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## Nabilone for the Treatment of Paraneoplastic Night Sweats: A Report of Four Cases

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### ABSTRACT

**Night sweats are one of many symptoms experienced by patients with advanced cancer. The prevalence of night sweats ranges from 10%–48% in cancer patients. Persistent night sweats tend to decrease quality of life through interference with sleep. A recent study has demonstrated that night sweats occur as part of a symptom pattern, and are associated with the anorexia–cachexia symptom cluster. In addition, night sweats represent one of the symptoms that displays a tendency not to improve as patients with advanced cancer approach end of life. This paper serves to report on the successful management of four patients suffering from persistent paraneoplastic night sweats using the synthetic orally administered cannabinoid nabilone. The four patients had been referred to a regional consultative palliative medicine program and identified night sweats as one of their most significant symptomatic concerns reported on their Edmonton Symptom Assessment System (ESAS) questionnaires.**

### INTRODUCTION

**P**ATIENTS WITH ADVANCED STAGES of cancer suffer from a multitude of symptoms. Night sweats occur in 10% to 14% of patients with advanced-stage cancer as a result of disease progression.<sup>1</sup> In patients with Hodgkin's lymphoma, night sweats, which persist with fluctuating fevers for weeks in some patients, may be the only presenting symptom.<sup>2</sup> A retrospective study among 63 patients with metastatic hormone-resistant prostate cancer identified night sweats, along with fever, back pain, and fatigue, as common signs of systemic inflammatory syndrome (SIS).<sup>3</sup> Similarly, in patients with liver metastases, night sweats were reported as a symptom in 48%.<sup>4</sup> The differential diagnosis of night sweats in cancer patients includes infection (pneumonia, tuberculosis, endocarditis, urinary tract infection, etc), drugs (allergic or hypersensitivity

reactions), graft-versus-host-disease (GVHD), hormonal withdrawal, and paraneoplastic syndromes.<sup>1</sup> Night sweats are capable of reducing the quality of life of cancer patients through interference with sleep.<sup>5</sup> Alterations in sleep patterns are associated with daytime fatigue, hypersomnolence, and depression, and decreased functional capacity.<sup>6</sup> In addition, night sweats are associated with the anorexia–cachexia symptom cluster.<sup>7,8</sup>

Tsai et al.<sup>7</sup> reported that night sweats are part of a symptom pattern in patients with advanced cancer that displays a tendency to remain static and eventually deteriorate as patients approach end of life. This suggests that treatments to date have been largely ineffective in the management of night sweats. Numerous therapies have been used to treat night sweats such as selective serotonin reuptake inhibitors,  $\alpha$ -adrenergic agonists,  $\beta$ -blockers, antidopaminergic agents, soy phytoestrogens,

vitamin E, and thalidomide.<sup>9</sup> Yet, the use of these agents is limited by lack of efficacy and/or side effects.<sup>1</sup> In a small proportion of cases, early symptomatic relief may be achieved with the use of nonsteroidal anti-inflammatory drugs (NSAID) and/or corticosteroids.<sup>3</sup> Emerging data suggest the cannabinoids, which are approved in the United States for the treatment of refractory chemotherapy-induced nausea and vomiting and appetite stimulation in patients with acquired immune deficiency syndrome (AIDS), and for the treatment of neuropathic pain in patients with multiple sclerosis in Canada, may be effective in the polysymptom management of advanced cancer patients.<sup>5,10</sup> The following describes a case series of four patients with advanced-stage cancer who were suffering from paraneoplastic night sweats and successfully treated, “off-label,” with the synthetic cannabinoid, nabilone.

