos refractarios inducidos por la quimioterapia: un ensayo cruzado de fase II, aleatorizado y controlado con placebo

Los estudios de observación de cohortes informan que el 46%miEl 57% experimenta náuseas significativas y el 9%miEl 37% experimenta vómitos. Las náuseas y los vómitos inducidos por quimioterapia (NVIQ) son provocados por una multitud de receptores de neurotransmisores, incluidos la serotonina, la dopamina, la sustancia P y potencialmente el receptor cannabinoide CB1. La evidencia limitada sugiere que el cannabis medicinal en forma de tetrahidrocannabinol (THC) puede reducir las CINV, y la adición de cannabidiol (CBD) puede mejorar la eficacia y la tolerancia. Los extractos de cannabis que contienen THC y CBD ofrecen ventajas clave sobre los cannabinoides alternativos. El CBD puede contrarrestar los efectos negativos del THC en el sistema nervioso central y tiene propiedades ansiolíticas inherentes. Un pequeño ensayo piloto doble ciego aleatorizado de nabiximols, una formulación de THC:CBD de absorción bucal en una proporción de 1:1, para la prevención secundaria de NVIQ demostró actividad, con una mejora en la respuesta completa del 22 % al 71 %, alta aceptabilidad por parte del paciente y efectos secundarios manejables. Este ensayo aleatorizado, doble ciego, controlado con placebo, de fase II/III tiene como objetivo evaluar un extracto de cannabis THC:CBD oral para prevenir las NVIQ refractarias durante múltiples ciclos de quimioterapia. El análisis final del ensayo determinará el resultado primario para 250 participantes, lo que representa 80 participantes de un componente cruzado de fase II y 170 participantes de un componente paralelo de fase III. Aquí informamos los resultados del componente cruzado de fase II del ensayo, que determinó que el ensayo de fase III con 170 pacientes adicionales podría continuar. Los pacientes elegibles tenían -18 años de edad, con cualquier malignidad de cualquier estadio que estuvieran recibiendo quimioterapia intravenosa de riesgo enteogénico moderado o alto, estuvieran programados para recibir al menos dos ciclos consecutivos más y tuvieran NVIQ refractarios (definidos como emesis y/o náuseas). De gravedad moderada en una escala de calificación de 5 puntos y/o que requiere el uso de medicamentos de rescate) en ciclos de quimioterapia anteriores a pesar de la profilaxis antiemética consistente con las guías que consiste en corticosteroides, un 5-HT3antagonista y un antagonista de NK-1 con o sin olanzapina cuando esté indicado. El punto final primario para el componente cruzado de fase II del ensayo fue la diferencia entre los ciclos A y B en las proporciones de participantes con respuesta completa, definida como sin vómitos y sin uso de

