Adjunctive Nabilone in Cancer Pain and Symptom Management: A Prospective Observational Study Using Propensity Scoring

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Abstract A prospective observational study assessed the effectiveness of adjuvant nabilone (Cesamet) therapy in managing pain and symptoms experienced by advanced cancer patients. The primary outcomes were the differences between treated and untreated patients at 30 days' follow-up, in Edmonton Symptom Assessment System (ESAS) pain scores, and in total morphine-sulfate-equivalent (MSE) use after adjusting for baseline discrepancies using the propensity-score method. Secondary outcomes included other ESAS parameters and frequency of other drug use. Data from 112 patients (47 treated, 65 untreated) met criteria for analyses. The propensity-adjusted pain scores and total MSE use in nabilone-treated patients were significantly lower than were those found in untreated patients (both $P < 0.0001$). Other ESAS parameters that improved significantly in patients receiving nabilone were nausea ($P < 0.0001$), anxiety ($P = 0.0284$) and overall distress (total ESAS score; $P = 0.0208$). The nabilone group showed borderline improvement in appetite ($P = 0.0516$). When compared with those not taking nabilone, patients using this cannabinoid had a lower rate of starting nonsteroidal anti-inflammatory agents, tricyclic antidepressants, gabapentin, dexamethasone, metoclopramide, and ondansetron and a greater tendency to discontinue these drugs.

Patients with advanced cancer generally suffer from many disease-related symptoms and treatment-associated side effects. Despite the plethora of therapeutic agents available to treat these ills, patients with advanced cancer continue to suffer from a significant burden of pain and other symptoms.[1–3] This burden impacts negatively on their quality of life (QOL), their functional status, and, potentially, their life expectancy.[3] The use of one agent to optimize the management of several symptoms/side effects may improve the overall supportive care of cancer patients.[4] In addition, overall drug use and polypharmacy may be lowered, thereby reducing the likelihood of drug interactions and associated side effects and having favorable pharmacoeconomic outcomes.

Recognizing the potential benefits of tetrahydrocannabinol (Δ^9-THC) use, scientists began developing derivatives and analogues of this compound in the mid-20th century.[5,6] During the late 1980s and early 1990s, identification and cloning of the cannabinoid receptors CB1 and CB2 in humans led to a better understanding of the mechanism of action of cannabinoids and supported their potential use in multiple clinical settings and various patient populations.[6–9]

Nabilone (Cesamet), a synthetic analogue of Δ^9-THC, has been used in Western Europe and Canada for over 20 years; it recently received US Food and Drug Administration approval for treating refractory chemotherapy-induced nausea and vomiting. A significant body of research evidence is showing that cannabinoids possess a broad-spectrum of activity and may be effective in managing other symptoms (eg, pain, anorexia, anxiety, depression).[9,10] In addition, preclinical data also suggest that this drug class may possess antineoplastic potential.[11–14]

Assessing the potential utility of a pharmaceutical agent such as nabilone in advanced cancer patients during randomized, controlled trials presents ethical, methodological, and practical issues.[15–18] Therefore, this type of research cannot be initiated without substantial evidence of benefit. Based upon observations of the drug's benefits from clinical experience, the authors conducted

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Table 1

Baseline Characteristics in Nabilone-Treated and Untreated Patients

	NABILONE-TREATED (n=47) VALUE (SD)	UNTREATED (n=65) VALUE (SD)	*P* VALUE*
Age, mean years	67.0 (12.8)	71.6 (12.2)	0.054
PPSv2, mean score	56.0 (14.1)	56.2 (13.0)	0.931
Comorbidities, mean n	7.6 (3.3)	8.7 (3.3)	0.083
Gender, n (%)			
Male	29 (61.7)	36 (55.4)	0.563
Female	18 (38.3)	29 (44.6)	
Race, n (%)			
Caucasian	45 (5.7)	59 (90.8)	0.464
Noncaucasian	2 (4.3)	6 (9.2)	
First contact, n (%)			
Home	34 (72.3)	61 (93.8)	0.003
Hospital	13 (27.7)	4 (6.2)	

*Independent samples *t*-test for age, PPSv2, and comorbidities; Fisher's exact test for gender, race, and first contact

Abbreviations: SD = standard deviation; PPSv2 = Palliative Performance Scale, version 2

an observational study on a case series of palliative medicine consultations to assess the efficacy of adjunctive cannabinoid therapy for managing multiple symptoms and side effects in advanced cancer patients.

