A phase 2b randomised, placebo controlled, dose-escalating, double-blind study of cannabidiol oil for the relief of symptoms in advanced cancer (MedCan1-CBD).

Janet Hardy [1,2], Ristan M Greer[2,3], Georgie Huggett[1], Alison Kearney [4,5], Taylan Gurgenci [1,2], Phillip Good [1,2,6]

Prof Janet Hardy (corresponding author)

[1]Department Palliative and Supportive Care,

Mater Health Services, SE Queensland

[2]Mater Research Institute – University of Queensland,

Brisbane, Queensland, 4101

Australia

janet.hardy@mater.org.au

Ph: +61 (07) 3163 2775 or +61 414 812 991(m)

Dr Ristan Greer.

[3]Torus Research, Brisbane, Australia

[2]Honorary A/Prof Mater Research Institute – University of Queensland,

Brisbane, Queensland, 4101, Australia

Mrs Georgie Huggett.

[1]Department Palliative and Supportive Care,

Mater Health Services, SE Queensland

Dr Alison Kearney.

[4]Dept Palliative and Supportive Care,

Royal Brisbane and Women's Hospital,

Herston, Brisbane

[5]Faculty of Medicine, University of Queensland,

Herston, Queensland, 4006

Dr Taylan Gurgenci.

[1]Department Palliative and Supportive Care,

Mater Health Services, SE Queensland

[2]Mater Research Institute – University of Queensland,

Brisbane, Queensland, 4101, Australia

Prof Phillip Good.

[6]Dept Palliative Care,

St Vincent's Private Hospital Brisbane,

[1]Department Palliative and Supportive Care,

Mater Health Services, SE Queensland

[2]Mater Research Institute – University of Queensland[2],

Brisbane, Queensland, 4101, Australia

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ABSTRACT

Purpose. To determine whether cannabidiol (CBD) oil can improve symptom distress in patients with advanced cancer receiving palliative care.

Methods. Participants were adults with advanced cancer and symptom distress (Edmonton Symptom Assessment Scale (ESAS) score of ≥10/90) who received titrated CBD oil (100mg/mL) or matched placebo for 28 days. The primary outcome was ESAS total symptom distress score (TSDS) at day 14. Response was defined as a decrease in TSDS by ≥6 at day 14. Secondary outcomes were: ESAS TSDS over time, individual symptom scores, patient determined effective dose, opioid use, Global Impression of Change, depression, anxiety, quality of life and adverse events.

Results. Of the 144 patients randomised, the planned sample size of 58 participants on CBD and 63 on placebo reached the primary analysis point (day 14). The unadjusted change in TSDS from baseline to day 14 was -6.2 (SD 14.5) for placebo and -3.0 for CBD with no significant difference between arms (p=0.24). Similarly, there was no detected difference in proportion of “responders” (placebo: 37/63 (58.7%), CBD: 26/58 (44.8%), p=0.13). All components of ESAS improved (fell) over time with no difference between arms. The median dose of participant selected CBD was 400mg/day with no correlation with opioid dose. There was no detectable effect of CBD on quality of life, depression, or anxiety. Adverse events did not differ significantly between arms apart from dyspnoea that was more common with CBD. Most participants (53% CBD and 65% placebo) reported feeling “better” or “much better” at days 14 and 70% and 64% at day 28.

Conclusion. CBD oil did not add to the reduction in symptom distress provided by specialist palliative care alone.

Context

Key objective

The use of cannabis for therapeutic benefit has risen exponentially over the last few years with strong public belief in its benefit. This is despite very limited evidence of benefit and no clear guidance around which cannabinoid or combination to use for which indication and at what dose. This trial aimed to determine whether cannabidiol (CBD), a key component of cannabis, resulted in better symptom control in patients with advanced cancer than standard palliative care.

Knowledge generated

CBD was no better than placebo in reducing symptom burden in cancer patients receiving standard palliative care. Although well tolerated, it did not improve individual symptoms, depression/anxiety, QoL or reduce opioid requirements.

Relevance

These findings are highly relevant for both for policy makers and for consumers paying for unsubsidised cannabis products.