medicamentos de rescate durante la fase general del tratamiento (0mi120 h), según consta en el diario del paciente. Los puntos finales secundarios incluyen diferencias para la "respuesta completa" autoinformada, "sin emesis", "sin náuseas clínicamente significativas", que se define como náuseas <2 en una escala de 10 puntos, y "sin uso de medicamentos de rescate" durante el agudo (0 mi24 h), retrasado (24mi120 h), y fase global (0mi120 h) de quimioterapia; escalas de resumen (náuseas y vómitos) de la FLIE con recordatorio de 5 días, e ítems individuales, dominios y utilidades de la AQOL-8D. Los eventos adversos se registraron de acuerdo con los Criterios de Terminología Común para Eventos Adversos del NCI, Análisis estadístico Régimen de quimioterapia doxorrubicinaþciclofosfamida FOLFOX biológico a base de cisplatino FOLFIRINOX Otro 20 (26), 13 (17), 12 (15), 6 (8), 27 (35). El tamaño de la muestra de 80 participantes para el componente cruzado de fase II del ensayo (40 por brazo), que aleatorizó a los participantes al fármaco del estudio seguido de placebo o al placebo seguido del fármaco del estudio, tiene una potencia del 80 % con un nivel de significación bilateral de 10 % para detectar un aumento del 20 % en la respuesta completa del 22 % en el grupo de placebo al 42 % en el grupo de cannabis durante los ciclos A y B de quimioterapia. Este tamaño de muestra permite una tasa de abandono/no elegibilidad del 20 %. Solo los participantes que recibieron ambas intervenciones se incluyeron en los análisis de eficacia. Los datos sobre seguridad se obtuvieron de la población de seguridad (todos los participantes que recibieron -1 dosis del fármaco del estudio). El análisis principal fue una comparación de la proporción de participantes con respuesta completa entre los dos brazos de tratamiento durante dos fases generales del tratamiento (0mi120 h) de los ciclos A y B, usando la prueba de McNemar para dar cuenta de la correlación dentro del paciente. Los resultados continuos se analizaron con un modelo lineal y representaron la correlación dentro de un participante. Todas las pruebas utilizaron un nivel de significación bilateral del 10%. Los análisis secundarios no se han ajustado para comparaciones múltiples. Los análisis se completaron con SAS. Se aleatorizó un total de 81 participantes de 10 sitios entre diciembre de 2016 y junio de 2019. Las características iniciales de los 78 participantes que no retiraron el consentimiento fueron las siguientes: edad media de 55 años (rango 29mi80 años); típicamente mujer con buen estado funcional ECOG (0 o 1); o recibe típicamente quimioterapia de primera línea para el cáncer de mama, colorrectal o de pulmón con intención curativa o paliativa (tabla 1). Un total de 72 participantes completaron los ciclos A y B de tratamiento y fueron elegibles para los análisis de eficacia. De los nueve participantes excluidos de los análisis de eficacia primarios, tres retiraron el consentimiento o no tenían

datos, cinco solo habían completado el ciclo A y uno había muerto; 68 participantes tenían datos completos de calidad de vida. La adición de THC:CBD a los antieméticos consistentes con las guías durante la quimioterapia aumentó la proporción de participantes con respuesta completa durante la fase general del tratamiento (0mi 120 h) del 14% al 25% [riesgo relativo (RR) 1,77, intervalo de confianza (IC) del 90% 1,12mi2.79, PAG¼0,041] en comparación con placebo, sin evidencia de una diferencia en la eficacia para los participantes que recibieron THC:CBD seguido de placebo o en orden inverso (PAG valor por efecto arrastre¼0,29;Tabla 2). Hubo efectos similares para las proporciones de participantes sin emesis, sin uso de medicamentos de rescate, sin náuseas significativas y respuesta completa sin náuseas significativas. También hubo una reducción estadísticamente significativa en el número medio y máximo de vómitos por día, y en las puntuaciones de náuseas media y máxima auto informadas.

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ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: a randomised, placebo-controlled, phase II crossover trial

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Background: This multicentre, randomised, double-blinded, placebo-controlled, phase II/III trial aimed to evaluate an oral THC:CBD (tetrahydrocannabinol:cannabidiol) cannabis extract for prevention of refractory chemotherapy-induced nausea and vomiting (CINV). Here we report the phase II component results.

Patients and methods: Eligible patients experienced CINV during moderate-to-high emetogenic intravenous chemotherapy despite guideline-consistent antiemetic prophylaxis. Study treatment consisted of one cycle of 1—4 self-titrated capsules of oral THC 2.5 mg/CBD 2.5 mg (TN-TC11M) three times daily, from days −1 to 5, and 1 cycle of matching placebo in a crossover design, then blinded patient preference for a third cycle. The primary end point was the proportion of participants with complete response during 0—120 h from chemotherapy. A total of 80 participants provided 80% power to detect a 20% absolute improvement with a two-sided *P* value of 0.1.

Results: A total of 81 participants were randomised; 72 completing two cycles were included in the efficacy analyses and 78 not withdrawing consent were included in safety analyses. Median age was 55 years (range 29—80 years); 78% were female. Complete response was improved with THC:CBD from 14% to 25% (relative risk 1.77, 90% confidence interval 1.12—2.79, $P = 0.041$), with similar effects on absence of emesis, use of rescue medications, absence of significant nausea, and summary scores for the Functional Living Index-Emesis (FLIE). Thirty-one percent experienced moderate or severe cannabinoid-related adverse events such as sedation, dizziness, or disorientation, but 83% of participants preferred cannabis to placebo. No serious adverse events were attributed to THC:CBD.