Methods

STUDY POPULATION

The consultative palliative medicine program of the William Osler Health Centre serves the northwest quadrant of Toronto, Canada, a catchment area having a population of over 750,000. Data were collected prospectively on patients who were referred to the program between January 2005 and October 2006. Inclusion criteria for the cannabinoid study were that patients receive a cancer diagnosis, survive for at least 48 hours after the initial consultation (baseline), and complete the Edmonton Symptom Assessment System (ESAS) questionnaire at baseline and at least once within 60 days of baseline. The patients were classified according to whether or not they were treated with nabilone; treatment had to start on the day of referral and continue for at least 48 hours.

All patients were managed by a specialist team that included a palliative medicine physician and nurse practitioner. None of the patients referred was being considered for further disease-modulating therapies (eg, chemotherapy). The decision to prescribe nabilone was based on the presence of severe symptom-related distress on the initial consultation. Patients also provided a history of refractory symptoms despite their use of other agents to manage pain and symptoms. All patients or their primary caregivers provided consent for use of nabilone for off-label purposes and medical records for data analyses. All data were prospectively acquired and recorded in a customized Microsoft (MS) Access database on an accrual basis.

The study protocol was approved by the center's Research Ethics Board.

MEASUREMENTS

Following normal practice, study baseline measurements were obtained during the assessment performed on the day of referral, and patients then were assessed at intervals determined by patient need. One-month study outcomes were obtained from a routine assessment performed closest to 30 days post baseline, since this interval allowed adequate titration of the study drug.

The ESAS, a 10-item, patient- or caregiver-rated, validated tool, was developed to assess the most prevalent symptoms in palliative care patients.[19] The severity of the 10 items—pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and other problems—was rated on a 10-point scale, with 0 indicating absence of the symptom and 10 reflecting the worst possible severity. The sum of the 10 items was the "distress score," which ranged from 0 (no distress) to 100 (worst possible distress). The Palliative Performance Scale, version 2 (PPSv2), which essentially was an enhanced Karnofsky performance scale, measured a patient's overall performance status in increments of 10%; it involved the composite evaluation of ambulation, activity level, self-care capacity, evidence of disease, intake, and level of consciousness.[20] This performance-assessment tool also has reflected prognosis and survival.[20,21]

For the 2 days representing the baseline and follow-up time points, all opioid dosages were converted to morphine sulfate equivalents (MSEs) according to generally accepted conversion ratios,[22] and these calculations were summed. Similarly, use versus non-use of nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (TCAs), gabapentin, dexamethasone, metoclopramide, and ondansetron was documented for these two time points.

STATISTICAL ANALYSIS

Data was imported from an MS Access database into S-PLUS 6.2 for Windows for statistical analysis. Histograms were made of continuous variables to check for skewness and outliers. Only total MSE was extremely skewed and necessitated the use of a logarithmic transformation.

Before analyzing data, the team decided to assess the treatment effect at 30 days of follow-up. To this end, the ESAS assessment performed closest to 30 days post baseline was selected for each patient; medication use also was assessed on this date. Median survival from referral was calculated using the product-limit method and was compared between the two groups using a log-rank test.

The main hypothesis was that treated patients would have lower ESAS pain scores and lower total MSE drug use at follow-up when compared with untreated patients after adjusting for baseline differences. As secondary outcomes, the other ESAS symptom scores and other indicators of using other drugs (eg, NSAIDs, TCAs, gabapentin, dexamethasone,

metoclopramide, ondansetron) were examined.