INTRODUCTION

Following widely reported claims of benefit, anecdotally and in social media, with robust social pressure, cannabinoid products have been legalised for medical use in several countries. In Australia, the approved indications include chronic pain, refractory child-hood epilepsy, chemotherapy-induced nausea and vomiting, multiple sclerosis related muscle spasm and palliative care. This has been despite a lack of strong objective evidence of benefit for most indications, particularly in palliative care.

Cannabis contains almost 500 bioactive compounds, including over 100 different phytocannabinoids.[1] In contrast to delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD) is not intoxicating. It is said to have a range of anxiolytic, antipsychotic, anti-inflammatory, anti-oxidative, anti-convulsant and neuroprotective effects.[2] CBD has

been used in clinical trials for a range of conditions, predominantly in child-hood epilepsy, usually in the dose range of 40 to 1280mg/day orally.[3] Most studies to date in palliative and supportive care have utilised combination CBD/THC products. There are no restrictions to driving a motor vehicle while taking CBD and it is generally well tolerated.[4] Therefore, many people will request a CBD-dominant product when sourcing medicinal cannabis. The evidence of benefit of CBD when used alone is sparse.[5]

Despite recent advances in medical care, patients with advanced cancer still experience substantial symptom distress.[6] While medication provides a core component of improving symptom burden, there remains a need for more effective options to improve symptom control especially in areas such as fatigue, anorexia and anxiety. Medicinal cannabis (MC) has been presented as an alternate “natural” option for managing these symptoms.

The aim of this study was to assess whether CBD oil, when used in conjunction with standard palliative care, reduced symptom burden in patients with advanced cancer.

METHODS

This phase 2b, randomised, dose-escalated placebo-controlled study of CBD was undertaken in five tertiary medical centres within south-east Queensland, Australia (Australian New Zealand Clinical Trials Registry ACTRN 126180001220257). The full protocol has been published previously.[7] Research ethics approval was obtained from all participating sites. The study was overseen by an independent data safety monitoring committee (DSMC) and monitored by independent parties.

Participants.

Those >18years, with advanced cancer who had a total symptom distress score (TSDS) as measured by an Edmonton Symptom Assessment Scale (ESAS)[8] of ≥10/90 (with at least one score ≥3), who had a negative baseline THC urine test, a performance status ≥30 (AKPS),[9] adequate cognitive function (as assessed by the St Louis University Mental Status Examination (SLUMS))[10] and able to take oral medications were deemed eligible.

Patients were excluded if they had severe hepatic or renal dysfunction, a history of significant psychiatric or substance use disorder (as assessed by the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)),[11] the potential for drug diversion or a new anticancer therapy or radiotherapy within 7 days. Regular review by the local palliative care team was a pre-requisite for entry.

Study procedure.

Standard palliative care (as defined by National Consensus)[12] was provided to all participants. The CBD oil was supplied by GD Pharma Ltd as a synthetic product with proven purity as shown by an independent Therapeutic Goods of Australia (TGA) audit.[13] Consenting patients were randomised to CBD oil 100mg/mL or matched placebo oil in identical 25mL bottles. Dose titration every third day over 14 days was from 50mg to a maximum of 600mg/day in divided oral doses as tolerated by the participant. Participants were then given the option of remaining on the selected dose for a further 2 weeks (28-day total). Telephone assessments of efficacy and adverse effects and to guide dose titration were undertaken every 3-4 days in the first two weeks with face-to-face medical assessments at baseline, and days 14 and 28. As a consequence of SARS-CoV-2 restrictions, day 7, 21 and 56 assessments could be undertaken by phone.

Study tools.

ESAS is a validated instrument assessing both physical and emotional symptoms (pain, tiredness, nausea, somnolence, shortness of breath, appetite, anxiety and depression) plus overall well-being on a scale of 0 (no problem) to 10 (worst possible problem over the previous 24 hours). The sum of scores provides a total symptom distress score (TSDS).[14] Oral morphine equivalents (OME) were calculated according to GP Pain Help.[15] Global impression of change was assessed by both clinicians and participants using a clinical global impression scale (CGI).[16] Adverse events were assessed according to National Cancer Institute Common Toxicity Criteria (v4.0).[17] Adverse events of special interest were those reported in the literature to be associated with CBD. Quality of life (QoL) scores were calculated according to the European Organisation for Research and Treatment of Cancer (EORTC) QLQ – C15 questionnaire.[18]

Main outcome measures.

