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Food intake behaviour in advanced cancer –

Implications of taste and smell alterations, orosensory reward, and cannabinoid therapy

by

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Abstract

Food intake is regulated by both appetite and orosensory reward systems. Appetite systems stimulate or reduce hunger, while orosensory reward motivates consumption of high fat sweet foods, resulting in food enjoyment. The majority of advanced cancer patients suffer from malnutrition and wasting, which may be caused by a loss of appetite due to physiological changes or a hindered orosensory reward system due to taste and smell (chemosensory) changes or both. Orosensory reward systems were hypothesized to be impaired in advanced cancer. To understand the influence of chemosensory alterations on food intake and enjoyment, the nature (intensity) of chemosensory alterations in cancer patients and their relationship with ingestive behaviour and quality of life (QOL) were investigated (*study 1*). Advanced cancer patients (n=192) more frequently self-reported tastes and odours to be heightened rather than diminished (p=0.035). Patients with perceived chemosensory alterations had poorer QOL (p=0.0176) and lower caloric intake (p=0.0018) compared to patients with no alterations. Cannabinoids (*e.g.* Δ-9-tetrahydrocannabinol, Δ-9-THC) increase food intake by stimulating both appetite and orosensory reward systems as well as potentially enhancing chemosensory function. To palliate chemosensory alterations and poor appetite, advanced cancer patients (n=21, *study 2*) with these symptoms were randomized to receive either Δ-9-THC (2.5mg) or placebo oral capsules twice daily for 18 days. Compared to patients receiving placebo, Δ-9-THC-treated patients reported that food *tasted better* (p=0.04), they had improved chemosensory perception (p=0.026), increased preference and intake of high protein foods (p=0.008), and improved appetite (p=0.05), quality of sleep (p= 0.025), and relaxation (p= 0.045). Like cancer patients, tumour-bearing rats appeared to experience a loss of orosensory reward, showing tumour-associated anorexia when fed a rewarding diet to the same degree as on a usual diet (*study 3*). Δ-9-THC significantly increased

caloric intake compared to vehicle for both tumour-bearing ($p=0.0146$) and healthy rats ($p=0.0004$), suggesting endocannabinoid-mediated appetite systems are functioning in this tumour model. The findings of this thesis suggest orosensory reward systems to be impaired in advanced cancer, decreasing the liking and motivation to eat. Δ-9-THC treatment may help to palliate perceived chemosensory alterations and loss of appetite and food enjoyment in advanced cancer.

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2-AG	2-arachidonoylglycerol
11-OH-THC	11-hydroxy-Δ-9-THC
ACE	Angiotensin-Converting Enzyme
AE	Adverse event
AgRP	Agouti-related peptide
AIC	Akaike's information criterion
AIDS	Acquired immune deficiency syndrome
ANOVA	Analysis of variance
Arc	Arcuate nucleus
BSIT	Brief Smell Identification Test
BW	Body weight
CART	Cocaine- and Amphetamine-regulated Transcript
CBr (1,2)	Cannabinoid receptor
CCK	Cholecystokinin
CNS	Central nervous system
CO_2	Carbon dioxide
EORTC	European Organization for Research and Treatment of Cancer
ESAS	Edmonton Symptom Assessment Scale
FAACT	Functional Assessment of Anorexia/Cachexia Therapy
FFQ	Food frequency questionnaire
Fig	Figure
FPC	Food (macronutrient) Preference Checklist
g	gram
GI	Gastro-intestinal
HC	High carbohydrate
HF	High fat
HFS	High fat sweet
HP	High protein
Il-1β	Interleukin -1β
INR	International normalized ratio
i.p.	Intraperitoneal
Kcal	Kilocalorie
Kg	Kilogram

LE	Low energy
MA	Megestrol acetate
MFB	Medial forebrain bundle
Mg	milligram
MJ	Megajoule
MPC	Macronutrient Preference Checklist
MPFC	Medial prefrontal cortex
N	Number of subjects
NAc	Nucleus accumbens
NPY	Neuropeptide Y
NTB	Non-tumour bearing
PGE	plasma prostaglandin
POMC	Proopiomelanocortin
Pro	Protein
PROC	Procedure
PTT	Partial thromboplastin time
PYY	Peptide YY
QOL	Quality of life
SAE	Serious adverse event
SAS	Statistical Analysis System
s.c.	Subcutaneous
SD	Standard deviation
SE	Standard error
SLIM	Satiety Labeled Intensity Magnitude scale
T3	Triiodothyronine
T4	Thyroxine
TB	Tumor bearing
THC/Δ-THC	Delta-9-tetrahydrocannabinol
THC-COOH	11-nor-Δ-9-THC-9-carboxylic acid
TNF-α	Tumor necrosis factor-α
TRPM5	Transient receptor potential M5
UK	United Kingdom
USDA	United States Department of Agriculture
µl	microliter

Veh	Vehicle
VP	Ventral pallidum
VTA	Ventral tegmental area
YAH	Yoshida Ascites Hepatoma AH130

Chapter 1

Food intake regulation: appetite and reward systems[1]

"Change in food appreciation can be one of the causes of poor dietary intake and thereby contributes to a deterioration of the cancer patient's general condition" [1]

1.1 Introduction

Food intake is regulated by both appetite and reward systems. These pathways work synergistically to maintain a healthy body weight [2]. The presence of involuntary weight loss or gain may be associated with a shift in these regulatory systems, causing a deficit (or surfeit) of food intake relative to metabolic activities. Historically, when food was scarce, the orosensory reward pathway played a critical role in survival by promoting over-consumption of available energy dense foods for calorie storage. Currently, in an environment of readily available energy dense foods, the orosensory reward pathway is suggested to be maladaptive, dominating food intake over appetite systems and causing excessive weight gain [3-5]. Conversely, there is an incomplete understanding of the etiology of low food intake associated with chronic diseases, such as cancer. A decline in food intake when ill or injured may be an adaptive response to limit foraging for food during a compromised state. The drivers for this response may then be either loss of motivation to eat (*i.e*. impaired reward system) or loss of appetite or a combination of the two. The majority of advanced cancer patients suffer from malnutrition and wasting [6], which may be caused by a loss of appetite due to physiological changes [7] or a hindered orosensory reward pathway (which may be partially due to taste and smell changes [8-10]) or both. In cancer anorexia, it is unknown which pathway (*i.e.* appetite and reward) primarily contributes to the prevailing level of food intake and if both are responsive to external stimuli, such as diet and drug.

1.2 Appetite regulation

To regulate appetite, the brain integrates signals from the periphery (sympathetic nervous system) and the hypothalamus. A long list of mediators control food intake (Table 1.1), such as Neuropeptide Y (NPY), Agouti-related protein (AgRP), melanin-concentrating hormone, and the orexins which stimulate feeding and melanocortins (α- and γ-melanocyte-stimulating hormone), cocaine- and amphetamine-regulated transcript (CART), thyrotropin-releasing hormone, corticotropin-releasing hormone, and urocortin, and pro-inflammatory cytokines (*e.g.* interleukin-1β and tumor necrosis factor-α) which inhibit food intake [2, 11, 12]. Systemic hormones which inhibit feeding include insulin, leptin, peptide YY (PYY), cholecystokinin (CCK), and glucagon-like peptide-1, while ghrelin stimulates feeding [2, 12].

For simplicity, food intake regulation will be divided into long-term and short-term control systems. The hypothalamus, specifically the arcuate nucleus, is involved in long-term feeding and energy homeostasis. The arcuate nucleus neurons are sub-divided into orexigenic (*i.e.* NPY/ AgRP neurons) and anorexigenic neurons (*i.e.*

[1] Section 1.3 and Table 1 have been published as a book chapter entitled Appetite loss/cachexia: basic science in *Cancer Symptom Science*, Cambridge University Press, editors Charles Cleeland, Michael Fisch, Adrian Dunn (authors Tristin Brisbois Clarkson, Wendy Wismer, Vickie Baracos)

Proopiomelanocortin (POMC)/ CART neurons) [2]. Leptin and insulin stimulate POMC/CART neurons and inhibit NPY/AgRP neurons to decrease food intake and maintain a normal body weight, while ghrelin stimulates NPY neurons to initiate feeding.

