Review Article

Health-related quality of life across cancer cachexia stages

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Abstract: Cancer cachexia (CC) is common in advanced cancer and is accompanied by negative effects on health-related quality of life (HRQOL). However, methods to identify the impact of CC on HRQOL are limited. Single questionnaire items may provide insight on the effect of CC on HRQOL. Specifically, the use of "feeling of wellbeing" (FWB) on the Edmonton Symptom Assessment System (ESAS) questionnaire and the Distress Thermometer (DT) have been explored. Assessing how these two surrogate measures of HRQOL are impacted among CC stages and what drives these negative effects may allow for focused treatments. Five-hundred and twelve patients referred to a Cancer Rehabilitation Program completed the ESAS, with the question on FWB and the DT at baseline. Patients were separated into CC stages: non-cachexia (NC), pre-cachexia (PC), cachexia (C), refractory cachexia (RC). A mixed model ANOVA with *post hoc* Tukey adjustment was used to compare means of FWB and distress among the CC stages. To understand what was driving the differences between CC stages, a robust regression model was created with either distress or FWB as the outcome measure, dependent on the other measures in ESAS, age and sex. Finally, the use of cannabinoids in treating appetite loss was examined, as it has a detrimental effect on FWB; 54 patients underwent cannabinoid treatment for appetite loss within a community-based, physician-lead, medical cannabis clinic. A *t*-test to assess changes in ESAS appetite score after 3 months of cannabinoid treatment was examined. RC patients had a significantly poorer sense of wellbeing than the other cachexia stages (RC: 6.07±0.33). Significant differences in distress were identified between RC patients and those with NC and C, but not with PC (RC: 4.87±0.38, NC: 3.35±0.26, PC: 4.11±0.30, C: 3.60±0.28). FWB was negatively affected by worsening appetite in all CC stages except NC (PC: 0.19±0.08, P=0.022; C: 0.26±0.06, P<0.001; RC: 0.23±0.08, P=0.007). ESAS score for lack of appetite significantly improved between baseline (5.07±3.21) and follow-up (3.56±3.15, P=0.003) after cannabinoid treatment, with no significant difference in weight (baseline: 70.7±14.6 kg, 3-month follow-up: 71.0±14.8 kg). Future research should validate both multidimensional and single-item tools to measure HRQOL in patients at different stages of CC. Improvement of HRQOL via appetite stimulation, may be achieved through a multidisciplinary approach, which includes cannabinoid therapy.

Keywords: Cachexia; quality of life; appetite; cannabinoids

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Introduction

Up to 80% of advanced cancer patients will experience cachexia in their disease trajectory (1,2). It is known that cancer cachexia (CC) has a negative effect on function, treatment tolerance and overall mortality, with cachexia being the cause of death in 30% of cancer patients (3). As such, understanding the effect of CC on health-related quality of life (HRQOL) is important. HRQOL is a multidimensional concept including, but not limited to, symptoms of disease, side effects of treatment, perception of wellbeing and life satisfaction and measures of physical, mental and social function (4). Significant associations have been identified between weight loss, malnutrition, CC and poor HRQOL outcomes (5-7). This paper will review the current definition and methods to classify CC. Tools used to measure HRQOL in cachexia will be identified. Additionally, results from our laboratory assessing HRQOL along the CC continuum and the factors driving poor HRQOL in CC will be presented. Finally, preliminary evidence for the use of cannabinoids to relieve symptoms that impair HRQOL will be put forth.

CC: definition and classification

In 2011, Fearon *et al.* published the following international consensus statement defining CC, "*A multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism*" (8). Furthermore, criteria for diagnosis were put forth, which included: (I) weight loss >5% in 6 months (in absence of starvation) or, (II) BMI <20 and any degree of weight loss >2% or, (III) appendicular skeletal muscle index <7.26 kg/m^2 in males or <5.45 kg/m^2 in females with weight loss of >2% (8). Once cachexia is diagnosed, Fearon *et al.* proposed a classification system dividing cachexia into three stages: pre-cachexia (PC), cachexia (C) and refractory cachexia (RC). PC is defined as a ≤5% weight loss with anorexia and metabolic change. C patients present with weight loss of >5%, or BMI <20 and weight loss of >2%, or sarcopenia and weight loss of >2%. They also often have reduced food intake and systemic inflammation. In RC, the cancer is pro-catabolic and not responsive to treatment. Additionally, patients will have low performance scores.