The primary outcome measure was ESAS total symptom distress score (TSDS) at day 14 as compared to baseline. Secondary outcome measures included: patient determined effective dose, ESAS TSDS at days 7, 21 and 28, physical and emotional ESAS sub-scores at each time point, individual symptom scores, oral morphine equivalent (OME) use at baseline and weekly, GIC, depression and anxiety (Depression Anxiety Stress Scale (DASS)) scores,[19] QoL and adverse events.

Randomisation.

Schedules for treatment allocation were developed for each site using permuted blocks with randomly allocated block sizes, computer generated at an independent

centre. Randomisation schedules were held by the central registry. Trial pharmacists dispensed active or inactive medication for the participant according to the schedule. The participant ID, allocation number, date of request, preparation and dispensing were recorded in a log maintained by the site pharmacist for each randomisation. All participants, caregivers, investigators and clinical staff remained blind to study assignment until trial completion and data analysis. All study drugs and placebo oil solutions were identical in appearance and matched for taste, colour and bottle size.

Sample size and analysis.

The primary outcome was the change in TSDS from baseline at day 14. A sample size of 60 participants per arm was calculated to detect an improvement in TSDS of ≥6, SD 11.7, with 20% power and Type I error of 5%. Allowing for 20% attrition, we aimed to enrol 72 participants per arm. Mean change in TSDS was based on previously described minimal clinically important difference of 5.7, SD 11.7.[14] Response was defined as a ≥6 point decrease in TSDS.

Continuous variables were assessed for normality. Normally distributed variables are described as mean, standard deviation (SD) or, for hypothesis tests, mean (95% confidence intervals (CI; and non-normally distributed variables as median, range, unless otherwise specified. Categorical variables are described as n/N (%).This was a per protocol analysis. Difference from baseline outcomes were calculated as value at day 14 (or day 28) minus baseline value, adjusted for baseline value[20] and, where appropriate, centre, using ordinary least squares regression.

Generalised estimating equations were used to compare the trajectory of response over time continuous outcomes (see Supp methods for detail). Non-normally

distributed variables were compared using Wilcoxon's Rank sum test, and categorical variables compared using Pearson's chi-square or Fisher's exact tests.

Any effect of dropouts was evaluated using Cox Proportional Hazards (CPH) regression.

Significance was set at alpha = 0.05 and all tests two-sided. P-values were not adjusted for multiple comparisons.[21] Analyses were conducted using Stata [22] and R software version 4.2.0.[23]

RESULTS.

To reach the predetermined sample size of 120 fully-informed consenting participants, 144 were randomised over a 33 month period (February 2019 - November 2021) (Figure 1). Two participants were subsequently deemed not to have met the eligibility criteria and were removed from the per protocol analysis. Fifty-eight participants on CBD and 63 on placebo reached the primary analysis point (day 14). Dropouts in each treatment arm were comparable at each timepoint of the study. CPH regression indicated that neither treatment arm nor TSDS at baseline were associated with dropout, hazard ratio (95% CI): 0.98 (0.70 – 1.38), p = 0.92, and 1.0 (0.99 – 1.01), p = 0.95, respectively.

Participant baseline demographics are shown on Table 1. Those randomised to placebo had a higher baseline TSDS than those on CBD oil (p=0.01).

Primary analysis

Total Symptom Burden

The unadjusted mean change in TSDS from baseline to day 14 was -6.2 (SD 14.5) for placebo and -3.0 (SD 15.2) for CBD with no significant difference between arms

(mean (95% CI) difference in change -3.2 (-8.5 to 2.1), p=0.24). Adjusted for baseline, the mean (95% CI) difference in change from baseline at day 14 was -0.07 (-5.0 to 4.8), p = 0.98. An ITT analysis with data imputation did not affect the result, nor did sensitivity analyses restricted to participants with complete data at each timepoint. Similarly, there was no statistical difference in proportion of "responders" (decrease in TSDS by >6 from baseline to day 14) (placebo: 37/63 (58.7%), CBD: 26/58 (44.8%), p=0.13) (Figure 2).

Secondary analyses.

Change in ESAS components over time

All components of ESAS improved (fell) over time for both groups (Figure 3). There was no detected difference between arms in TSDS change from baseline in physical, emotional) or well-being subsets at days 14 or 28, nor in any of the individual ESAS components including pain, anxiety, depression, nausea and appetite scores (Supp Table 1 or tumour type.