## METHODS

All four patients were referred to a specialist outpatient consultative palliative medicine program that serves a population of over 750,000 in the northwest quadrant of Toronto, Canada. None of the patients were being considered for further attempts with disease-modulating therapies as their advanced disease states and co-morbidities precluded such options. In addition, all patients expressed the wish for their care to be focused strictly on comfort and dignity measures, to be achieved exclusively through pain and symptom management. All patients were found to be mentally competent at baseline and provided informed consent for an empiric trial of “off-label” cannabinoid therapy. They completed the Edmonton Symptom Assessment System (ESAS) questionnaire on initial consultation and at 48-hour intervals thereafter. The ESAS, a 10-item, patient- or caregiver-rated, validated tool, was developed to assess symptoms in palliative care patients.<sup>11</sup> The severity of the symptoms is rated on an 11-point scale where 0 indicates absence of the symptom and 10 reflects worst possible severity. The tenth item on the ESAS is “other,” where patients can cite a symptom not on the questionnaire that is particularly bothersome. The four patients in this case series reported night sweats as being their most bothersome “other” symptom. Their overall performance status was assessed using the Palliative Performance Scale, version 2 (PPSv2). This tool measures a patient’s overall performance status through the composite evaluation of ambulation, activity level, self-care capacity, evidence of disease, intake, and level of conscious-

ness.<sup>12</sup> Performance is scored as a percentage in 10%-step increments from 0% to 100%, and a lower score indicates greater impairment in performance and function. Data were analyzed using MS Windows based SAS 9.1 software (SAS Institute, Cary, NC). Comparisons were made using the Student’s *t* test. The study protocol was approved by the hospital’s research ethics board.

## RESULTS

Three of the four patients were men, and all were older than age 66 years (Table 1). Two patients had non-Hodgkin’s lymphoma, one had acute lymphocytic leukemia, and one suffered from gastrointestinal stromal tumor (GIST). Despite advanced-stage disease and several comorbidities, three of the four patients demonstrated relatively good performance and functioning, as reflected by a PPSv2 score of 60% or higher. At baseline, all patients underwent a medical work-up that included blood cultures, hemogram, biochemical profile, urinalysis, urine culture, chest radiograph, and abdominal ultrasound. None of the patients presented with clinical or laboratory evidence to suggest infection or febrile neutropenia. None of their concurrent medications were known to cause night sweats. Therefore, through a process of exclusion it was concluded that their night sweats were a paraneoplastic phenomenon.

All patients reported experiencing night sweats for at least 2 weeks prior to referral. Patient 1 and patient 4 had reported experiencing low-grade elevated oral temperatures between 37°C and 38°C. Both patients experienced a normalization of their oral temperatures with nabilone therapy. Unfortunately, consistent serial temperature measurements were not documented during the follow-up period. Two patients (patients 1 and 3) reported no improvement with the NSAID, ibuprofen (400–800 mg/d), while two patients (patients 2 and 4) reported no improvement with the NSAID naproxen (250–750 mg/d). All NSAID agents were used for at least 7 to 10 days and were discontinued prior to the baseline assessment. Patient 2 was prescribed prednisone 5 mg daily 4 weeks prior to baseline, and patient 3 began taking prednisone 10 mg daily 2 weeks prior to baseline. Both patients 2 and 3 continued with their original dosage of prednisone during the follow-up period. Three of the patients had hepatosplenomegaly, while the fourth had liver metastases. Three of the patients displayed lymphadenopathy in the periphery, abdomen, or mediastinum.

All patients were prescribed nabilone on the date of their initial (baseline) assessment. Two patients (pa-