Following this very important work, Vigano *et al.* established a CC classification system that uses clinically available tools (*Figure 1*) (9). Classification is based on five criterion that can be determined using the results of a simple blood test and the abridged Patient-generated Subjective Global Assessment (aPG-SGA) questionnaire. Using these criteria, PC is classified as a combination of abnormal biochemistry with decreased food intake or moderate weight loss, or decreased food intake with moderate weight loss. C is identified by a severe weight loss with either abnormal biochemistry or decreased food intake. RC is classified as C with decreased activities and function, or albumin <20 g/L with decreased activities and function.

Methods to assess HRQOL in CC patients

Tools for assessing HRQOL in CC are limited. In a 2013 review, Wheelwright *et al.* identified the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) as the only cachexia-specific instrument available at the time (10). The FAACT tool assesses five domains: physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing and CC specific symptoms. However, weaknesses in the methodology used to validate the tool, the absence of additional psychosocial domains affecting patients with CC and doubt in the ability to use the tool internationally led the authors to conclude that a robust instrument to assess HRQOL in CC is lacking (10).

Since then, the European Organization for Research and Treatment of Cancer (EORTC)-CAX24 scale has been developed to fill this void (11). To be used with the more generic HRQOL assessment tool, the EORTC-QLQ-C30 (12), it proposes five domains and four individual items capturing relevant issues affecting CC patients. These include: food aversions (5 questions), eating and weight loss worry (3 questions), eating difficulties (3 questions), loss of control (6 questions), physical decline (3 questions) and dry mouth, indigestion/heartburn, forcing self to eat and inadequate information. This tool is currently in the process of being fully validated on an international scale (11).

A recent study by Zhou *et al.* used the Chinese version of the MD Anderson Symptom Inventory (13), with the addition of 8 cachexia-specific symptoms (feeling dizzy, early satiety, lack of energy, changes in taste and smell, diarrhea, constipation, anxiety, and depression), to assess symptom burden among the CC stages (14). Results suggested that lack of appetite was the most frequent and severe symptom among the four CC groups, followed by fatigue, disturbed sleep, lack of energy and distress. The