Participant selected dose

The median (range) final volume of trial medication taken at day 14 at the end of the dose escalation phase was 6 (0.5 to 6) mL for placebo and 4 (0.5 to 6) mL for CBD (p=0.05). This equates to a median dose of CBD of 400mg/day (range (50 - 600 mg).

Oral Morphine Equivalent

There was no detected difference between arms in change of OME from baseline (Table 2). At day 14, 8/63 (12.7%) participants in the placebo arm and 10/57 (17.5%)

in the CBD arm were able to reduce their total daily opioid dose. There was no difference in proportion between these and the remaining participants, who had either no change (27/62 (43.5%) placebo, 30/55(54.6%) CBD), or an increase in total opioid dose (27/62, 43.5% placebo, 14/55, 25.4% CBD), p = 0.11.

At day 28, only 6/44 participants (13.6%) on placebo and 3/42 (7.1%) CBD had an OME dose reduction from baseline, 21/42, 50% (placebo) and 20/42, 47.6% (CBD) had no change and 16/42(38.1%) vs 18/42 (42.9%) an increase in total opioid dose (p = 0.91). There was no difference in change in OME between treatment groups at day 14 or at day 28. Apart from 4 participants (3 CBD, 1 placebo), the dose reductions at study end were related to a decrease in "as required" breakthrough doses rather than a decrease in background opioid doses.

Concomitant medications

There was no correlation between participant selected dose of CBD/Placebo and opioid dose, nor any association with use of benzodiazepines or antipsychotics(Supp Tables 2 and 3).

Global Impression of Changes

Most participants in both arms (53% on CBD and 65% on placebo) reported feeling "better" or "much better" at days 14 and 28 (70% and 64%) (Supp Figure 1) often despite no objective improvement in ESAS score. There was no difference between arms. These results were very similar to those reported by clinicians.

Depression, anxiety and stress scores

Mean total DASS scores fell slightly over time from baseline to days 14 and 28 in both arms. There was no difference in the change in DASS score from baseline for

DASS depression, anxiety or stress at either day 14 or day 28 between placebo and CBD (Supp Table 4).

QoL

There was no detectable effect of CBD on change in physical or emotional functioning, overall quality of life, fatigue, nausea and vomiting, pain, dyspnoea or appetite loss from baseline to day 28 (Supp Table 5) with minor improvement over time in both groups.

Adverse Events

There was a high prevalence of “adverse effects” of special interest at baseline and no statistical difference between arms at days 14 and 28 (Table 3), with a trend towards increased somnolence and abdominal pain in the CBD arm and increased vomiting and in the placebo arm.

Multiple adverse events other than those of special interest were recorded. None had a grade >3. The ten most frequent categories were pain, dyspnoea, constipation, fatigue, anxiety, insomnia, peripheral neuropathy, diarrhoea, anorexia and oedema. There was no difference detected between treatment groups except for dyspnoea, where 8 participants in the CBD group and 2 participants in the placebo group experienced new or worse dyspnoea during the study, $p = 0.04$ (Supp Table 6).

Eight serious adverse events resulting in hospitalisations (5 CBD, 3 placebo) were reported and reviewed by the DSMC. None were considered related to the study drug. There was no difference in survival between arms (median, 95% survival 278 (range 160-426) days CBD and 190 (137-317) days placebo, $p = 0.22$).

DISCUSSION.

Despite widespread public belief in the benefits of cannabis, this study failed to demonstrate an improvement in symptom control from CBD oil in patients with advanced cancer over that obtained from palliative care alone. Hui et al have shown a 6-point improvement in total ESAS score to be clinically significant with respect to symptom control in patients with advanced cancer receiving palliative care.[14] We demonstrated a median improvement in symptom burden of this magnitude following the continued provision of standard palliative care with no difference between those participants on CBD and those on placebo. Total symptom burden rather than individual symptoms was chosen as the primary outcome measure as this was thought more likely to reflect overall QoL in these patients. Moreover, previous research has failed to demonstrate a meaningful beneficial effect on individual symptoms, for example in pain and appetite. [24,25]

The secondary analyses supported our primary findings. CBD did not contribute to improvements in anxiety and depression or quality of life. The initial fall in opioid dose seen at day 14 in both arms was not maintained to day 28. This is consistent with a recent systematic review that demonstrates opioid sparing effects of cannabinoids in preclinical and observational studies but not in RCTs.[26] The oil was well tolerated, with no adverse effects over and above those seen with placebo oil apart from dyspnoea that for some reason was more common in the CBD arm. There was no suggestion of deleterious drug interactions in participants. The lower median dose (in mLs) of CBD oil selected by participants was possibly explained by the trend towards increased somnolence in the CBD arm.