TABLE 1. CHARACTERISTICS OF PATIENTS WITH PARANEOPLASTIC NIGHT SWEATS

Patient	Gender	Age at referral (yrs)	Primary diagnosis	Medical history	Current co-morbidities	PPSV2 at referral	Concomitant medications	Nabilone dosage
#1	F	93	Metastatic Gastrointestinal Stromal Tumour (GIST)	Vertebral compression, fracture, hypertension, hyperlipidemia, hypothyroidism, CVA, OA, depression, right shoulder rotator cuff tear, vertigo, hysterectomy, cholecystectomy, appendectomy, osteoporosis	Anemia, CHF, diabetes, COPD, liver metastases, RP adenopathy, DVT	65	hydromorphone, lorazepam, oxycodone, heparin	1 mg qhs
#2	M	66	Non-Hodgkin's lymphoma	Appendectomy, tonsillectomy, peptic ulcer disease	Chronic lymphocytic leukemia, thrombocytopenia, mediastinal nodes, peripheral adenopathy, pleural effusion, chronic renal failure, hepatosplenomegaly, RP adenopathy	70	prednisone, hydromorphone, lorazepam, oxycodone	1 mg qhs
#3	M	82	Non-Hodgkin's lymphoma	Hernia surgery, TURP, hypertension, OA, hyperlipidemia, blunt facial trauma, hypothyroidism, varicose veins	Acute leukemia, diabetes, anemia, RP adenopathy, mesenteric adenopathy, pleural effusions, hepatosplenomegaly, mediastinal adenopathy	60	prednisone, hydromorphone, lorazepam, oxycodone	1 mg bid
#4	M	78	Acute lymphocytic leukemia	Left knee injury, CABG, gout, OA	CAD, COPD, diabetes, hepatosplenomegaly	40	lorazepam, morphine sulfate	1 mg bid

Laboratory results						
Patient	Uh (g/L)	WBC ( $\times 10^9/L$ )	Platelets ( $\times 10^9/L$ )	ESR (mm/hr)	CRP (mg/L)	Albumin (g/L)
#1	93	7.7	387	127	52.7	25
#2	109	4.1	9	67	47	23
#3	95	11	22	40	4	37
#4	86	1.6	41	24	38	38

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVA, cardiovascular accident; DVT, deep venous thrombosis; ESR, erythrocyte sedimentation rate; GIST, gastrointestinal tumor; Hb, hemoglobin; OA, osteoarthritis; PPSV2, Palliative Performance Scale, version 2; RP, retroperitoneal; TURP, transurethral resection of the prostate; WBC, white blood cell.

tients 1 and 2) were prescribed nabilone at a dose of 1 mg, taken at bedtime, while the other two (patients 3 and 4) were given nabilone at a dose of 1 mg twice daily. Patients 3 and 4 were prescribed a higher nabilone dosage because of their reported high levels of pain, nausea, and anorexia. All patients reported improvement within 48 hours of initiating therapy with nabilone. At 48 hours after baseline, there was an average  $5.00 (\pm 2.58)$  point decrease in their ESAS score pertaining to night sweats ( $p = 0.03$ ; Fig. 1). At 14 days after baseline, there was an average  $5.75 (\pm 2.65)$  point decrease in their ESAS score pertaining to night sweats ( $p < 0.01$ ; Fig. 2). None of the patients experienced any significant burden of side effects from the addition of nabilone.