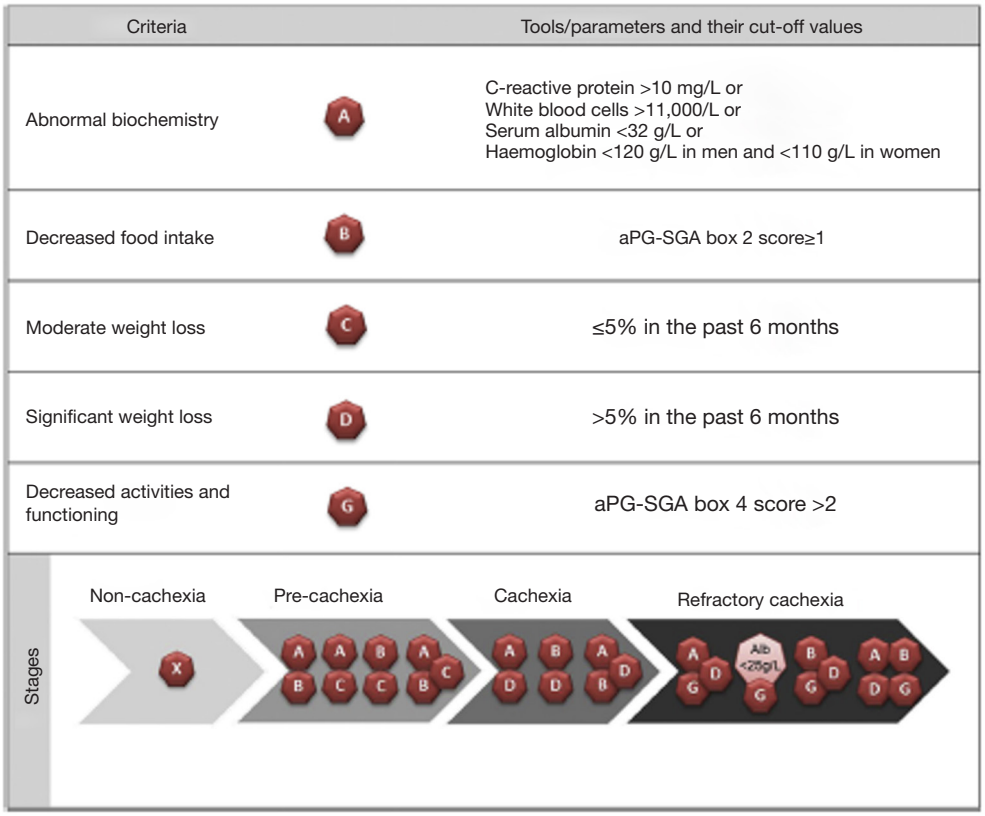


Figure 1 Criteria and cut-offs for the clinical application of the cachexia stages. aPG-SGA, abridged Patient-Generated Subjective Global Assessment (box 2, food intake; box 4, activities and functioning); X, insufficient number of criteria or criteria that do not correspond to any combinations mentioned for the cachexia stages.

authors cite limitations of this study, which include (I) the lack of validation of the new tool developed; and (II) the CC staging method used, based on the work of Blum *et al.* (7), which the authors criticize as not using sarcopenia as part of their classification system, and only weight loss as the definition for RC (14).

Non-cachexia specific tools to assess HRQOL in CC

Due to the paucity of CC specific instruments to assess HRQOL, surrogates must be identified. Ideally, tools would be simple to use and not burdensome to patients. There has been some work pursuing correlations between "feeling of wellbeing" (FWB) as a single item on a questionnaire, and total scores on multi-item HRQOL assessment instruments. Stiel *et al.* (15) analyzed the relationship between the "How do you feel today?" question on the German Minimal Documentation System (MIDOS) (16) and total scores of the EORTC-QLQ-C30 and the Functional Assessment of Cancer Therapy-General (FACT-G) (17). In both instances, social domains were not captured by the single question. However, it was significantly associated with the physical (r=0.38, P<0.01), cognitive (r=0.34, P<0.01), emotional (r=0.33, P<0.01) and role functioning (r=0.26, P<0.05) domains of the EORTC-QLQ-C30 and the physical (r=0.58, P<0.01), functional (r=0.42, P<0.01) and emotional (r=0.38, P<0.01) domains of the FACT-G (15). Similarly, Bush *et al.* found a moderate association between the FWB question on the Edmonton Symptom Assessment System (ESAS) (18) and total FACT-G score (r=0.48, P<0.0001) (19). In a smaller study, Paiva *et al.* compared ESAS FWB and the EORTC-QLQ-C30, with a moderate association with the overall symptom scales (r=0.61, P<0.0001) (20).

Another single item that may prove useful in identifying poor HRQOL is the Distress Thermometer (DT) (21). The DT is a vertical scale ranging from 0 to 10 asking patients to rate their feeling of distress in the past week,

Table 1 Participant characteristics

Characteristics	Data
Age (year), mean ± SD	62.1±13.5
Cancer cachexia stage, n (%)	
Non-cachexia	172 (33.6)
Pre-cachexia	115 (22.5)
Cachexia	154 (30.1)
Refractory cachexia	71 (13.9)
Diagnosis, n (%)	
Lung	123 (24.0)
GI	81 (15.8)
Pancreatic	60 (11.7)
Other	248 (48.4)
Metastatic disease, n (%)	
Yes	295 (57.6)
No	217 (42.4)
On treatment, n (%)	
Yes	263 (51.4)
No	249 (48.6)

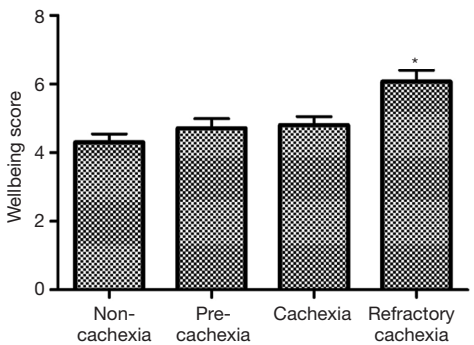


Figure 2 Wellbeing among cancer cachexia stages. Mixed model ANOVA controlled for age, sex, diagnosis, current treatment, metastatic disease. Data reported as mean ± standard deviation. * denotes significance P>0.05.

with zero denoting "no distress" and ten indicating "extreme distress." The National Comprehensive Cancer Network defined distress as, "a multifactorial, unpleasant, emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis" (22). High levels of distress are associated with poor effect on quality of life (23). The DT is comparable to longer screening tools in its ability to correctly identify distress among cancer patients; a cutoff of four has been associated with the best sensitivity and specificity (24). To the knowledge of the authors, there is no specific tool identifying distress among CC patients.