In contrast to many other uncontrolled trials of medicinal cannabis, this study adhered to Cochrane guidance with minimal risk of bias and was correctly powered to determine whether CBD is more effective than placebo in reducing symptom distress.[27] The participant selected median dose is well within the range reported in other studies to be "beneficial".[3] The blinded prospective adverse event reporting gave an accurate indication of tolerability. The trial utilised a quality product of proven purity as assessed by an independent TGA audit. The blinded comparison against placebo allows for the progressive course of malignant disease over time, the large number of concomitant medications (including ongoing cancer treatments) and participant preconceptions of benefit.

The major criticism of this study is likely to be the use of pure CBD. Many believe that THC contributes more to symptom control and that combination CBD/THC products are more beneficial. Others have postulated that one of the main benefits of CBD is to reduce the toxicity of THC although this has never been definitively proven. The "entourage effect" further suggests that multiple different cannabinoids and even terpenes act synergistically to produce the beneficial effects seen from plant products.[28]

The lower bioavailability of oral cannabinoid preparations as compared to inhaled has been highlighted.[29] However, the fact that the median dose of CBD selected by participants in this dose escalated study was lower than that of placebo, suggests that they were receiving a clinically relevant dose.

Most participants in this study were of relatively good performance status. There was heterogeneity in tumour type and symptom profile between participants. A 14-day end-point was chosen as attrition rates in studies of patients with advanced cancer

tend to be high after this time. This was confirmed by the attrition rates seen in this study of 15% prior to day 14 and almost 40% prior to day 28. Most participants (75%) were recruited from one of the five centres. This study was not powered to specifically assess the effect of CBD on individual symptoms, for example pain and nausea but none of the secondary analyses suggested any signal of benefit for any individual symptom. Similarly, ESAS covers a limited number of symptoms, others, for example sleep quality, or bowel problems were not specifically addressed. Although the mean TSDS was over 30 (with a total possible score of 90), the range was wide. Those with lower scores would be less likely to have a significant reduction in symptom scores over time, but this applies to both arms of the study.

Are the correct outcome measures being used when assessing the effect of medicinal cannabis? Just over one-third (36%) of participants elected to purchase a medicinal cannabis product post trial despite a lack of objective evidence of benefit even when they believed they had been on the active arm. Many participants reported a non-specific improvement in overall well-being that has led us to consider some form of “happiness” scale in future studies. Similarly, does CBD have a benefit in symptoms not specifically address in this study, for example sleep quality? There was a non-significant trend towards increased somnolence in participant on CBD and anecdotally, the dose selected by participants on the active arm was often because of reports of increased drowsiness. Ongoing studies by this group are assessing these factors and the contribution that THC might have in symptom management.

This study has significant implications for policy makers regarding both approved indications for medicinal cannabis and its safe use. Medical cannabis has been approved in several countries for “palliative care” in the belief that it might improve

the QoL of patients with advanced disease. CBD is a popular cannabis product in the community as it has no psychoactive effects and does not impair driving ability. With current evidence, it is difficult to justify government subsidisation of the cost of CBD, nor recommend that patients pay for CBD products.

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Figure legends

Figure 1. Participant flow. * symptoms not related to advanced cancer ** patient randomised to placebo, not eligible because of deteriorating liver function.

Figure 2. Proportion of responders (fall in TSDS ≥ 6 between baseline and day 14) in each arm (placebo: 37/63 (58.7%), CBD: 26/58 (44.8%), p=0.13).

Figure 3. Total symptom distress score over time. Placebo (Pl) and CBD indicate the number of participants at each time point. Change per day 0.1 (95%CI -0.06 to 0.26), p = 0.21. Note missing data at days 7 (2), 21 (2) and 28 (1).

Supplementary Figure 1. Patient Global Impression of Change over time.