It was known a priori that patients with the greatest amount of pain, distress, and polysymptom burden who still had reasonable functional levels at baseline were preferentially selected for cannabinoid treatment. Treated and untreated patients' baseline characteristics were compared to explore and confirm these differences by calculating means and standard deviations (SD) and performing Fisher's exact test for categorical variables and *t*-tests for numerical variables.

Methods of adjustment. Two methods of adjustment were used to adjust for baseline differences in the groups.

In the first, the analysis of covariance (ANCOVA) method, each outcome was corrected for differences in its baseline levels (for example, the outcome ESAS pain at follow-up was corrected for differences in the baseline ESAS pain scores between the two groups and similarly for the other variables).

In the second, the propensity score,[23] defined as the conditional probability of being treated given the individual's covariates, was obtained for each patient from a multivariate logistic model for treatment group; predictors such as gender, site of first contact and age, PPSv2, number of comorbidities, ESAS pain score, total ESAS score excluding pain, and log of total MSE were measured at baseline. The propensity score then was added to the ANCOVA model as an additional adjuster. The effectiveness of the propensity score was checked by recomparing important baseline characteristics in treated and untreated patients with propensity adjustments and calculation of the *c*-statistic (area under the receiver operating characteristic curve). For well-behaved models, this statistic takes on values of 0.5–1, with higher values indicating better performance.

For pain, log of total MSE and the ESAS symptom subscores and total were used via multiple linear regression and the *P* value for treatment status, which was obtained from the corresponding *t*-statistic in the regression model. For the secondary drug-use variables, specified in binary "yes/no" form, logistic regression had to be used instead of linear regression; these deviance tests were applied to obtain the *P* value for treatment status.

To demonstrate the size of the effects seen in the study, adjusted mean values for the treated and untreated groups were obtained from each model, with the adjusting variables set to their mean values. The unadjusted means are also shown. *P* values were considered significant when smaller than 0.05.

Results

In all, 468 cancer patients were referred for palliative medical management during the study period. Of these patients, 446 lived at least 2 days; 132 (29.6%) completed the ESAS at baseline and at least once within 60 days thereafter. The low completion rate of ESAS questionnaires illustrated the significantly reduced performance status of the study population at baseline.

Of these 132 patients, 47 received nabilone at referral; 20 of 85 untreated individuals received nabilone at a later date and were excluded for this reason. Thus, the final study group consisted of 112 patients, 65 (58%) untreated and 47 (42%) treated. Of the treated patients, 24 (51%) were prescribed nabilone for pain relief, 12 (26%) were prescribed the drug to relieve nausea, and 11 (23%) were prescribed the medication for anorexia.

Table 2

Baseline Symptoms and Medication Use

	ESAS SYMPTOM SCORE		
	NABILONE-TREATED (n = 47) MEAN (SD)	UNTREATED (n = 65) MEAN (SD)	*P* VALUE
Symptom*			
Pain	7.1 (2.4)	5.6 (2.7)	0.0029
Tiredness	5.7 (1.8)	4.8 (1.9)	0.0109
Nausea	4.7 (2.7)	3.4 (2.0)	0.0024
Depression	5.1 (2.5)	3.5 (1.9)	0.0003
Anxiety	5.2 (2.5)	4.0 (1.9)	0.0038
Drowsiness	4.4 (2.1)	3.4 (1.7)	0.0041
Appetite loss	6.0 (2.4)	4.8 (2.2)	0.0113
Lack of well-being	5.7 (2.3)	4.3 (1.9)	0.0010
Shortness of breath	2.8 (2.4)	3.2 (2.2)	0.2765
Total score	46.7 (15.6)	37.1 (11.2)	0.0002
Medication use†			
Total MSE	60.3 (64.6)	67.3 (101.0)	0.8259
NSAIDs	19 (40.4)	20 (30.8)	0.3198
TCAs	10 (21.3)	15 (23.1)	1.0000
Gabapentin	9 (19.1)	7 (10.8)	0.2757
Dexamethasone	19 (40.4)	16 (24.6)	0.0987
Metoclopramide	27 (57.4)	40 (61.5)	0.6993
Ondansetron	4 (8.5)	5 (7.7)	1.0000

**P* value: independent samples *t*-test

†P value: independent samples *t*-test applied to log-transformed total MSE; Fisher's exact test for the rest

Abbreviations: ESAS = Edmonton Symptom Assessment System; MSE = morphine sulfate equivalent; NSAIDs = nonsteroidal anti-inflammatory drugs; TCAs = tricyclic antidepressants

Each patient was assessed as closely as possible to 30 days post baseline. The mean duration from baseline to this assessment was 23.8 days (range, 5–48 days) in the treated group and 23.2 days (range, 3–54 days) in the untreated group.