Assessing HRQOL in CC using single-item measures: original research

Given the current lack of a validated CC-specific HRQOL assessment tool, we decided to retrospectively examine how the single-item of FWB from the ESAS questionnaire and the DT would differ between the CC stages. Five hundred and twelve patients who were referred to the Cancer Rehabilitation Program of the McGill University Health Centre (Montreal, Canada), completed these two questionnaires and were separated into CC stages, as per the classification system of Vigano *et al.* (9). Participant characteristics are reported in *Table 1*. Mixed model ANOVA with *post hoc* Tukey adjustment was used to identify differences in wellbeing and distress between CC groups. The models controlled for age, sex, diagnosis, current treatment and the presence of metastatic disease. Significance was determined at P<0.05. *Figures 2* and *3* illustrate the results. RC patients had a significantly greater poor sense of wellbeing than the other cachexia stages (RC: 6.07±0.33) (*Figure 2*). Significant differences in distress were identified between RC patients and those with NC and C, but not with PC (RC: 4.87±0.38, NC: 3.35±0.26, PC: 4.11±0.30, C: 3.60±0.28) (*Figure 3*).

With the data suggesting differences between CC stages and the HRQOL-surrogate measurements of FWB and distress, we then wanted to understand what is driving these differences. To achieve this, a robust regression model was created with either distress or FWB as the outcome measure, which was dependent on the other measures in ESAS, namely pain, tiredness, nausea, depression, anxiety, drowsiness, appetite and shortness of breath (SOB). Additionally, age and sex were considered in the model. Results for each are shown in *Tables 2* and *3*. FWB is negatively affected by worsening appetite in all CC stages

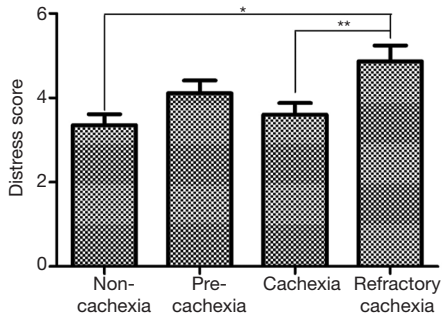


Figure 3 Distress among cancer cachexia stages. Mixed model ANOVA controlled for age, sex, diagnosis, current treatment, metastatic disease. Data reported as mean ± standard deviation. * denotes significance P>0.05.

except NC. This mirrors results from Zhou *et al.* (14). Additionally, anxiety had a poor effect on FWB in all CC stages. Fatigue was also predictive of poor wellbeing in the C and RC stages. Feelings of distress increased in all CC stages, except RC, as anxiety increased. The relationship between distress and anxiety has previously been demonstrated in ambulatory cancer patients (21). None of the ESAS symptoms were significantly related to feelings of distress in RC patients.

Symptom of interest: anorexia

The presence of anorexia leads to decreased food intake, which is a characteristic of cachexia; in our laboratory's previous work creating a CC staging system, 63% of patients reported decreased intake, reflecting a lack of appetite (9). While the cluster of other CC symptoms such as anxiety, fatigue, pain and depression have effective pharmacological and nonpharmacological interventions available, the ability to treat anorexia remains difficult. Orexigenic agents used to reverse anorexia include corticosteroids, megestrol acetate, serotonin antagonists, anamorelin (ghrelin-mimetic) and cannabinoids.

Corticosteroids

Corticosteroids have been used effectively in the treatment of many symptoms in advanced disease. Improvements have been demonstrated in anorexia, but also in relieving symptoms of pain, fatigue, chemotherapy-induced nausea and vomiting and overall quality of life (25). Unfortunately, the reversal of anorexia using corticosteroids is short lived, generally lasting less than 4 weeks (26). Additionally, long-term use of corticosteroids is associated with myopathy, gluconeogenesis leading to insulin resistance, immunosuppression, bone loss and mood disturbances (25).