Table 1. Baseline demographics

	CBD N=70	Placebo N=72	All participants N=142
Age, years, Mean (SD)	63.6 (14.0)	65.5 (11.4)	64.6 (12.8)
Sex (Male, %)	39 (55.7)	36 (50.0)	75 (52.8)
Primary cancer			
Prostate	17 1(24.3)	13 (18.1)	30 (21.1)
Breast	11 (15.70	11 (15.3)	22 (15.5)
Colorectal	10 (14.3)	11 (15.3)	21 (14.8)
Gynaecological	9 (12.90	9 (12.5)	18 (12.7)
Lung	4 (5.7)	9 (12.5)	13 (9.2)
Haematological	4 (5.7)	3 (4.2)	7 (4.9)
Other	15 (21.4)	16 (22.2)	31 (21.8)
ESAS (TSDS), Mean (SD)	30.7 (13.5)	36.4 (13.4)	33.6 (13.7)
AKPS, Median (range)	70 (30 to 90)	70 (30 to 90)	70 (30 to 90)
RUG-ADL total score, Median (range)	4 (4 to 14)	4 (4 to 11)	4 (4 to 14)
SLUMS, Mean (SD)	26.8 (2.3)	27 (2.4)	26.9 (2.4)
Background opioid dose, mg, (OME), Median (range)	45 (0 to 590)	40 (0 to 555)	50 (0 to 590)
Concomitant medications, N (%)			
Antipsychotics	13 (18.6)	16 (22.2)	29 (20.4)
Benzodiazepines	21 (30.0)	28 (38.9)	49 (34.5)
EORTC QoL, Mean (SD)			
Physical functioning	59.5 (21.9)	56.3 (23.5)	57.88 (22.7)
Emotional functioning	78.2 (19.2)	72.7 (25.2)*	75.41 (22.7)
Overall quality of life	54.0 (20.9)	51.2 (22.8)**	52.61 (21.8)
DASS Severity Rating(%)			
Depression			
Normal/mild	51 (72.9)	49 (68.1)	100 (70.4)
Moderate	16 (22.9)	9 (12.5)	29 (20.4)
Severe/extremely severe	3 (4.3)	10 (13)	13 (9)
Anxiety			
Normal/mild	39 (55.8)	34 (47.2)	73 (51.4)
Moderate	18 (25.7)	24 (33.3)	42 (29.6)

Severe/extremely severe	13 (13.5)	14 (19.4)	27 (19.0)
Stress			
Normal/mild	58 (81.4)	58 (80.5)	115 (81.0)
Moderate	8 (11.4)	7 (9.7)	15 (10.6)
Severe/extremely severe	5 (6.4)	7 (9.8)	12 (8.4)

*N=71 ** N = 70

AKPS: Australian modified Karnofsky Performance Scale, RUG-ADL: activities of daily living, OME: oral morphine equivalents, ESAS (TSDS): Edmonton Symptom Assessment Scale (Total Symptom Distress Score), SLUMS:St Louis University Mental Status; EORTC QoL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30)

Table 2. Change in OME from baseline

	Medicinal cannabis(CBD) Change in OME from baseline (mg/24 hr) median(range)	Placebo Change in OME from baseline (mg/24 hr) median (range)	p-value†
day 14	0 (-205 to 140), n=57	0 (-200 to 160), n=63	0.10
day 28	0 (-28 to 140), n=42	0 (-160 to 120), n=44	0.39

†Wilcoxon rank-sum test

Table 3. Adverse events of special interest

AE of interest	CBD Number at baseline, n=70 (%)	CBD Number new or worse days 1-28, n=66 (%)	Placebo Number at baseline, n=72 (%)	Placebo Number new or worse days 1-28, n=68 (%)	p-value
Dry mouth	49(70)	16(24)	48(67)	19(28)	0.63
Somnolence	43(61)	30(45)	53(74) *	21(31)	0.08
Dizziness	21(30)	16(24)	25(35)	14(21)	0.61
Nausea	28(40)	15(23)	26(36)	16(24)	0.91
Vomiting	8(11)	5(8)	3(4)	13(19)	0.07†
Abdominal pain	18(26)	21(32) *	28(39)	13(19)	0.09

†Fisher's Exact Test

*1 episode grade 3, all others grade 1-2

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