Conclusion: The addition of oral THC:CBD to standard antiemetics was associated with less nausea and vomiting but additional side-effects. Most participants preferred THC:CBD to placebo. Based on these promising results, we plan to recruit an additional 170 participants to complete accrual for the definitive, phase III, parallel group analysis.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12616001036404; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370473&isReview=true.

Key words: antiemetic, cannabidiol, cannabis, chemotherapy-induced nausea and vomiting, randomised trial

INTRODUCTION

Despite adherence to the Multinational Association of Supportive Care in Cancer antiemetic guidelines for chemotherapy of high or moderate emetic risk, recent observational cohort studies report that 46%—57% experience significant nausea, and 9%—37% experience vomiting.[1—3] Chemotherapy-induced nausea and vomiting (CINV) is triggered by a multitude of receptors for neurotransmitters including serotonin, dopamine, substance P, and potentially the cannabinoid CB1 receptor.[4—6]

Limited evidence suggests that medicinal cannabis in the form of tetrahydrocannabinol (THC) may reduce CINV, and addition of cannabidiol (CBD) may improve efficacy and tolerance.[7] Prior studies evaluating smoked cannabis, synthetic oral THC (Dronabinol), or THC analogue (Nabilone)

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medicines showed limited efficacy, were underpowered, or did not compare cannabis with modern antiemetic regimens.[5,6] Furthermore, THC-only medications can have a range of dose-dependent side-effects including dizziness, sedation, anxiety, and psychomotor impairment.[5,8] None of these cannabinoid products are routinely prescribed for CINV prophylaxis, conceivably because of concerns regarding poor tolerability, limited accessibility, perceived insufficient evidence for efficacy, and effective alternatives.[4] Cannabis extracts containing both THC and CBD offer key advantages over alternate cannabinoids. CBD can counteract the negative effects of THC on the central nervous system, and has inherent anxiolytic properties.[7,9] A small pilot double-blind randomised trial of nabiximols, a buccally absorbed THC:CBD formulation in a 1:1 ratio, for the secondary prevention of CINV demonstrated activity, with an improvement in complete response from 22% to 71%, high patient acceptability, and manageable side-effects.[10] These results provided the rationale for our study.

This randomised, double-blind, placebo-controlled, phase II/III trial aims to evaluate an oral THC:CBD cannabis extract in preventing refractory CINV over multiple chemotherapy cycles. The final analysis of the trial will determine the primary outcome for 250 participants, representing 80 participants from a phase II crossover component and 170 participants from a phase III parallel component. Here we report results from the phase II crossover component of the trial, which determined that the phase III trial with an additional 170 patients could continue.

METHODS

Patients

Details of the study protocol have been previously published.[11] Study schema is shown in Figure 1.

Eligible patients were aged ≥18 years, with any malignancy of any stage who were receiving intravenous chemotherapy of moderate or high emetogenic risk, were scheduled to receive at least two more consecutive cycles, and had refractory CINV (defined as emesis, and/or nausea of moderate severity on a 5-point rating scale, and/or requiring use of rescue medications) in earlier chemotherapy cycles despite guideline-consistent antiemetic prophylaxis consisting of corticosteroids, a 5-HT_3 antagonist, and an NK-1 antagonist with or without olanzapine where indicated. Patients were excluded if they had an Eastern Cooperative Oncology Group (ECOG) performance status of >2; a contraindication to medicinal cannabis such as unstable cardiovascular disease, substance use disorder, or significant mental health disorder; were experiencing disease-related nausea and vomiting; were receiving concomitant oral chemotherapy; or had received/were planned to receive radiotherapy to the brain or gastrointestinal tract during the study period. Participants were required to abstain from extraneous cannabis products prior to and during the trial, to provide a urine sample negative for cannabinoids within 30 days prior to trial enrolment, and were not permitted to drive during and for 3 days following the last ingestion of study treatment due to state legislation. All participants provided written informed consent. The protocol and all amendments were approved by the Human Research Ethics Committee at all participating centres. The trial is registered in the Australian New Zealand Clinical Trials Registry (Registration No. ACTRN12616001036404).