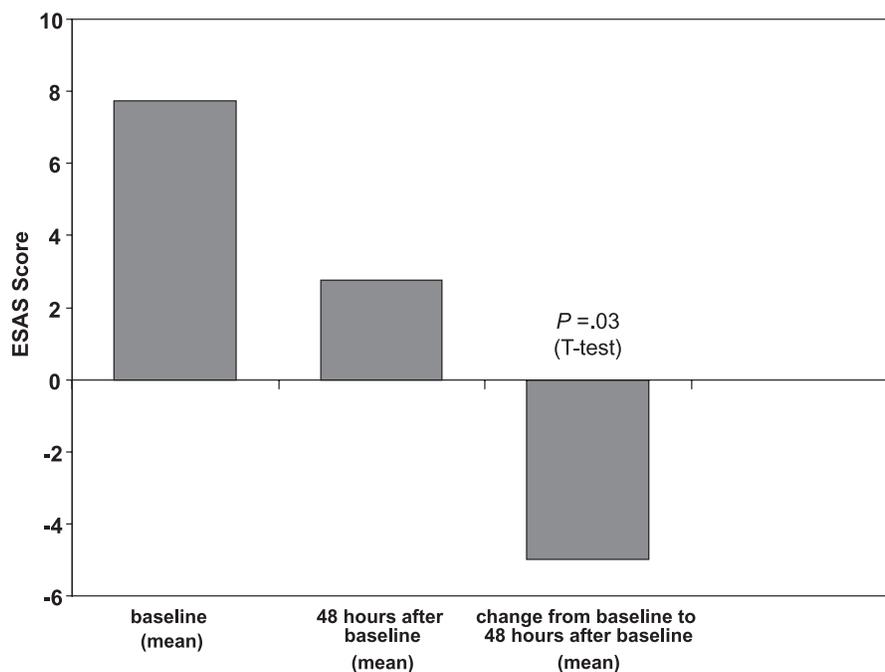
## DISCUSSION

Treatment of four patients with advanced cancer with the synthetic orally administered cannabinoid, nabilone, resulted in the successful management of persistent symptomatic paraneoplastic night sweats. This is evidenced by statistically significant reductions in their ESAS scores pertaining to the "other" symptom that they identified as night sweats. The improvement occurred within 48 hours of initiating ther-

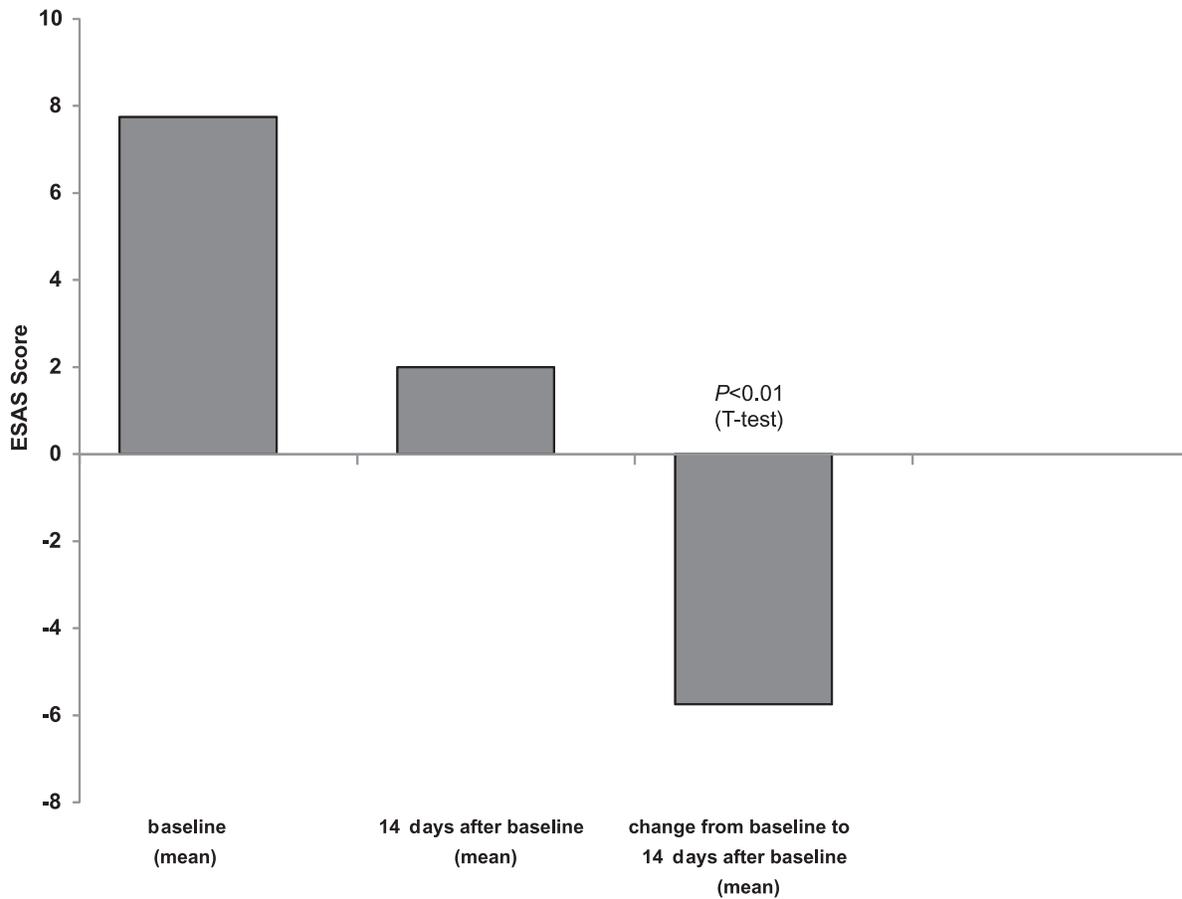
apy and demonstrated further improvement after 2 weeks. The limitations of this study include the small sample size, lack of a control group, and possible placebo effect.