Megestrol acetate

A recent updated Cochrane Review on the effectiveness of megestrol acetate for the reversal anorexia in cancer

Table 2 Relationship between wellbeing and ESAS symptoms by CC stage

CC stage	Category	B	SE	P	R^2
Non-cachexia (n=167)	Pain	0.24	0.07	<0.001	0.33
	Anxiety	0.19	0.08	0.022	
Pre-cachexia (n=111)	Pain	0.22	0.09	0.012	0.44
	Anxiety	0.23	0.10	0.017	
	Appetite	0.19	0.08	0.022	
	SOB	0.15	0.07	0.042	
Cachexia (n=152)	Fatigue	0.32	0.10	0.002	0.37
	Anxiety	0.20	0.09	0.026	
	Appetite	0.26	0.06	<0.001	
Refractory (n=67)	Fatigue	0.60	0.13	<0.001	0.53
	Anxiety	0.33	0.15	0.029	
	Appetite	0.23	0.08	0.007	

ESAS, Edmonton Symptom Assessment System; CC, cancer cachexia; SE, standard error; SOB, shortness of breath.

Table 3 Relationship between distress and ESAS symptoms by CC stage

CC stage	Category	B	SE	P	R^2
Non-cachexia (n=156)	Pain	0.13	0.06	0.026	0.55
	Depressed	0.21	0.07	0.004	
	Anxiety	0.58	0.07	<0.001	
Pre-cachexia (n=105)	Fatigue	0.29	0.11	0.01	0.43
	Anxiety	0.28	0.11	0.014	
Cachexia (n=136)	Depressed	0.28	0.10	0.003	0.47
	Anxiety	0.53	0.09	<0.001	
	Age	−0.03	0.01	0.041	
Refractory (n=61)					0.35

ESAS, Edmonton Symptom Assessment System; CC, cancer cachexia; SE, standard error.

patients demonstrated favorable results (27). Megestrol acetate was effective in significantly improving both appetite when compared to placebo [RR 2.19 (1.4–3.4)] (27). Modest weight gain was also observed: 1.96 kg (95% CI: 1.11–2.81 kg) (27). Despite this, the quality of evidence for the improvement of anorexia versus placebo was graded as "very low" due to possible bias introduced from unclear blinding methods, sequence generation and allocation concealment. Additionally, side-effects such as edema, dyspnea, thromboembolic events and death were associated with the use of megestrol acetate versus placebo in both low and high doses (±800 mg/day) (27).

Serotonin antagonist: cyproheptadine

The use of cyproheptadine as an orexigenic agent for advanced cancer patients has yielded few benefits. Kardinal *et al.* only demonstrated a moderate improvement in appetite over placebo, with weight loss in both groups (4.5±0.72 versus 4.95±1.01 lb, P=0.72) (28).

Ghrelin mimetic: anamorelin

Recent phase III trials have demonstrated a positive effect of anamorelin on both appetite and weight vs placebo in stage III/IV non-small cell lung cancer patients. In the ROMANA 1 and ROMANA 2 studies, participants were given 100 mg anamorelin/day or placebo for 12 weeks (29). Pooled analysis of the studies demonstrated the anamorelin group had modest increases in mean total body weight (ROMANA 1 anamorelin: 2.2±0.33 kg, placebo: 0.14±0.36 kg; ROMANA 2 anamorelin: 0.95±0.39 kg, placebo: −0.57±0.44 kg) and median lean body mass (ROMANA 1 anamorelin: 0.99 kg (95% CI: 0.61 to 1.36 kg), placebo: −0.47 kg (95% CI: −1.00 to 0.21 kg); ROMANA 2 anamorelin: 0.65 kg (95% CI: 0.38 to 0.91 kg), placebo: −0.98 (95% CI: −1.49 to −0.41 kg) (29). Strength, as measured by handgrip dynamometry, was not significantly improved. Overall mean anorexia-cachexia scale score, as measured by FAACT, was significantly greater in the anamorelin group (29). There were no differences in treatment-related adverse events between study groups; the most common were hyperglycemia, nausea and edema (29). While its effect in treating anorexia seems promising, anamorelin is not yet commercially available.