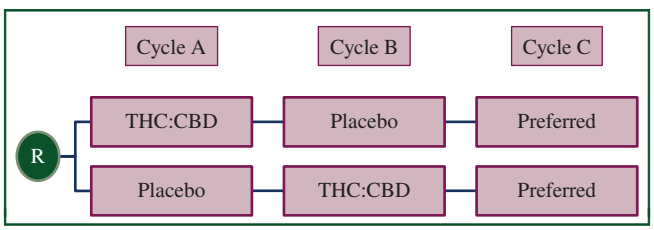

Figure 1. Study schema for crossover phase II component of trial (planned $N = 80$).
R, randomised; CBD, cannabidiol; THC, tetrahydrocannabinol.

Trial design and intervention

The crossover phase II component of this multicentre randomised, double-blind, placebo-controlled trial was conducted in New South Wales, Australia. Using a central web-based randomisation system, participants were randomised in a 1:1 ratio to receive either oral THC:CBD or matching placebo starting the day prior to 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 gradually self-titrate dose of study treatment (each capsule containing 2.5 mg THC and 2.5 mg CBD, or matching placebo) up or down based on experience 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 (see supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.07.020). For cycle A (the initial trial cycle), participants received either oral THC:CBD or placebo. For cycle B, (the second trial cycle), participants received the alternative treatment. For cycle C (the third trial cycle), where relevant, participants received their 'preferred' treatment with the blind maintained. Unblinding after cycle C allowed participants to receive ongoing THC:CBD, following completion of the study, if they had perceived a benefit and were continuing the same chemotherapy regimen. In addition to study treatment, all participants received the guideline-recommended CINV prophylaxis including rescue medications in the event of vomiting or distress by nausea.[12–14]

Assessments

Participants underwent clinical assessment on days −1 and 8 of each cycle, and between 30 and 42 days after the end of study treatment. 'Day 1' represents the first day of the chemotherapy cycle, and 'day −1' is one day prior to 'day 1'. Self-reported experience of nausea and vomiting, use of rescue medications, and dose of study treatment were recorded in a patient diary for days −1 to day 6 of each cycle. Quality of life was assessed by the Functional Living

Index-Emesis (FLIE)[15] and Assessment of Quality of Life-8 dimensions (AQOL-8D) multiattribute utility instrument[16] questionnaires at baseline, day −1 of each cycle (relating to the previous cycle), and end of treatment. Following completion of cycle B, participants were asked to consider both control of nausea and vomiting as well as other side-effects from medications, and nominate an overall preference for the regimen administered during cycle A, cycle B, or no preference. There was daily contact with trial staff on the days of study treatment to ensure appropriate use of study medication, accuracy of the patient diary, recording of a structured checklist of cannabinoid-specific adverse events, and advice on management of adverse events.

Objectives and end points

The primary end point for the crossover phase II component of the trial was the difference between cycles A and B in the proportions of participants with complete response, defined as no vomiting and no use of rescue medications during the overall phase of treatment (0—120 h), as recorded in the patient diary. Secondary end points include differences for self-reported 'complete response', 'no emesis', 'no clinically significant nausea', which is defined as nausea <2 on a 10-point scale, and 'no use of rescue medications' during the acute (0—24 h), delayed (24—120 h), and overall phase (0—120 h) of chemotherapy; summary scales (nausea and vomiting) of the FLIE with 5-day recall, and individual items, domains, and utilities of the AQOL-8D. Adverse events were recorded according to the NCI Common Terminology Criteria for Adverse Events version 4.03,[17] and a structured checklist of cannabinoid-specific adverse events.[18] Acceptability was recorded by study drug adherence (patient diaries and pill counts), and patient preference between cycles A and B.