The short-term regulatory system involves signals from the periphery, which project to the hindbrain (*i.e.* nucleus of solitary tract) via the vagus nerve [11, 12]. This system informs the brain about the quantity and quality of food consumed. The nucleus of solitary tract then relays the information to the hypothalamic brain centers (*e.g.* the paraventricular nucleus). The main peripheral areas include the gastro-intestinal (GI) tract, the mouth and nose (sensory cues), and the liver. This system is also referred to as the gut-brain axis. The gut-brain axis involves three categories of signals [11]:

1. **Meal initiation/motivation:** signals from ghrelin and sensory stimuli (*i.e.* visual, olfactory, taste, and other oral stimuli)
2. **Maintaining food intake/meal duration**: balance between sensory stimuli and negative feedback of GI satiety signals (*e.g.* CCK, PYY) , thus eating continues until feedback signals override sensory aspects integrated with descending hypothalamic input
3. **Termination of meal**: signals from GI / liver, which create a negative feedback loop

Our senses play a critical role in the short-term regulation of food intake. The odour and sight of food are involved in meal initiation, the positive feedback from our senses perpetuates eating during a meal, and the satisfaction obtained from our senses triggers the termination of a meal. Thus alteration of sensory inputs can disrupt meal initiation and motivation to eat (*i.e.* orosensory reward). In cancer, taste and smell alterations are frequently reported (15-100%), which negatively impact food intake and food enjoyment [8-10], suggesting alterations in food-related reward systems. Taste and smell alterations in cancer are rarely studied and no studies have investigated their impact on orosensory reward, regardless of the obvious impact on food intake.

1.3 Reward and food intake

Human beings derive pleasure from food properties, particularly the qualities of sweetness and fattiness. A preference for foods with these properties promotes consumption of foods with high energy density and this is generally understood to have had adaptive value over the course of human evolution. The intrinsic sensory attractiveness of food is mediated by brain pathways referred to as reward pathways. Thus, in addition to the hypothalamic control of appetite, reward systems are also involved in food intake regulation.

Reward pathways promote various types of pleasure and it has been found that particular neurochemical transmitters are involved including dopamine, endogenous opioids and cannabinoids, together with their specific receptors. Reward is defined as both *wanting* (motivation) and *liking* (hedonic) [13]. *Wanting* is the incentive motivational value of a stimulus (*i.e.* the drive to obtain the reward), whereas *liking* is purely hedonic (*i.e.* the pleasure that is obtained from the reward). The reward pathway is thought to have the capacity to override appetite control, generating net energy storage in response to exposure to high energy density foods [14]. The combination of an environment saturated with high energy density foods and the genetic susceptibility of some individuals to food reward stimuli, is an important current theme of obesity research.

Conversely, the status of the reward pathway in cancer anorexia is largely unknown, however it has been suggested that stimulating the reward pathway through pleasant and varying visual, textural, gustatory, and olfactory food stimuli or through exogenous agents such as cannabinoids, may prove to be effective approaches for cancer anorexia [15].

The reward system involves several brain regions, the ventral tegmental area (VTA), nucleus accumbens, ventral pallidum, and medial prefrontal cortex [16]. These areas of the brain are linked together and to the medial forebrain bundle by synaptically interconnected neurons to form a circuit [17]. Stimulation of this circuit induces pleasure in humans [16] resulting in increased dopamine levels in the nucleus accumbens [18]. Two types of dopamine receptors (D1-like and D2-like) are involved in mediating the action of rewards [19].

Both the endogenous opioid and cannabinoid systems are involved in reward. The endogenous opioid system consists of three types of opioid receptors (μ, δ, and κ with the μ–opioid receptor primarily involved in food reward [17]), and several endogenous opioids such as β–endorphin, enkephalin, and dynorphin. Opioid receptors are concentrated in brain areas involved in food intake and reward (*e.g.* hypothalamus and VTA). The endogenous opioid system is directly connected to the dopamine brain reward axis and is more involved in the hedonic aspects of rewards [13, 20]. It is of note that chronic stimulation with morphine results in a down-regulation of G-coupled proteins involved in reward systems, such as cannabinoid receptors [21]. Thus for cancer patients chronically treated with opioid analgesics the reward pathway may have a lowered responsiveness as a consequence. We speculate that chronic opioid use is potentially a highly important limitation to reward – based ingestive behaviour; this remains to be tested.

The endocannabinoid system consists of endogenous cannabinoid receptors (CB1r, CB2r) and their endogenous agonists, such as anandamide. CB1r are found in the hypothalamus, VTA, and nucleus accumbens as well as in the periphery (*i.e.* epithelial cells of GI tract, myenteric neurons, hepatocytes, adipose tissue, olfactory receptors, and vagus nerve/nodose ganglion) (Figure 1.1). Cannabinoids increase appetite through activation of the CB1r, which causes increases in NPY [22] and decreases leptin signalling [23] (Figure 1.2). How cannabinoids interact with the reward pathway is not completely understood, however they have been shown to increase dopamine levels in various reward-related areas [16]. Thus stimulation of the CB1r with either endogenous or exogenous agonists (*e.g.* Δ-9-tetrahydrocannabinol, Δ-9-THC) increases extracellular dopamine levels in the brain causing a rewarding effect [24]. This increase in dopamine levels can be mitigated with CB1 antagonists (*e.g.* SR141716) [25].

Sensory features such as sight, texture, taste, and smell determine the reward value of food [26] The evaluation of the pleasantness of food takes place in the orbitofrontal cortex (the secondary gustatory cortex) [27]. The orbitofrontal cortex is mediated by dopamine levels in the striatum, thus stimulation of the orbitofrontal cortex increases the desire for food [28]. Overall, the ventral striatum is the interface between taste perception (*i.e.* brainstem visceral taste nuclei and gustatory cortex) and reward related behaviour [29]. Since the taste and smell of food heavily impact the rewarding aspects of eating (*i.e.* the motivation to eat and the liking of food), it seems important that taste and smell changes which are commonly experienced by cancer patients may undermine the

pleasure incentives of food. These chemosensory alterations have been noted to decrease the pleasure of eating [1, 8].

Enhanced sensory cues, food variety, or exogenous agents such as cannabinoids which activate the reward pathway may be useful approaches to restore rewarding aspects of food. These interventions, with the exception of cannabinoids, have been tried in elderly individuals to promote food intake with some success [30, 31]. One approach to increase dopamine levels is to consume a variety of foods. The orbitofrontal cortex is responsible for rating the pleasure aspects of food and is involved with sensory specific satiety. When a food is eaten to satiety, even if it is palatable, it becomes unappealing [26]. In other words, repeated exposure to the same food causes dopamine signals to adapt, resulting in a tolerance to the natural reward similar to the tolerance effect of drugs [18]. Replacing the food item with a different palatable food reinstates reward (*i.e.* re-increases dopamine levels in the nucleus accumbens), and thus increases overall food intake and reinstates the pleasure of eating [18]. Thus increasing food variety, such as changing the flavour, texture or even appearance of foods may increase overall food intake and food enjoyment.

Based on our understanding of the reward system, stimulating the reward pathway with exogenous cannabinoids is also a plausible approach. Cannabinoids increase the motivation to eat and increase sensitivity to the sensory properties of foods, creating a preference for highly palatable foods even when satiated [32, 33]. In animals, cannabinoids increased the pleasantness of sucrose solutions and decreased the aversiveness of bitter solutions [34]. Cannabinoids have been shown to increase food intake in healthy [35-37] and AIDS populations [38, 39], but their effectiveness in cancer anorexia is limited and difficult to interpret [40-42]. There are only 5 published studies to date investigating the efficacy of Δ-9-THC for appetite loss in cancer [39-43]. Study designs, outcome parameters, and results vary greatly among these studies. Moreover, no study has investigated the potential of Δ-9-THC to improve other aspects of food intake behaviour, such as perceived taste and smell alteration and loss of food enjoyment in cancer.