Cannabinoids

The potential effect of cannabinoids on appetite and weight has been repeatedly reviewed in patients with cancer and HIV/AIDS (30-33). Two studies looked at natural extracts, six studies looked at dronabinol, a synthetic cannabinoid, as orexigenic agents and one study assessed nabilone. In 2006, the Cannabis-In-Cachexia-Study-Group compared the effects of cannabis extract, delta-9-tetrahydrocannabinol (THC), and placebo on appetite and quality of life in patients with cancer-related anorexia-cachexia syndrome (34). The cannabis extract, administered at a dose of 2.5 mg of THC and 1 mg of cannabidiol (CBD), was well tolerated by patients with anorexia. However, no significant differences in appetite and HRQOL were found for cannabis extract as compared to placebo (34). In another study, higher

Table 4 Demographic and clinical characteristics

Characteristics	Data
Age (years)	47.3±16.1[†]
Gender	
Males	34 (63.0)[‡]
Females	20 (37.0)
Diagnosis	
Cancer	23 (42.6)
Non-cancer	31 (57.4)
Cannabinoid therapy	
THC/CBD (1:1 ratio)	With SC[§]: 2; no SC: 4; total: 6 (11.1)
THC-rich	With SC[§]: 8; no SC: 9; total: 17 (31.5)
CBD-rich	With SC[§]: no SC: 0; total: 0
Combined therapies	
THC/CBD and THC-rich	With SC[§]: 7; no SC: 10; total: 17 (31.5)
THC/CBD and CDB-rich	With SC[§]: 3; no SC: 4; total: 7 (13.0)
THC-rich and CBD-rich	With SC[§]: 8; no SC: 9; total: 17 (31.5)
THC/CBD, THC-rich, CBD-rich	With SC[§]: 0; no SC: 1; total: 1 (1.9)
Route of administration	
Oral	11 (20.4)
Inhaled	14 (25.9)
Combined oral and inhaled	29 (53.7)
Adverse effects	
Mild	11 (20.4)
None	41 (75.9)
Not recorded	2 (3.7)

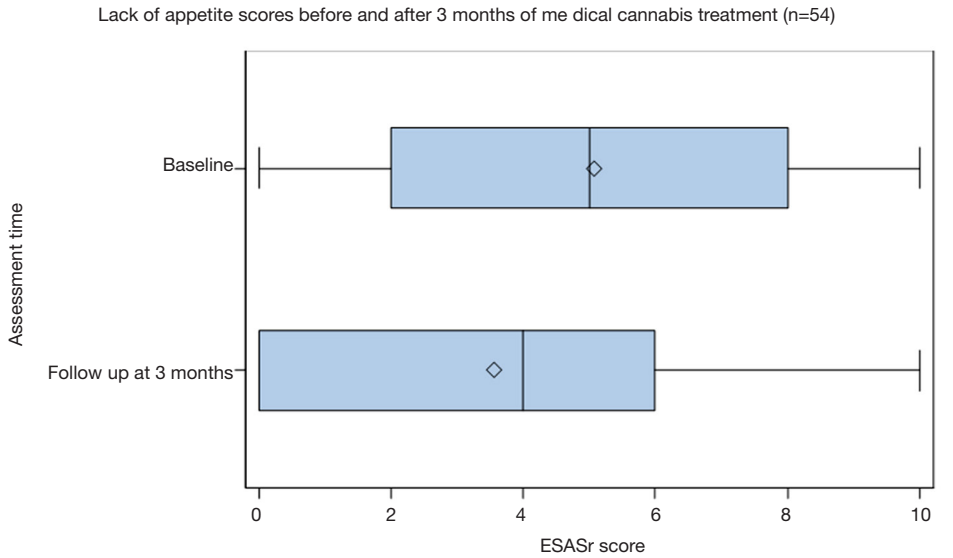
[†], values expressed as mean ± standard deviation; [‡], all values expressed as number of patients; [§], nabilone—synthetic cannabinoid product. Round bracket indicates percentage. SC, synthetic cannabinoid co-treatment. THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol.

doses of natural cannabinoids (up to 22.5 mg/day of THC) provided more consistent and favorable results for appetite stimulation and decreased weight loss associated with cancer (total weight gain of 1.25 lb; on placebo: total weight loss of 21.25 lb) (30). Equally, the combination of both oral and inhaled methods of administration provided favorable results for an increase and stabilization of weight in HIV patients (30). Studies that examined dronabinol also found limited and low-quality evidence supporting cannabinoids for appetite stimulation and weight gain in cancer patients. More recently, a randomized, double-blind, placebo-controlled study evaluated the effect of nabilone (0.5 mg/day/2 weeks followed by 1.0 mg/day/6 weeks) in patients with advanced non-small cell lung cancer. Patients on nabilone (n=9) showed an increase in their average caloric intake (342 kcal/day) and significant improvements in their quality of life particularly for role functioning, emotional functioning, social functioning, pain, and insomnia, which were not seen in the patients on placebo (n=13) (35).