Characteristics of the treated and untreated groups are shown in Table 1. Treated patients were started on 0.5 or 1 mg of nabilone at bedtime for the first week to limit side effects that may occur in patients naive to cannabinoid therapy. The nabilone dosage was titrated by increments of 0.5 or 1 mg thereafter, and the total daily dosage was divided into a twice-daily schedule. At follow-up, 32 of the treated patients (68%) were given a daily 2-mg dose of nabilone, 14 were given a 1- to 2-mg dose, and 1 received a 2.1-mg dose. The mean daily dose of nabilone among the 47 treated patients was 1.79 mg.

Baseline symptoms and drug usage are shown in Table 2. All baseline ESAS scores, except those for shortness of breath, were higher in the nabilone group, reflecting their higher burden of disease.

Propensity adjustment was successful in balancing the groups with respect to variables shown in Tables 1 and 2 with all *P* values > 0.24 after adjustment, except for shortness of

Table 3

Adjusted and Unadjusted Means at Follow-up

	UNADJUSTED			ADJUSTED FOR BASELINE SYMPTOM LEVEL			ADJUSTED FOR BASELINE SYMPTOM LEVEL AND PROPENSITY SCORE		
	MEANS AT FOLLOW-UP			MEANS AT FOLLOW-UP			MEANS AT FOLLOW-UP		
	NABILONE-TREATED	UNTREATED	*P* VALUE FOR TREATMENT EFFECT	NABILONE-TREATED	UNTREATED	*P* VALUE FOR TREATMENT EFFECT	NABILONE-TREATED	UNTREATED	*P* VALUE FOR TREATMENT EFFECT
ESAS symptom score									
Pain	3.7	5.0	0.003	3.2	5.3	< 0.001	3.0	5.5	< 0.001
Tiredness	6.3	6.0	0.492	6.0	6.2	0.704	6.1	6.1	0.969
Nausea	2.7	3.3	0.101	2.3	3.6	< 0.001	2.0	3.8	< 0.001
Depression	4.1	3.6	0.183	3.7	3.9	0.542	3.7	4.0	0.411
Anxiety	4.0	4.2	0.590	3.7	4.4	0.076	3.6	4.5	0.028
Drowsiness	5.3	5.0	0.414	5.2	5.1	0.879	5.2	5.1	0.855
Appetite loss	5.4	6.0	0.144	5.2	6.1	0.023	5.2	6.1	0.052
Lack of well-being	6.1	5.4	0.072	5.9	5.6	0.425	6.0	5.5	0.242
Shortness of breath	3.2	3.5	0.513	3.4	3.3	0.884	3.6	3.2	0.248
Total distress	40.7	42.0	0.592	38.2	43.8	0.011	38.1	43.8	0.021
Medication use: total MSEs									
Log (total MSE)*	3.8	4.3	0.016	3.8	4.3	< 0.001	3.7	4.3	< 0.001

* In the original units, for the propensity adjusted model, this corresponds to untreated patients using 1.8 times as many MSEs as did treated patients.

Abbreviations: ESAS = Edmonton Symptom Assessment System; MSE = morphine sulfate equivalent

breath, which had a *P* value of 0.02. The *c*-statistic for the propensity model was 0.81, indicating that it discriminated fairly well between treated and untreated patients. The most important predictors of receiving nabilone therapy were baseline pain and total ESAS score, excluding pain. The higher these scores, the more likely patients were to receive nabilone.