1.4 Thesis goals and objectives

The role of the orosensory reward pathway and implications of taste and smell alterations in cancer anorexia are unknown. Very few studies have attempted to palliate chemosensory alterations and loss of food enjoyment in cancer, none of which have considered the use of cannabinoids. The following chapters discuss the role of sensory alterations and orosensory reward on food intake behaviour in advanced cancer as well as the efficacy of cannabinoid therapy to palliate chemosensory alterations and loss of food enjoyment and appetite. I hypothesize that orosensory reward systems are hindered in advanced cancer. My objectives were to determine 1) the nature (intensity) of chemosensory alterations in advanced cancer patients and their relationship with ingestive behaviour and psychosocial parameters (*Chapter 3*); 2) if Δ-9-THC is able to overcome chemosensory abnormalities in advanced cancer patients to stimulate food intake and re-instate food enjoyment (*Chapter 4*); and 3) if reward systems are responsive to a palatable high fat sweet diet and drug (Δ-9-THC) in cancer using a tumour-bearing rat model (*Chapter 5*).

It is clear that sensory inputs are critical to food intake behaviour and arguably an important link between appetite and reward systems. Sensory perceptions are involved in short-term food intake and partially determine the orosensory reward of food. Thus sensory experiences influence food intake through both systems, increasing intake when sensory inputs are perceived as positive and decreasing intake when perceived as negative. The following chapter (*Chapter 2*) presents an argument for the use of sensory science to further our understanding and aid in the palliation of anorexia in cancer.

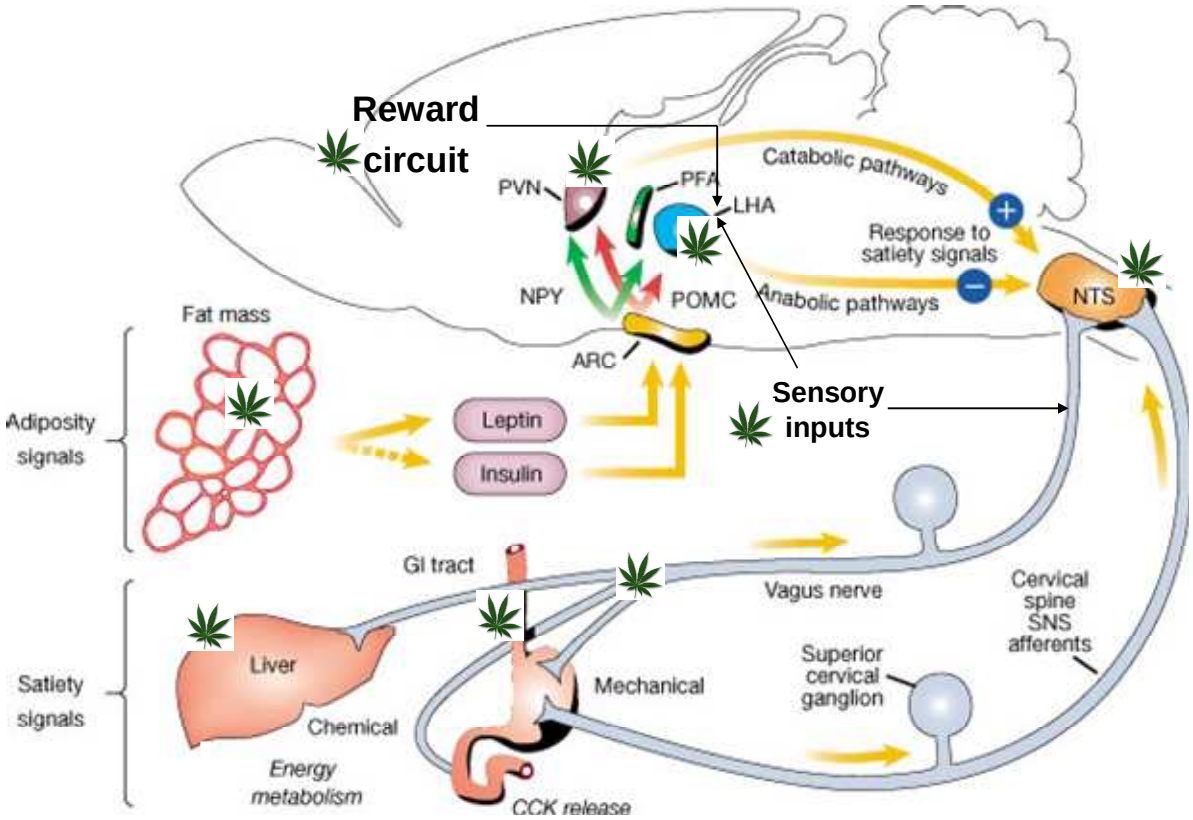

Figure 1.1 Model of food intake regulation including peripheral signals to central controls of appetite, involvement of reward and sensory inputs, and potential sites of involvement of the endocannainoid system. Location of cannabinoid receptors (CB1r) are depicted with the marijuana leaf. The lateral hypothalamus (LH) receives information from reward, appetite, and sensory inputs, and is considered the site of integration for the three systems. Taste inputs travel through cranial nerves to the nucleus of the solitary tract (NTS), which then projects to the LH and orbitofrontral cortex (not shown). Olfactory stimuli project directly to the LH and orbitofrontal cortex. Adapted from Schwartz, 2000 [2]