Nabilone, a synthetic analogue of  $\Delta$ -9-tetrahydrocannabinol ( $\Delta$ <sup>9</sup>-THC), is a potent agonist at cannabinoid receptors (CB1 and CB2).<sup>10,13</sup> It has demonstrated efficacy in reducing spasticity-related pain and chronic pain, and decreasing the frequency of vomiting and lessening the severity of nausea associated with chemotherapy.<sup>14-17</sup> The significant reduction in the severity of night sweats experienced by the four patients described herein suggests nabilone may offer additional benefits to patients with cancer.

Given their association with the anorexia-cachexia syndrome, it is postulated that paraneoplastic night sweats are also caused by pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), IL-6, and prostaglandins secreted both by cancer cells and inflammatory cells.<sup>18</sup> In one study of patients with prostate cancer with SIS, IL-6 was elevated, which is a common finding in patients with hormone-refractory disease.<sup>3</sup> The cannabinoid ligand, anandamide, modulates the production of IL-6, as well as cellular responses to IL-6.<sup>19</sup> Cannabinoids have demonstrated anticytokine activity in a number of animal models.<sup>20</sup> An additional mechanism for the ob-



**FIG. 1.** Reduction in nights sweats in cancer patients receiving nabilone at 48 hours after baseline. The mean baseline Edmonton Symptom Assessment System (ESAS) score for night sweats in four cancer patients was  $7.75 (\pm 0.50)$ . At 48 hours after baseline, the mean score was  $2.75 (\pm 2.50)$ , a mean change of  $-5.00 (\pm 2.58)$  from baseline ( $p = 0.03$ ,  $t$ -test).



**FIG. 2.** Reduction in nights sweats in cancer patients receiving nabilone at 14 days after baseline. The mean baseline Edmonton Symptom Assessment System (ESAS) score for night sweats in four cancer patients was  $7.75 (\pm 0.50)$ . At 14 days after baseline, the mean score was  $2.00 (\pm 2.00)$ , a mean change of  $-5.75 (\pm 2.65)$  from baseline ( $p < 0.01$ , *t*-test).

served reduction in night sweats may relate to the ability of cannabinoids to produce relative hypothermia via CB1 agonism. Investigators showed that administration of  $\Delta^9$ -THC induced hypothermia in mice, an effect that was reversed by the administration of a CB1 antagonist.<sup>21</sup> Although many patients with cancer experience nocturnal fevers in conjunction with their night sweats, only two of four patients in this case series reported having fevers on a subjective basis. It is also interesting to note that hepatosplenomegaly and/or adenopathy was present in all four patients in the case series. CB2 receptors are found in greatest density in the spleen, as well as in the liver, lymph nodes, white blood cells, and mast cells.<sup>22</sup> Nabilone has also been shown to reduce prostaglandin induced inflammation in a rat model via agonism of CB2 receptors.<sup>23</sup> The interrelationship among these factors, as well as others, might explain, at least in part, the effects of nabilone on paraneoplastic night sweats in the four patients described.

## SUMMARY

Paraneoplastic night sweats are a relatively prevalent symptom experienced by advanced cancer patients. They are part of a symptom pattern that tends to deteriorate as patients approach end of life. This symptom is also associated with the anorexia–cachexia symptom cluster. Night sweats may impact negatively on the functional capacity and quality of life of affected patients. Beyond disease-modulating therapies, few effective palliative modalities are available to manage symptoms such as paraneoplastic night sweats. The significant and rapid reduction in paraneoplastic night sweats in a case series of four advanced cancer patients referred for palliative care might have important implications in regards to managing this symptom in patients with earlier stages of their malignancies. Further research is needed to elucidate their exact mechanism of action in this context. In addition, validation of the efficacy of nabilone should be eval-

uated through prospective, randomized, controlled trials.

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