Statistical analyses

The sample size of 80 participants for the phase II crossover component of the trial (40 per arm), randomising participants to either study drug followed by placebo or placebo followed by study drug, has 80% power at a two-sided significance level of 10% to detect a 20% increase in complete response from 22% in the placebo group to 42% in the cannabis group during cycles A and B of chemotherapy. This sample size allows drop-out/ineligibility rate of 20%. Only participants who have received both interventions have been included in the efficacy analyses. Data on safety were sourced from the safety population (all participants who received ≥1 dose of study drug). The primary analysis was a comparison of the proportion of participants with complete response between the two treatment arms during two overall phases of treatment (0—120 h) of cycles A and B, using McNemar's test to account for the within-patient correlation. Continuous outcomes were analysed with a linear model, and accounted for the correlation within a participant. All tests used a two-sided significance level of 10%. Secondary analyses have not been adjusted for multiple comparisons. Analyses were completed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). In accordance with the study protocol, the results of the within-patient crossover comparison analyses for the phase II crossover component were provided to the Independent Data Safety Monitoring Committee (IDSMC) with study investigators and trial management committee remaining blind to study results, and only released after the IDSMC decided to proceed from the phase II crossover component to the phase III parallel trial component. The results of the between-patient parallel comparison analyses remain blinded to the IDSMC.

Table 1. Baseline characteristics ($N = 78$)

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)

RESULTS

Patients

A total of 81 participants were randomised from 10 sites between December 2016 and June 2019. Baseline characteristics of the 78 participants who did not withdraw consent were as follows: mean age of 55 years (range 29—80 years); typically 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 1). A total of 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 2); 68 participants had complete quality of life data. The typical number of capsules [median (interquartile range)] taken per dose was 2 (1—3) for THC:CBD, equating to 5 mg THC and 5 mg CBD tds, and was 3 (2—4) for placebo.

Efficacy

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—120 h) from 14% to 25% [relative risk (RR) 1.77, 90% confidence interval (CI) 1.12—2.79, $P = 0.041$] compared with placebo, with no evidence of a difference in efficacy for participants who received THC:CBD followed by placebo or the reverse order (P value for carryover effect = 0.29; Table 2). There were similar effects for proportions of participants with no emesis, no use of rescue medications, no significant nausea, and complete response