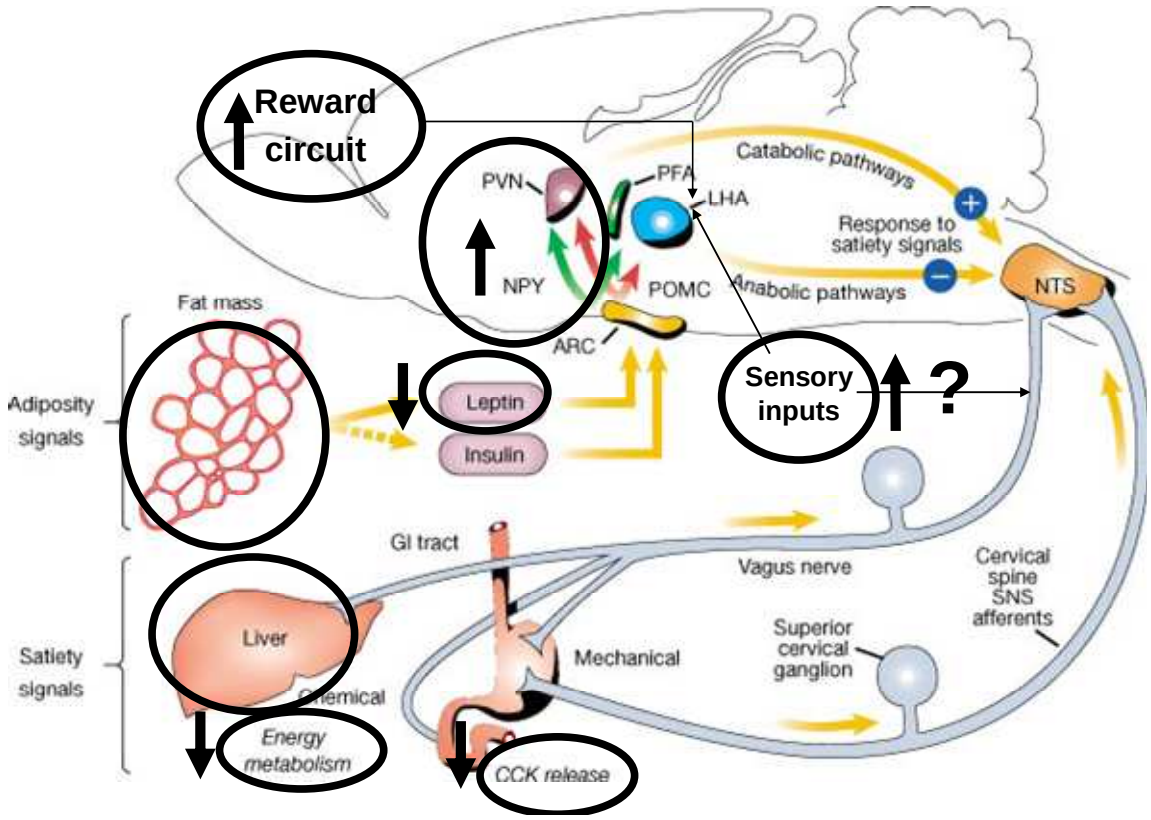

Figure 1.2 Model of the potential involvement of the endocannabinoid system in food intake regulation. Cannabinoids are inversely associated with leptin levels likely resulting in increased NPY neuronal activity and release. Cannabinoids are inversely related to CCK likely reducing satiety signals to central controls during eating. Energy expenditure appears to be reduced with stimulation of cannabinoid receptors and the endocannabinoid system has been suggested to regulate lipid metabolism. Cannabinoids are accepted to stimulate reward systems, likely increasing the reward value of food. Cannabinoids have been suggested to be involved in chemosensory function, particularly odour processing, in which THC has been shown to increase afferent input to the olfactory bulb enhancing smell perception. Adapted from Schwartz, 2000 [2]

Table 1.1 Signaling Molecules in Appetite Regulation: Abbreviations and Actions

Abbreviation	Molecule Name	Effect on Feeding
2AG	2-arachidonylglycerol (endocannabinoid)	+
5-HT	Serotonin	-
AgRP	Agouti-related protein	+
α-MSH	α-melanocyte–stimulating hormone	-
Amylin	Gut peptide	-
Anandamide	N-arachidonylethanolamine (endocannabinoid)	+
CART	Cocaine- and amphetamine-regulated transcript	-
CCK	Cholecystokinin	-
Cort	Corticosterone, cortisol (species-dependent)	+
CRF = CRH	Corticotropin-releasing factor	-
DA	Dopamine	+
Gal	Galanin	+
Ghrelin	Natural ligand of GHS-R	+
GHS-R	Growth hormone secretagogue receptor	+
GIP	Gastrin inhibitory peptide	-
GLP-1, GLP-2	Glucagon-like peptide-1 and 2	-
IL-1β	Interleukin-1β proinflammatory cytokine	-
Insulin	Natural ligand of insulin receptor	-
Leptin	Adipocyte-secreted hormone	-
MC4-R	Melanocortin-4 receptor	-
MCH	Melanin-concentrating hormone	+
Norepinephrine	Noradrenaline	+
NPY	Neuropeptide Y	+
OEA	Oleoylethanolamide	-
OX	Orexin A and B	+
POMC	Proopiomelanocortin	-
PYY	Peptide YY – Y2 receptor ligand	-
TNF-α	Tumor necrosis factor proinflammatory cytokine	-
TRH	Thyrotropin-releasing hormone	-
UCN 1, 2, 3	Urocortins 1, 2, 3	-
UCP 1, 2, 3	Uncoupling proteins 1, 2, 3	-
Y1R, Y5R	NPY-1 and NPY-5 receptors	+
Y2R	NPY-2 receptors	-

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Chapter 2

Taste and smell abnormalities as an independent cause of failure of food intake in patients with advanced cancer – an argument for the application of sensory science[2]

"And suddenly the memory revealed itself. The taste was that of the little piece of madeleine which...my aunt Léonie used to give me, dipping it first in her own cup of tea or tisane." **Marcel Proust** 1871-1922: *Swann's Way* (1913)

2.1 Introduction

The chemical senses of taste and smell are essential to life. They alert us to gas, fire and spoiled foods, warning us against life threatening dangers. These senses are an integral part of our nutritional behaviour as omnivores; olfaction and gustation inform and guide our food selection and intake [1, 2]. Reward pathways in the brain (involving motivation and the hedonic aspects of eating) provide feedback with sensations of gratification [3-5]. Our senses are essential to capture the enjoyment of a meal [6], as well as the emotive dimensions of love, comfort, security, and reward [1].

For healthy individuals, the ability to taste and smell and to consume and appreciate food is taken for granted and the psychosocial aspects of food enjoyment are not consciously registered. By contrast, patients with advanced malignant disease are affected by many barriers to food intake, of which one key problem is distortion of taste and smell [7-12]. The abnormalities described by these patients encompass phantom smells, persistent bad tastes, hypersensitivity to odours and elements of food flavour [7, 10], and food aversions to the point of nausea [13]. Some evidence is available to suggest that these changes, where severe, substantially limit food intake [11, 13-16] and, not surprisingly, self-perceived quality of life (QOL) [10-12].

Taste and smell disorders of advanced cancer patients are generally neglected by healthy people who are unlikely to consider these disorders to be severe handicaps or to have important health consequences [17]. This is unfortunate for the patient trapped in a nightmare of noxious sensations. It is our thesis that the application of sensory science to the identification and palliation of taste and smell disorders will improve nutritional status and QOL for the patient and their family. New research should aim to identify and characterize chemosensory abnormalities, to understand the experience, and to use potential resources to overcome these alterations. The purpose of this article is to highlight the application of sensory science to address chemosensory abnormalities in advanced cancer.

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2.2 Why chemosensory abnormalities should not be ignored

2.2.1 Prevalence and possible causes

Taste and smell abnormalities are reported in 50 - 90% of advanced cancer patients not undergoing active treatment [8, 11, 14, 15] demonstrating that factors other than active therapy are likely to contribute to chemosensory alterations in this population. Factors that may affect chemosensory function are numerous and include micronutrient deficiencies (*e.g.* zinc, vitamin A and niacin) [18-24], medications [10], infections, poor oral hygiene, smoking, dentures [19], dry mouth or sticky saliva [10], nerve damage to head or neck [24], and altering or disrupting the renewal cycle of taste and smell receptors [17]. Cancer patients consistently rate severe taste and smell alterations as a highly distressing problem [7-10]. Nevertheless, taste and smell disorders are left untreated [17], and they are rarely volunteered in oncology consultations [25].

2.2.2 Consequences of chemosensory abnormalities

Chemosensory abnormalities can cause alterations in digestion since salivary and pancreatic flow rates, gastric contractions, and intestinal motility are affected by taste stimuli [26]. Chemosensory disorders can lead to a decreased appreciation of food [27] and cancer patients commonly complain that food tastes metallic, bitter, distorted or bland, and that smells are unpleasant or different [7, 10]. Food avoidance [12, 28], altered food choices, and lower food intake ensue [11, 17]. Food odours commonly cause food aversions and can induce nausea [13]. Patients with chemosensory abnormalities consume substantially fewer calories (*i.e.* 900 to 1000 kcal/day [11]) with an almost total aversion to food in some individuals. High rates of weight loss are associated with severe chemosensory changes [11, 13-16].

In addition to their effects on food intake, chemosensory distortions can induce stress, depression, and anxiety [17], all of which contribute to a poor QOL for both patients [10-12] and caregivers [29]. The inability to participate in a meal or special occasion because the smell of the food makes a patient physically ill can be very upsetting. A caregiver may become frustrated after spending hours preparing a previously favourite dish, only to have the meal rejected [9, 30]. Often the effects of chemosensory abnormalities on food intake lead to misunderstandings that can create conflict between the patient and caregiver.

In many settings appetite stimulants, such as glucocorticoids or progestational agents (*e.g.* megestrol acetate) [23, 31-33] are prescribed to improve dietary intake. However, these appetite stimulants are effective for less than 30% of advanced cancer patients [34]. Could the low success rates of appetite stimulants be attributed in part to chemosensory abnormalities which may over-ride their effects? If these drugs are unable to reduce or abolish the chemosensory problem, using these drugs is futile and comes with an economic and potential side-effect cost.