Assessing cannabinoids for increasing appetite and stabilizing weight in chronic cancer and non-cancer diseases: original research

In order to gather more specific data on the effect of different types of cannabinoids on appetite and weight in chronic cancer and non-cancer diseases, a retrospective chart review was conducted at Santé Cannabis, the only community-based, physician-lead, medical cannabis clinic in Quebec, Canada. At baseline, 54 patients with "increase appetite" as a treatment goal completed the ESAS question on appetite, with 51 subjects also having their weight measured. These assessments were repeated at 3-month follow-up. The mean age of patients was 47.3±16.1 years; 63% were male and 43% of our sample was represented by patients with a cancer diagnosis (*Table 4*).

Of the 54 patients analyzed, the ESAS score for lack of appetite significantly improved between baseline (5.07±3.21) and follow-up (3.56±3.15, paired *t*-test P=0.0026) (*Figure 4*). Bivariate regression reveals a significant improvement with the use of nabilone (–2.73, 95% CI: –4.19 to –1.27, P=0.0358). Route of administration also had an effect on appetite: (I) favoring only inhaled *vs.* only oral (–2.36, 95% CI: –4.17 to –0.54, P=0.024) and (II) favoring combined oral and inhaled *vs.* only oral (–2.00, 95% CI: –3.26 to –0.74, P=0.023). With regression models adjusted for age and gender (multivariate), only a marginal improvement was detected for the use of nabilone (–2.84, 95% CI: –4.34 to –1.34, P=0.0521). A more pronounced



ESASr: Edmonton system assessment system revised (0 =no lack of appetite; 10 =worst lack of appetite). The bars provide minimun, Q1(25%), median, mean (diamond), Q3 (75%) and maximum of the variables. The p-value for the difference test is 0.0026.

Figure 4 Box-plot demonstrating appetite at baseline and follow-up.

improvement was demonstrated among the methods of administration: (I) favoring only inhaled *vs.* only oral (–2.01 to 95% CI: –4.85 to –1.17, P=0.006) and (II) favoring combined oral and inhaled *vs.* only oral (–2.34 to 95% CI: –3.61 to –1.07, P=0.009).

Among the 51 subjects who were examined for weight change over time, there was no significant difference found and weight remained stable between baseline (70.7±14.6 kg) and 3-month follow-up (71.0±14.8 kg). Regression models, with and without adjustment for age and gender, did not show any difference in weight associated with nabilone use or with different routes of administration.

The majority of study patients did not report any side effects to cannabinoids (*Table 4*). Eleven patients reported mild side effects, including anxiety, fatigue, dizziness and dry mouth.

Conclusions

Despite the incidence and prevalence of CC, there is still a paucity of data regarding its impact on HRQOL. Latest research in this area has focused on developing and/or applying routinely available criteria to identify CC stages in clinical practice, specific multidimensional tools (such as FAACT or EORTC-CAX24) or non-specific single-item scales (such as DT and FWB scale from ESAS) to assess HRQOL across CC stages and orexigenic agents such as anamorelin and cannabinoids. Original research from our group suggests wellbeing is negatively affected by anorexia and anxiety in all CC stages, with fatigue also being predictive of poor wellbeing in the cachexia and RC stages. Cannabinoids, when prescribed through an interdisciplinary, physician-lead, care model appear to be promising orexigenic agents in chronic cancer and non-cancer diseases, particularly if used concomitantly through the oral and the inhalation route of administration. Future research should further validate both multidimensional and single-item tools to measure HRQOL in patients at different stages of CC, for whom the above pharmacological interventions are trialed to improve appetite and stabilize weight.

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Footnote

Conflicts of Interest: A Vigano is the Research Director of Santé Cannabis—a medical cannabis clinic specializing in clinical research; the principal investigator for a phase II and a phase III clinical trial sponsored by Tetra Bio-Pharma, Inc. The other authors have no conflicts of interest to declare.

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