Estimates of the effect of treatment on the follow-up ESAS symptom scores and medication use are shown in Tables 3 and 4. The two primary outcomes, pain and opioid use in the form of total MSEs, were reduced significantly in treated patients relative to untreated patients according to all three methods shown in Table 3: unadjusted ($P = 0.003$ and $P = 0.016$), adjusted by the ANCOVA method (both $P < 0.0001$), and adjusted by the propensity method (both $P < 0.0001$). Of the other ESAS symptom parameters, nausea ($P < 0.0001$), anxiety ($P = 0.0284$), and total distress ($P = 0.0208$) also were reduced significantly according to the propensity-adjusted method; appetite improved in the treated group, although this symptomatic result fell just short of achieving statistical significance ($P = 0.0516$).

The secondary medications were recorded as present or absent at baseline and again at follow-up. In this fashion, the initiation and the discontinuation of various drugs were tracked. The unadjusted percentages in Table 4 showed that a smaller percentage of treated patients used NSAIDs, TCAs, or ondansetron than did untreated patients at follow-up. When considering baseline conditions, both the ANCOVA and propensity-adjusted models showed that the nabilone-treated group had a larger percentage of patients who discontinued NSAIDs, TCAs, dexamethasone, and ondansetron during the follow-up period (all $P \leq 0.0011$). The treated group also had a smaller percentage of patients who required initiation of gabapentin, dexamethasone, and metoclopramide (all $P \leq 0.0070$) during follow-up.

Median survival did not differ significantly between the two groups ($P = 0.43$). Median survival in the nabilone-treated group was 57 days (95% confidence interval [CI], 35–78 days) and 41 days in the untreated group (95% CI, 2–61 days).

Side effects from nabilone consisted mainly of dizziness, confusion, drowsiness, and dry mouth. Including patients who did not meet study entry criteria, 125 patients were treated with nabilone at the health center during the study period. Only eight (6.4%) discontinued nabilone within 24 hours due to side effects. All of these side effects abated within 24 hours of discontinuation.

Discussion

Patients with advanced cancer rarely experience symptoms in isolation; instead, they tend to experience them in clusters.[24] Among 1,000 advanced cancer patients, the median number of symptoms experienced was 11; pain occurred in 84%.[25] Assessment of data from patients with early- or late-stage lung cancer identified a symptom cluster consisting of fatigue, nausea, weakness, appetite loss, altered taste, and vomiting.[26]

Chen and Tseng[27] reported that a sickness symptom cluster consisting of pain, fatigue, sleep disturbance, lack of appetite, and drowsiness was more likely to afflict patients with advanced cancer, and especially those with pain, than it was to affect patients with disease at an earlier stage. The sickness symptom cluster correlated negatively with patients' functioning as well. Such symptom clusters challenge clinical decision-making and often lead to the prescription of several medica-

Table 4

Adjusted and Unadjusted Percentage of Patients Using Medication at Follow-up

	UNADJUSTED				ADJUSTED FOR BASELINE USAGE			ADJUSTED FOR BASELINE USAGE AND PROPENSITY SCORE		
	% OF PATIENTS USING DRUG AT FOLLOW-UP				% OF PATIENTS USING DRUG AT FOLLOW-UP			% OF PATIENTS USING DRUG AT FOLLOW-UP		
	NABILONE-TREATED	UNTREATED	*P* VALUE FOR TREATMENT EFFECT	BASELINE USE	NABILONE-TREATED	UNTREATED	*P* VALUE FOR TREATMENT EFFECT	NABILONE-TREATED	UNTREATED	*P* VALUE FOR TREATMENT EFFECT
NSAIDs	0	33.9	< 0.001	No	0	4.4	< 0.001	0	2.2	< 0.001
				Yes	0	100		0	100	
TCAs	2.1	27.7	< 0.001	No	0	6	< 0.001	0	7.1	< 0.001
				Yes	10	100		3.8	100	
Gabapentin	19.2	23.1	0.616	No	0	13.8	0.004	0	17.8	< 0.001
				Yes	100	100		100	100	
Dexamethasone	29.8	41.5	0.200	No	0	22.5	< 0.001	0	20.9	< 0.001
				Yes	73.7	100		76.9	100	
Metoclopramide	53.2	67.7	0.120	No	0	16	< 0.001	0	17.3	0.007
				Yes	92.6	100		92.1	100	
Ondansetron	0	7.7	0.018	No	0	0	< 0.001	0	0	0.001
				Yes	0	100		0	100	

Abbreviations: NSAIDs = nonsteroidal anti-inflammatory drugs; TCAs = tricyclic antidepressants

tions, with each one associated with side effects and potential drug-drug interactions.