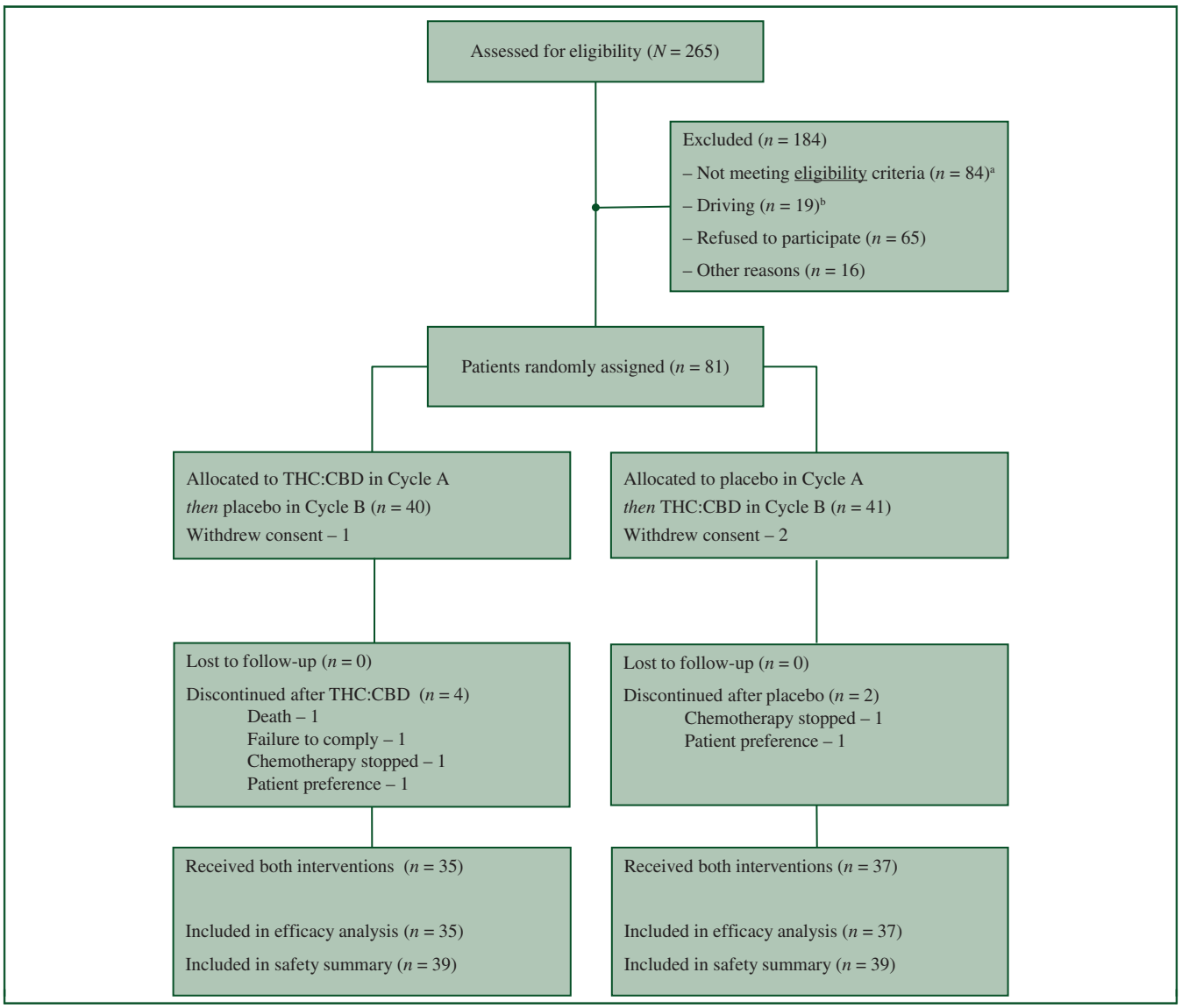

Figure 2. CONSORT diagram.

CBD, cannabidiol; THC, tetrahydrocannabinol.

[a]Most common reasons for not meeting eligibility criteria: contraindication to cannabinoid treatment ($n = 15$), <2 cycles of chemotherapy remaining ($n = 11$), use of cannabis or cannabinoid-based medications within 30 days of study entry and/or unwilling to abstain for the duration of the study ($n = 10$).

[b]'Driving': Unwilling to avoid driving or operating machinery during and for 72 h after taking study medication.

Table 2. Efficacy of THC:CBD versus placebo during 0–120 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).

with no significant nausea. There was also a statistically significant reduction in the mean and maximum number of vomits per day, and self-reported mean and maximum nausea scores.

Adverse events

Grade 3 or 4 adverse events occurred in 14 participants while receiving THC:CBD, and 10 participants while receiving placebo during cycles A and B (Table 3). Serious adverse events occurred in five participants while receiving THC:CBD and seven participants while receiving placebo during cycles A and B (Table 3). All grade 3 or 4 and serious adverse events were attributed to background chemotherapy, disease, or other medical conditions, and none to study treatments.

Self-reported cannabinoid-related adverse events

Self-reported moderate-to-severe cannabinoid-related adverse events occurred in 22 participants (31%) while receiving THC:CBD, compared with 5 (7%) while receiving placebo (Table 4). The most common moderate-to-severe cannabinoid-related adverse events were sedation, dizziness, and disorientation. Anxiety was uncommon, and no moderate or severe hallucinations or palpitations were reported.

Table 3. Grade 3 or 4 adverse events and serious adverse events for cycles A and B ($N = 78$)

	THC:CBD, *n* (%)	Placebo, *n* (%)
Grade 3 or 4 adverse event (AE) by CTCAE criteria		
Any AE grade 3–4	14 (18)	10 (13)
Infection/fever/febrile neutropaenia	3 (4)	4 (5)
Nausea/vomiting	3 (4)	2 (3)
Anaemia	3 (4)	1 (1)
Neutrophil count decreased	3 (4)	2 (3)
Platelet count decreased	1 (1)	0 (0)
Hypertension	1 (1)	0 (0)
Atrial flutter	0 (0)	1 (1)
Serious adverse event (SAE)		
Any SAE (by participant)	5 (6)	7 (9)
Infection/fever/febrile neutropaenia	3 (4)[a]	4 (5)
Vomiting	1 (1)	0 (0)
Atrial flutter	0 (0)	1 (1)
Neutrophil count decreased	1 (1)	1 (1)
Anaemia	1 (1)	1 (1)

CBD, cannabidiol; CTCAE, Common Terminology Criteria for Adverse Events; THC, tetrahydrocannabinol.
[a] Includes two events in one participant.