2.3 Addressing the problem

2.3.1 Identifying and categorizing taste and smell abnormalities

Initially, it is necessary to identify the presence of chemosensory abnormality within the overall profile of nutrition impact symptoms that the patient is experiencing. Validated

instruments for the screening of cancer patients, (*e.g.* Patient Generated Subjective Global Assessment [35]) normally include a checklist of symptoms affecting food intake including “things taste funny or have no taste” and “smells bother me”. These are useful tools for detecting the possible presence of chemosensory abnormality, which can subsequently be evaluated in more depth by a number of more detailed questionnaires [16, 36]. More thorough examinations include clinical objective measures, such as threshold testing (*e.g.* basic taste modalities [37] and n-butanol odour detection [38]) or smell identification tests [39], that can provide detailed evaluations of taste and smell capabilities and clarify the identity of chemosensory distortions, as patients may have difficulties discriminating between changes in taste versus smell [40]. Qualitative approaches, such as interviews, supplement objective measures and provide an understanding of the overall experience (*i.e.* when the abnormalities occur, how they are affecting the patients, and how the patients adapt to them, in order to identify if and how to overcome these disturbances). Comprehensive testing including both objective and qualitative measures is essential in generating effective clinical strategies to manage abnormal chemosensation. Sensory science provides us with a range of validated tools for this purpose [16, 36-39].

2.3.2 Possible interventions

Treatment of chemosensory abnormalities can take two approaches that are complementary. It may be possible on the one hand to retrieve normal chemosensation and on the other hand the elements of the diet and their presentation may be adapted to match the individual’s unique taste and smell perceptions. In practice, neither of these approaches are applied, and at best patients may receive suggestions to eat cold foods to avoid nausea-inducing food odours, to use mouthwash or plastic utensils to decrease the metallic taste, or to chew on a candy to increase the salivary flow rate [41, 42]. These strategies are limited and their efficacy to manage the sensory experience and improve dietary intake has not been demonstrated.

Several interventions require investigation regarding their potential efficacy to correct chemosensory abnormalities. Chemosensory problems are a well known consequence of certain chronic nutritional deficiencies, and dietary supplementation with vitamin A [18], copper, nickel [19], zinc [20, 21], niacin [22, 23], or iron [24] may improve taste and smell abilities, but empirical proof is lacking for cancer patient populations.

Drugs that have the potential to alter perception directly also merit further clinical trials to determine their effectiveness. For instance, cannabinoids (*e.g.* Marinol® and marijuana) have the potential to not only stimulate appetite [43-46], but also improve the taste of food through the endocannabinoid –mediated reward pathway [47, 48]. Thus, these agents should be investigated for their ability to increase both food intake and food enjoyment.

The perception of food through taste and smell is unique for each person, and the usual activities of many sensory scientists consist of the optimization of the chemosensory features of a food to a target consumer population. This discipline has simply never, to our knowledge, been applied to the unique chemosensory profiles of patients affected by cancer. Once chemosensory abnormalities are more fully understood, food products catering to food related desires and aversions can be developed. Developing a variety of nutrient dense foods that differ in flavour, texture, or appearance would overcome sensory specific satiety [41, 49] and better satisfy the heterogeneous food preferences and

aversions experienced by patients with cancer. It has been suggested that in some instances dietary advice may be more beneficial than supplements for increasing caloric intake and improving QOL [50]. We argue that both dietary change and supplementation need to be applied within the context of the sensory experience to successfully increase intake and enhance food enjoyment [51, 52]. In essence, taste and smell alterations must be identified and investigated before they can be properly managed through dietary strategies.

2.4 Making it work

We know that chemosensory abnormalities are distressing and detrimental to nutritional status, but would treating these abnormalities make a difference in the advanced cancer population? There is some record of success in other patient groups. In elderly people, where loss of taste or smell is a problem, adding spices, herbs, or flavour enhancers (such as monosodium-glutamate and simulated food flavours) to foods may increase caloric intake [51]. Where heightened taste sensitivity is a problem, a possible intervention is the use of masking agents to block sour and bitter flavours [52]. Schiffman *et al* [51, 52] demonstrated that the sensory enhancement of food results in increased appetite and dietary intake, and improved grip strength and immune function in elderly subjects. We speculate that interventions that cater to the unique chemosensory symptomology of advanced cancer patients will also have the potential to improve dietary intake and nutritional status and reinstate the pleasure of eating.

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Chapter 3

Self-assessed taste and smell alterations in adults with advanced cancer[3]

3.1 Introduction

Chemosensory alterations are common and distressing among cancer patients [1-4]. Both increased and decreased clinical thresholds have been reported for basic tastes (bitter, sweet, and sour) [5-9]. It is unclear whether this lack of consensus between studies is due to different techniques (*i.e.* the previously popular Henkin-3-drop stimulus method versus the currently accepted whole-mouth stimulus method) or due to other sources such as tumour type [10]. Odour threshold alterations in cancer have been infrequently studied, but higher odour thresholds have been observed in females with estrogen receptor positive breast cancer [11].

Taste and smell disorders are usually diagnosed using clinical evaluation of the molar concentrations of odorants (or tastants) an individual is able to detect or recognize. Threshold tests generate objective data against which deviations from normal perception can be tested. The majority of chemosensory disorders diagnosed with clinical testing are characterized as a loss of sensation (*e.g.* in the elderly, head trauma patients, Alzheimer's disease, disorders of the endocrine and nervous system, and malnutrition [12-15]), with a few conditions being associated with a heightened sensation, most often a heightened sense of smell. For conditions where a heightened sensation is experienced, such as pregnancy, adrenocortical insufficiency (Addison's disease), epilepsy, and multiple chemical intolerances, lower odour or taste thresholds have been observed [12-15].

Chemosensory function as measured by concentration thresholds is not the sole dictator of ingestive behaviour, rather sensory perception encompasses more complex concepts (*i.e.* flavour). For this reason, sensory evaluation is also informed by approaches involving questions that reveal these complex facets [2-4, 16-20]. It has been suggested that measuring perceived chemosensory alterations rather than clinical taste and smell thresholds may prove to be more effective in determining the influence of these alterations on food intake [2, 4]. In an earlier study with an advanced cancer population, we used a survey tool to evaluate self-perceived chemosensory alterations [16]. We noted that those subjects who perceived their chemosensory alterations to be severe had the lowest caloric intakes and poorest QOL. We also noted that subjects perceived bitter and sour tastes to be stronger more often than weaker, however our sample size limited further investigation into these perceived differences in intensities.

Olfaction and gustation contribute to the incentive and motivation to eat [21]. Chemosensory alterations can affect food intake and related quality of life (QOL). The nutritional consequences of aberrant chemosensation is unclear; a loss of sensation has been associated with both decreased and increased food intake, and a heightened or distorted chemosensory experience has been associated with a decrease in food intake and food aversions [22, 23].

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Describing chemosensory perception may help to explain food intake behaviours and further our understanding of the physiology of these alterations. As it is unclear whether individuals with cancer primarily experience heightened or reduced chemosensation, our goal was to determine the nature (intensity) of chemosensory alterations and their relationship with ingestive behaviour. The specific objectives were to investigate a) perceived chemosensory complaints among adults with advanced cancer using a taste and smell questionnaire designed to capture changes since the onset of their illness, b) how these perceived alterations relate to the quantity and quality of foods consumed, and c) the relationship between aberrant chemosensory perceptions and well-being using a QOL questionnaire.

3.2 Materials and Methods

3.2.1 Subjects

Adults with advanced cancer (defined as locally recurrent, locally advanced, or metastatic, n=192) were recruited from either the palliative home care program or outpatient clinics at the local cancer clinic in Edmonton, Alberta, Canada over a 5 year period (2003-2008, Table 1.1). Subjects were ineligible if they could not consume food orally or were receiving radiation therapy to the head/neck area. The majority of subjects (68%) had ended active treatment (*i.e.* chemotherapy) for reasons of progressive disease for at least 2 weeks prior to data collection; the remaining 32% were receiving active therapy and continuing progress of chemotherapy cycles for their tumor type at the time of data collection. Subjects were living at home and were assumed to make their own food choices based on personal preference. The majority of subjects (n=133) answered questions regarding factors known to impact their chemosensory perception: 5% had been previously diagnosed with a taste and smell problem; less than 20% were currently bothered by hay fever, allergies, or sinusitis; 63% were former or current smokers; and 56% wore dentures. All subjects spoke English and provided informed consent. The study was approved by the Research Ethics Board of the Alberta Cancer Board.