Opioids, in particular, are associated with a substantial number of side effects in these patients, yet their use is necessary to relieve pain in the majority of cancer patients with pain.[28] Constipation, nausea, and sedation all are common side effects of opiates that may affect patients' QOL and functioning and that may impact negatively on drug compliance and adherence. Other bothersome side effects of these medications include myoclonus, urinary retention, and pruritus. Preclinical studies are demonstrating that high-dose opioid therapy is associated with inhibitory effects on such humoral and cellular immune responses as antibody production, natural killer cell activity, cytokine expression, and phagocytic activity.[29] These negative effects of opioids have been associated with an increased risk for infection and neoplasia.[30] Therefore, any strategies aimed at minimizing opioid use will be a benefit to patients.

Availability of effective adjunctive pain medications may have important implications for advanced cancer patients. Further, the use of one medication to treat multiple symptoms effectively may reduce the need for polypharmacy, decrease overall drug dosages, lessen suffering, and improve QOL. In the current study, patients receiving the cannabinoid nabilone experienced significant benefit—specifically, reduced pain, nausea, and anxiety and relief of overall distress as reflected by the total ESAS score. Appetite improved in the nabilone group; however, this benefit fell just short of achieving statistical significance. Additionally, patients treated with nabilone required fewer MSEs, demonstrated less tendency to initiate additional new medications, and could reduce or discontinue baseline medications. Nabilone itself was well tolerated and caused few side effects.

Because this cohort was assembled to reflect current practice in the setting of advanced cancer, patients were not randomized into nabilone-treated and -untreated groups; instead, they were given the medication at their physicians' discretion. Patients with the greatest amount of pain, polysymptom burden, and overall distress who maintained reasonable functional levels were selected preferentially for nabilone treatment. Thus, baseline differences between the two groups of patients existed.

To adjust for these differences, the authors used propensity-score analysis, a method commonly used to attain balance in nonrandomized trials,[31–33] as the main analytical method. The propensity score's strength is its efficiency in adjusting for a large number of baseline variables. In our models, the propensity-adjusted results were largely the same as were those obtained with ANCOVA models, which adjusted only for baseline values of the outcomes and showed the latter to most strongly influence outcome. Unfortunately, neither adjustment method can ensure balance on unmeasured variables.

LIMITATIONS

One limitation of the study was that the two groups may have been unbalanced on unmeasured variables. Another limitation was that the investigator was not blinded to patient status when evaluating outcomes at baseline and follow-up. Nonetheless, the results suggested that nabilone provided benefits for patients with advanced cancer who were suffering from multiple symptoms.

Summary

Findings from propensity-score analysis of data obtained prospectively from a case series of advanced cancer patients referred to a consultative palliative medicine service suggested that the

synthetic cannabinoid nabilone offers benefits beyond its official indication to treat treatment- refractory chemotherapy-induced nausea and vomiting. This study demonstrated that patients who used nabilone enjoyed significantly improved management of pain, nausea, total distress, and anxiety when compared with untreated patients. Nabilone use also was associated with lower overall use of drugs such as opioids, NSAIDs, TCAs, gabapentin, dexamethasone, metoclopramide, and ondansetron.

These findings added to emerging data suggesting a role for cannabinoids beyond their officially approved indications. Nabilone appears to be an effective adjuvant therapy for optimizing pain and polysymptom management in advanced cancer patients. The positive effects of nabilone demonstrated in this patient population also suggested benefits for patients with earlier stage disease. Therefore, nabilone use should be evaluated further in randomized clinical trials involving cancer patients.

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