Patient preference

At the completion of cycle B, 60 of the 72 (83%) participants who completed the study reported a preference for THC:CBD, and 11 of 72 participants (15%) reported a preference for placebo ($P < 0.001$). One participant reported no preference.

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 domain (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 5). 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, $P < 0.001$; Table 5). Small improvements

Table 4. Self-reported cannabinoid-related adverse events rated moderate or severe ($N = 78$)

Side-effects	THC:CBD, *n* (%)	Placebo, *n* (%)	P*
Any (by participant)	22 (31)[a]	5 (7)	0.002
Sedation	15 (19)	3 (4)	0.008
Anxiety	1 (1)	1 (1)	1.0
Disorientation	2 (3)	0 (0)	0.5
Dizziness	8 (10)	1 (1)	0.03
Hallucinations	0 (0)	0 (0)	
Palpitations	0 (0)	0 (0)	

CBD, cannabidiol; THC, tetrahydrocannabinol.
[a] Four participants experienced moderate or severe sedation and dizziness while receiving THC:CBD.
* Comparison for 72 participants who received both interventions; excludes those with [side-effect (*n* for THC:CBD, *n* for placebo)] any (3, 0), sedation (2, 0), and dizziness (1, 0) who did not receive both interventions.

Table 5. Self-reported quality of life: comparison of Functional Living Index (FLIE) and Assessment of Quality of Life-8 dimensions (AQOL-8D) scores by study allocation

	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.

were also observed in the AQOL-8D mental health and pain dimensions.

DISCUSSION

The phase II crossover component of this randomised, double-blind, multicentre placebo-controlled, phase II/III trial has demonstrated the activity and tolerability of an oral THC:CBD cannabis extract for prevention of refractory CINV, and a sufficient accrual rate to complete the phase III parallel component of the trial. There was an improvement with oral THC:CBD cannabis extract in the control of nausea and vomiting.

We found that the additional side-effects were tolerable. Although almost one-third of participants experienced moderate-to-severe cannabinoid-related adverse events such as sedation, dizziness, and disorientation, 85% of participants preferred THC:CBD to placebo. Adverse events were as expected for background chemotherapy.

With regard to health-related quality of life, an overall improvement was observed in utility; however, this may not be a clinically meaningful improvement, as previous studies have suggested an improvement of 0.06 measured by AQOL instruments is required.[19] Further research is necessary to determine the significance and durability of improvements observed in specific AQOL-8D dimensions.

Strengths of our trial include the novel multistage phase II/III design including crossover and parallel components, the success of recruiting 81 eligible patients over 2.5 years, and the excellent compliance of participants in completing the patient diary. Furthermore, this is the first adequately powered, randomised study of medicinal cannabis for CINV to include background modern guideline-consistent antiemetics, whereas previous studies compared cannabis with outdated antiemetics.[5,6] The patient preference question was a unique addition to the trial, which allowed participants to consider both control of nausea and vomiting, and side-effects from cannabinoids and other medications. We restricted study eligibility to patients with refractory CINV to avoid the potential adverse events, driving restrictions, and other legal ramifications of medicinal cannabis for patients whose CINV is well controlled with standard antiemetics, and increased the power of the study to detect an effect in an enriched population. However, this does limit the ability to compare our results with studies of antiemetics as *primary* prophylaxis for CINV. The main limitation of the results is the underlying phase II randomised crossover design, designed to guide further research, not to definitively establish that the addition of oral THC:CBD is more effective than guideline-consistent antiemetic prophylaxis alone. Completion of the phase III component of the trial is required to demonstrate more robust outcomes utilising a traditional between-patient comparison for cycle A for all 250 patients, and determine longer-term effectiveness, cost-effectiveness, and tolerability over multiple cycles of chemotherapy. Finally, few participants received olanzapine, which since commencement of our trial has been added as an option for highly emetic regimens.[13,17]

Future research could explore whether 'nonresponders' would benefit from higher doses (although we allowed self-titration), or indeed whether different ratios of THC and CBD may impact upon efficacy or safety outcomes.[20,21] Second, it is also unclear to what extent the properties of THC such as sedation, drowsiness, and euphoria contributed to most participants preferring oral THC:CBD over placebo. Third, our trial raises questions about the acceptability of prescribed cannabis products to some cancer patients

receiving chemotherapy, given that a large proportion assessed for eligibility were not enrolled, and male patients were underrepresented. Finally, future trials could compare the efficacy of cannabinoids with other antiemetics such as olanzapine.