3.2.2 Methods

Subjects completed questionnaires that have been previously used with the advanced cancer population by this research group to evaluate self-assessed taste and smell perception since the onset of cancer, nutrient intake, nausea, and quality of life. These questionnaires included a validated Taste and Smell questionnaire [24], a 3-day dietary record [25], the Edmonton Symptom Assessment Scale (ESAS) [26], and the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire [27]. Self-reported percent weight loss over the 6 months preceding participation in the study was also recorded.

3.2.2.1 Perceived chemosensory intensity groups

Five questions within the Taste and Smell Survey discriminate changes in perceived intensity for the 4 basic tastes (salty, sweet, sour, bitter) and sense of smell; *e.g. comparing my sense of taste now to the way it was before I was diagnosed with cancer: salt tastes a) stronger; b) as strong; c) weaker; or d) I cannot taste it at all*. Based on the answers to these questions, subjects were stratified into 4 perceived chemosensory

intensity groups: *no change*, *stronger*, *weaker*, and *mixed*. Subjects who perceived at least one sensation to be 'stronger' were labeled as *stronger*, subjects who perceived at least one sensation to be 'weaker' or 'cannot perceive at all' were labelled as *weaker*, and subjects who perceived all intensities to be 'as strong' compared to pre-diagnosis were labelled as *no change*. As there were 5 questions, it was possible for subjects to perceive some tastes/smell to be 'stronger' while others to be 'weaker/cannot perceive at all', these individuals were labelled *mixed*. The *no change* group served as the control group to which all comparisons were made; this approach permitted comparisons to be made within a population of patients with similar demographic and clinical features.

3.2.2.2 Chemosensory complaint scores

The Taste and Smell Survey [24] consists of 8 questions related to taste and 6 questions pertaining to smell. Briefly, to score the survey, a point was awarded for each complaint; for two of the questions 2-points were earned if the complaint was *severe* or *incapacitating*. The overall chemosensory complaint score was the combined score from taste and smell sections. Scores ranged from 0-16, with 0 indicating no chemosensory change and 16 indicating the greatest number and severity of changes. Subjects were stratified based on their chemosensory complaint score: 0-1 *insignificant*, 2-4 *mild*, 5-9 *moderate* and 10-16 *severe* [16]. The *insignificant* chemosensory change group served as the control group to which all comparisons were made.

3.2.2.3 Open-ended survey questions

The Taste and Smell Survey also included open-ended questions for subjects to elaborate on their chemosensory change(s) since the onset of cancer and how these changes have affected the subjects' QOL: *Have you noticed any changes in your sense of taste/ smell? Have you ever noticed that a food tastes/smells different than it used to? How has your abnormal smell/taste affected your QOL?* Where subjects answered yes, they were prompted to elaborate. The comments to these 6 open-ended questions were reviewed and categorized based on common themes.

3.2.2.4 Nutrient intake, nausea, and quality of life

Subjects completed a 3-day dietary record; this method has been shown to provide a valid and reliable estimate of an individual's usual daily intake [25, 28, 29]. To further validate the dietary data, 38 subjects completed a 24-hr urine collection during one day of their 3-day food record. Twenty-four hour urine nitrogen is a biological marker used to determine the amount of protein consumed [30]. The 24-hr urine nitrogen analysis has been tried in the cancer population and was found to effectively validate dietary records [31]. Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR) was used to analyze caloric intake and macronutrient composition of the diet from the food records.

Heightened chemosensory perceptions might be in part due to nausea. Odours can trigger nausea [32] and thus may be perceived as heightened in intensity. The same may be true for tastes if a conditioned taste aversion occurs (*i.e.* a gastro-intestinal disturbance following the ingestion of a specific food) [33]. Consequently, the validated Edmonton Symptom Assessment Scale (ESAS) [26] was used to assess nausea. Subjects rated

nausea on an 11-point scale where 0=no nausea and 10=worst possible nausea. Nausea scores $\geq$4 were considered clinically significant [34].

To evaluate QOL, the validated Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire [27] was used. The FAACT questionnaire consisted of 40 questions, assessing 5 domains of QOL: physical; functional; social/family; emotional well-being; and nutritional QOL (extent of anorexia/cachexia). Responses were evaluated on a 5-point Likert-type scale (0=not at all and 4=very much) and an individual score was obtained for each of the 5 QOL domains. Global QOL scores were calculated by summing the scores from the 5 QOL domains, with higher scores indicating better QOL.

3.2.3 Data analysis

All statistical analyses were performed in Statistical Analysis System (SAS) [35]. Descriptive statistics were used to describe the prevalence, nature, and severity of chemosensory complaints. Data did not meet assumptions of normality and thus non-parametric statistical techniques were used.

Subjects were stratified for analyses 3 different ways. Firstly, they were stratified for analyses into 4 perceived overall chemosensory intensity groups (*weaker, stronger, no change, mixed*) based on responses to 5 chemosensory intensity questions described above. Secondly, subjects were stratified by perceived chemosensory intensity for each individual basic taste and sense of smell. Finally, subjects were stratified into 4 chemosensory complaint groups based on the total score of the taste and smell survey (*insignificant, mild, moderate, severe*) for further analyses [16]. From results of the 3-day dietary record, individual food items were grouped into 1 of 20 pre-defined food categories, based on macronutrient composition and culinary role [36]. The 20 food groups were *butter, margarine, fats; beans; cereals; cheese; dark bread; desserts; egg; fruit; ice cream; milk; nut; pasta; potato; meats; salty snacks; soups; nutritional supplement drinks; vegetables; white bread;* and *other* [36]. The term *food choice* will be used to describe the proportion of total intake (energy and protein) contributed by the individual 20 food groups.

The Wilcoxon's rank-sum test procedure was used to compare nutrient intake, food groups, quality of life scores, nausea scores, and demographics among the chemosensory intensity groups and chemosensory complaint groups. All comparisons were pre-planned in attempt to reduce Type I error. Chi-square or Fischer exact test were used to determine differences in frequency distributions of nausea scores and still receiving chemotherapy treatment (*yes, no*) among perceived chemosensory intensity groups and among chemosensory complaint groups. Logistic regression was used to predict energy intake and global QOL scores from age, chemosensory complaint scores, months to death, nausea scores, and gender. Dependent variables (*i.e.* energy intake and QOL scores) were dichotomized into *high* and *low* using their median values as the breakpoint as the median provided the model of best fit (compared to mean values). Standard model building technique and goodness of fit statistic, Akaike's information criterion **(**AIC), were used to determine the model of best fit.

3.3 Results

3.3.1 Perceived chemosensory intensity, nutrition impact factors, and QOL

For the individual sensations of bitter, sour, sweet, and salty tastes and sense of smell, the greatest number of subjects were affected by stronger sensation (Figure 3.1). A very small proportion (<5%) could not perceive one or more sensations at all; these subjects were grouped with the weaker perception group in subsequent analyses.

Subjects experienced either a) no alteration in any of the 5 sensations (26% of subjects), b) stronger sensation overall (42%), c) weaker sensation overall (18%), or d) mixed sensation (14%) (Table 3.2). Energy intakes were approximately 430 kilocalories (kcal)/day lower for the 3 altered chemosensory intensity groups (*weaker*, *stronger*, and *mixed*) compared to subjects who did not perceive a change in chemosensory intensity (*no change*). Weight loss was greater in the *weaker* and *mixed* chemosensory intensity groups compared to the *no change* group and there was a trend for the *stronger* group to also have higher weight loss compared to the *no change* group (p=0.0605, Table 3.2). Weight loss appeared to be more severe in the *mixed* group compared to the *stronger* intensity group.