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. Based on our results, we are continuing recruitment to the phase III parallel component of our trial.

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REFERENCES

1. Aapro M, Molassiotis A, Dicato M, et al. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Ann Oncol*. 2012;23:1986–1992.
2. Gilmore JW, Peacock NW, Gu A, et al. Antiemetic guideline consistency and incidence of chemotherapy-induced nausea and vomiting in US community oncology practice: INSPIRE Study. *J Oncol Pract*. 2014;10:68–74.
3. Molassiotis A, Saunders MP, Valle J, et al. A prospective observational study of chemotherapy-related nausea and vomiting in routine practice in a UK cancer centre. *Support Care Cancer*. 2008;16:201–208.
4. Navari RM, Aapro M. Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;374(14):1356–1367.
5. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*. 2010;35:764–774.
6. Kramer JL. Medical marijuana for cancer. *CA Cancer J Clin*. 2015;65:109–122.
7. Chow R, Valdez C, Chow N, et al. Oral cannabinoid for the prophylaxis of chemotherapy-induced nausea and vomiting—a systematic review and meta-analysis. *Support Care Cancer*. 2020;28:2095–2103.
8. Wilkie G, Sakr B, Rizack T. Medical marijuana use in oncology: a review. *JAMA Oncol*. 2016;2(5):670–675.
9. Bonaccorso S, Ricciardi A, Zangani C, Chiappini S, Schifano F. Cannabidiol (CBD) use in psychiatric disorders: a systematic review. *Neurotoxicology*. 2019;74:282–298.
10. Duran M, Perez E, Abanades S, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol*. 2010;70:656–663.
11. Mersiades AJ, Tognela A, Haber PS, et al. Oral cannabinoid-rich THC:CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: a study protocol for a pilot and definitive randomised double-blind placebo-controlled trial (CannabisCINV). *BMJ Open*. 2018;8:e020745.
12. Roila F, Molassiotis A, Herrstedt J, et al. MASCC and ESMO consensus guidelines for the prevention of chemotherapy and radiotherapy-induced nausea and vomiting: ESMO clinical practice guidelines. *Ann Oncol*. 2016;27(suppl 5):v119–v133.
13. Appro M, Gralla R, Herrstedt J, Molassiotis A, Roila F. *MASCC/ESMO Antiemetic Guideline 2016 with Updates in 2019*; 2019. Available at: https://www.mascc.org/antiemetic-guidelines. Accessed April 1, 2020.
14. Cancer Institute NSW. Prevention of chemotherapy induced nausea and vomiting. Available at: https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/gastrointestinal/7-prevention-of-chemotherapy-induced-nausea-and. Accessed April 1, 2020.

15. Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindley C. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the Functional Living Index-Emesis (FLIE) with 5-day recall. *Support Care Cancer*. 2003;11:522—5227.
16. Richardson J, Iezzi A, Khan MA, Maxwell A. Validity and reliability of the Assessment of Quality of Life (AQoL)-8D multi-attribute utility instrument. *Patient*. 2014;7:85—96.
17. *Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0*. Bethesda: National Cancer Institute; 2009. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed August 14, 2020.
18. Lintzeris N, Bhardwaj A, Mills L, et al. Nabiximols for the treatment of cannabis dependence: a randomized clinical trial. *JAMA Intern Med*. 2019;179(9):1242—1253.
19. Hawthorne G, Osborne R. Population norms and meaningful differences for the Assessment of Quality of Life AQoL measure. *Aust N Z J Public Health*. 2005;29:136—142.
20. Zeyl V, Sawyer K, Wightman RS. What do you know about Maryjane? A systematic review of the current data on the THC:CBD ratio. *Subst Use Misuse*. 2020;55(8):1223—1227.
21. Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. *Br J Clin Pharmacol*. 2019;85:1888—1900.