Subjects with chemosensory intensity change had poorer global QOL (FAACT scores), physical well-being, and anorexia-cachexia-related nutritional well-being compared to those who did not perceive chemosensory changes. Chemosensory intensity was not related to tumour type (p=0.1760) or gender (p=0.1867) or to the distribution of subjects still receiving chemotherapy treatment (p= 0.4356). Subjects in the *mixed* and *stronger* chemosensory intensity groups were closer to death compared to subjects who perceived no change in chemosensation (p=0.0021), but there were no differences in survival between the *stronger*, *weaker*, and *mixed* intensity groups.

Subjects were stratified by perceived chemosensory intensity for each individual basic taste and sense of smell (Table 3.3). Subjects who perceived sour taste or smells to have changed in intensity since the onset of their cancer had lower energy intakes compared to subjects who perceived no change. There were no differences in food choice among intensity groups when subdivided based on basic tastes and smell (data not shown). In general, subjects who perceived chemosensations to be stronger were younger compared to subjects who perceived no change in chemosensory intensities.

3.3.2 Chemosensory complaints, nutrition impact factors, and QOL

Total chemosensory complaint scores from the Taste and Smell Survey ranged from 0 to 14 out of a possible 16. A total of 171 subjects (89%) reported some chemosensory alteration involving at least one and often several of the 5 sensations. About 60% had both a taste and smell complaint, 26% had only taste complaints, while 3% had only smell complaints.

Subjects were grouped by total chemosensory complaint score (Table 3.4). Energy and protein intakes decreased as chemosensory complaints increased. Subjects who perceived *severe* chemosensory changes ingested 680 kcal/day less than subjects who perceived no change in chemosensation. Not surprisingly, weight loss increased with the severity of chemosensory complaints with subjects in the *moderate* and *severe* chemosensory complaint groups experiencing the highest rates of weight loss. Moreover, subjects in the

severe and *moderate* chemosensory complaint categories received a greater proportion (6-11%) of their daily calories from nutritional supplement drinks, such as Ensure™ or Boost ™ compared to subjects in the *insignificant* chemosensory complaint category. However, this increase in nutritional supplements did not seem to detract from one specific macronutrient or food group.

Lower QOL scores were associated with higher chemosensory complaint scores for all QOL domains, except social/family well-being. QOL scores declined linearly with increasing chemosensory complaints for global QOL, physical well-being and anorexia-cachexia-nutrition related well-being. Survival decreased with increasing severity of chemosensory complaints. There were no differences among the 4 chemosensory complaint groups for tumour type ($p=0.8840$) or gender ($p=0.2860$) or in the distribution of subjects still receiving chemotherapy treatment ($p= 0.2141$).

From logistic regression analyses, age and chemosensory complaint scores were significant predictors of energy intake (Table 3.5). Gender and months to death were not able to predict the model and therefore were removed. For a one year increase in age the odds of having an energy intake of < 1820 kcal/day increased by 6% and for a one point increase in chemosensory complaint score the odds of having low energy intake increased by 13%. Only chemosensory complaint scores were significant predictors of global QOL. For a one point increase in chemosensory complaint score, the odds of having a global QOL score < 105 increased by 20%. Age and gender were not able to predict the model and therefore were removed.

3.3.3 Nausea scores

Based on the 11-point ESAS nausea score, at least 70% of subjects had no nausea (score of 0), 20% had negligible nausea (score of 1-3) and approximately 10% had clinically significant nausea (score of ≥ 4). The overall frequency of significant nausea scores ≥ 4 (11%) was very limited in this population in spite of a higher frequency (57%) of moderate or severe chemosensory dysfunction. These symptoms were not necessarily concurrent nor were they highly related; only 13% of subjects with moderate or severe chemosensory dysfunction also had nausea.

The mean ($\pm$ SD) chemosensory complaint score for subjects with nausea scores ≥ 4 was 8.4 ± 3.8 versus 5.6 ± 4.1 for subjects with nausea scores <4 ($p=0.007$). Of those with nausea scores ≥ 4, the majority (71%) perceived chemosensations to be stronger.

3.3.4 Reported protein intake and urinary nitrogen analyses

Of the 38 subjects who completed a 24-hr urine collection during their food record, half showed reported protein intakes (on food records) to be within ~10g of the estimated protein intake from urinary nitrogen analysis (range $\pm$ 0.21 to $\pm$ 11.13g protein). Reported protein intakes outside this 10g range were not consistently higher or lower compared to estimated protein intakes. Therefore, no systematic over or under-reporting is apparent in this advanced cancer population.

3.3.5 Response to open-ended survey questions

The Taste and Smell Survey included 6 open-ended questions prompting subjects to describe their chemosensory alterations; 149 subjects (78%) provided comments. Of those who did not comment, 70% had an *insignificant* chemosensory complaint score. Overall, perceived changes in taste were more distressing and highly related to QOL compared to changes in smell, which were often said to be non-significant. Comments described 3 themes of chemosensory changes; weaker chemosensation, stronger chemosensation, and chemosensory distortion.

A weaker sense of taste was described by subjects as food tasting *blah, like cardboard, bland,* or *tasteless*. Subjects complained that they became bored with food as *everything tasted the same*. Some subjects had *difficulty differentiating foods or flavours,* suggesting a loss of smell in addition to taste. In general, a loss of smell seemed to be less distressing and was sometimes attributed to age or chemical exposure.

A stronger sense of taste was described as increased sensitivities to the 4 basic tastes, with equal numbers of complaints for each. Heightened odours of perfume, cologne, and food were said to be *too strong* and cooking odours were *offensive.* Increased sensation was sometimes described as *nauseating* (especially odours) and related to aversions and changes in food preferences. However, some subjects appreciated the increase in sensation as smells were *more acute* and some foods *more flavourful*.

Regarding distorted perception, subjects complained of *foods tasting* or *smelling "off"* or *different* from what they remembered. Subjects commonly complained that everything tasted of one specific taste, such as *medicinal, woody, acidic, sweet, bitter, sour, salty, metallic,* or *burnt.* Some subjects perceived phantom odours, or complained of a persistent taste in their mouth. The most common persistent tastes were *bitter, sour, salty, metallic, sweet, dull* or *old*. Several subjects could not identify the persistent taste.

Subjects often complained of food tasting good one day and unpleasant or even nauseating the next; *one day something is appealing and tastes good, the next day I can't look at it*; the same was true for odours – *some days odours are offensive, some days they are ok*. These experiences were said to be *distressing*, *annoying*, and *irritating*, determining the subjects' food intake. It appears that patients sometimes experience hedonic (preference) changes and describe these as perceived chemosensory changes when responding on questionnaires.

Consequences of perceived chemosensory alterations that were most commonly mentioned were *loss of appetite, changes in food preference* and *food choice, decrease in food appeal* and *food enjoyment,* all of which led to a decreased food intake: *so many things I used to enjoy, I can't enjoy anymore.* Subjects stated that they had *no desire to eat*, and that they had to force themselves to eat: *I eat because I have to, not because I want to.* Subjects also reported *weight loss, fatigue,* and *weakness* due to inadequate food intake. Food preparation was also difficult and some subjects complained that *cooking no longer appealed* to them and for some was no longer possible. These consequences appeared to be more bothersome when chemosensory perceptions were either heightened or distorted. Foods that were commonly avoided or said to taste differently were (in order of prevalence): *meats (12%), acidic foods (especially tomatoes) (7%), fruits and vegetables (6%), coffee (5%), potatoes (3%), alcoholic beverages (3%), pickles (2%), and milk products (2%).*

Perceived chemosensory alterations were related to several aspects of QOL. For instance, subjects complained that they *could not smell flowers*, or alternatively, that body or pet odours were so *repulsive* that the subjects avoided crowds: *I stay at home because smells make me nauseous*. One woman was forced to give up her cat due to the intolerable smell of the litter box. Subjects also commented on the social impact from chemosensory alterations. Subjects stated that they could not enjoy or even attend meals with family and friends: *I do not enjoy eating or going to restaurants.* Some individuals were embarrassed because food made them *gag* or *vomit* and this was unpredictable.

3.4 Discussion

We explored the nature of self-perceived chemosensory alterations and their association with food intake behaviour and QOL of life in advanced cancer. The majority of subjects perceived chemosensory alteration, most often involving both taste and smell. A total of 143 subjects (74%) perceived a change in intensity for at least 1 basic taste or sense of smell, of which the greatest number (42%) perceived a heightened sensation, 18% perceived a loss of sensation and 14% perceived mixed changes. The distinctions of these 3 groups (stronger, weaker, and mixed chemosensory perceptions) were also supported by subjects' comments. The 3 altered chemosensory intensity groups had lower caloric intake, increased weight loss, and poorer QOL compared to subjects without chemosensory alterations. Even though subjects more often perceived sensations to be stronger rather than weaker, there were no differences amongst the 3 altered chemosensory groups (*i.e. stronger, weaker, and mixed*) for food intake behaviour or QOL. However, subjects' comments suggest that stronger chemosensory perception was more distressing than a loss of sensation, especially a stronger sense of smell. Odours were said to be *repulsive* and *offensive*, leading to food aversions and affecting not only food enjoyment but also emotional and social aspects of QOL, as suggested previously [1, 2, 4].

Our research relied heavily on patient – reported outcomes. The self-reported chemosensory alteration questionnaire captured perceived changes since the onset of disease and the open-ended questions further clarified the experience. Repeated assessment by the questionnaire over time would be needed to detect oscillations in chemosensory alterations, however the comments allowed for any daily variations in chemosensory experience to be expressed. The comments suggest the nature of chemosensory alterations was consistent over time, but hedonic changes could oscillate daily. The accuracy of food records has been questioned as under-reporting is common especially in obese populations [37-39]. However, it is unknown if populations that have lower caloric intake, such as advanced cancer also misreport. Bruera *et al* [28] demonstrated 24hr food records to correlate with actual protein and caloric intakes among advanced cancer patients. We noted no systematic higher or lower reported protein intakes compared to estimated intakes, suggesting no consistent over or under-reporting on food records.

Nausea has previously been associated with taste and smell alterations [4, 40]. We chose to assess nausea with an 11-pt scale as this is common in clinical practice and has low participant burden. However, the scale assesses acute nausea, potentially missing bouts of nausea experienced by the subject. Our objective was to determine if chemosensory alterations exist in the absence of nausea, and from our results this appears to be the case as so few subjects were currently experiencing nausea compared to the majority experiencing chemosensory alterations. Still repeated measures of nausea are needed to clearly depict its influence on perceived taste and smell alterations.

It is notable that more subjects were experiencing stronger chemosensory perception, rather than the expected loss of chemosensation due to anti-cancer therapies or ageing [40, 41]. Chemotherapy and radiation therapy can destroy taste buds and olfactory receptors, alter the cell renewal process, and modify receptor cells [40, 41]. Radiation to the head or neck area can damage the mucosa and salivary glands, all of which can cause a loss of chemosensation. However none of our subjects were receiving radiation to the head or neck area and close to 70% of subjects had ended active treatments (*i.e.* chemotherapy) at least 2 weeks prior to data collection. Moreover, there were no differences in the distribution of subjects receiving chemotherapy among perceived chemosensory intensity groups or chemosensory complaint groups, suggesting that acute chemotherapy was not associated with chemosensory disorders. Rather, it appears that chemosensory alterations persist well after chemotherapy treatments have ended. By 60 years of age, taste and smell noticeably decline and these losses are severe at age 70 [42]. An age-related sensory loss might be expected in this study, given that the mean age of the population was 64 years. However, subjects with weaker chemosensory perception showed no particular relationship with age. The only age-related outcome was the association of stronger sensations with younger subjects, for which the reasons are unclear. Stronger chemosensations have been reported to be more distressing for younger healthy subjects [23]. For older individuals, a heightened sensation might balance their age-related loss of chemosensation and go unnoticed or create a positive experience. Some subjects reported that stronger sensations were pleasurable, as smells were *more acute* and some foods *more flavourful*, which could suggest the correction of an age-related loss with a heightened sensation.

Berteretche *et al* [43] speculated that after anti-cancer treatments, many cells renew simultaneously, which may cause misconnection of taste cells with nerve fibres due to the sudden renewal of a high proportion of taste cells. Misconnections to nerve fibres may persist despite taste cell turn-over, leading to chronic taste and smell alterations. As most of our subjects were no longer receiving anti-cancer treatments at the time of data collection, such a neurological problem leading to changes in chemosensory perception is plausible. Bartoshuk [44] described the perception of altered chemosensations in cancer as a hedonic change, suggesting that for subjects with cancer, a tuna salad still tasted like tuna, but no longer tasted “good”. Many of our subjects made comments about food not tasting good or not being enjoyable, alluding to hedonic changes. It is plausible that both neurological and hedonic changes contributed to the perceived chemosensory alterations reported by our subjects. Future research should aim to clarify the role of chemosensory alterations and food preference changes in the self-reported chemosensory changes described by subjects with advanced cancer.

Although more subjects perceived sensations to be stronger rather than weaker, the influence of these alterations on caloric intake was identical. Food choice did not associate clearly with self-assessed chemosensory function. Although 27% of subjects perceived sweet tastes to be stronger, these subjects did not appear to avoid sweet foods, as there were no significant differences for any of the 20 food groups, including desserts, among chemosensory intensity groups. Similarly, subjects who perceived bitter tastes to be stronger (19%) did not appear to avoid meats or protein rich foods. Few people reported the avoidance of specific foods in the open-ended survey questions and no food was avoided by more than 12% of the 149 subjects who provided comments. Previous studies have reported that approximately 25% of cancer patients avoid meats and protein rich foods because they are perceived as too bitter [6, 17], but our analyses do not concur. These previous studies did not include a dietary record and thus did not capture the actual

foods selected for consumption. In this study, only nutritional supplement drinks differed significantly in % of daily calorie consumption and this was associated with higher overall chemosensory complaint score, but not the nature of the complaint per se. It appears that the number of chemosensory complaints influences food choice to a greater degree than the nature (intensity) of these complaints. As such, the original scoring of the Taste and Smell Survey [24] which allots a point per complaint regardless of the intensity (*i.e.* weak or strong) correctly associates chemosensory complaint scores with total caloric intake and QOL.

As food intake is regulated by both appetite and reward systems [21], it follows that subjects who perceived taste and smell to be altered may eat less due to low food enjoyment. In the open ended responses, subjects often stated that they had no desire to eat and food was no longer enjoyable. This parallels the findings of Shragge *et al* [45], where subjects felt compelled to eat for survival, not pleasure. Poor QOL was associated with chemosensory alterations, especially physical and nutritional well-being, which is in agreement with previous studies [2, 17, 46]. Other aspects of QOL, such as socializing, were reported by some subjects to be severely impacted by chemosensory alterations. However, social/family well-being scores on the FAACT QOL questionnaire were not different among perceived chemosensory complaint groups suggesting that either the questionnaire is insensitive to changes in social aspects of eating or the changes in social eating were not experienced by the majority of patients with perceived chemosensory alterations.

It is not possible from our data to determine if chemosensory alterations are the cause of poor nutritional status and QOL or if chemosensory alterations are part of a symptom cluster associated with poor nutritional and health status. Strasser *et al* [47] noted taste changes to cluster with anorexia, early satiety, and weight loss. Recent qualitative data reported perceived chemosensory alterations to both influence and to be influenced by other symptoms, such as appetite loss, early satiety, nausea, and oral problems [4]. Results from our logistic regression demonstrate chemosensory alterations to be predictors of QOL and caloric intake, further confirming an association between chemosensory alterations and poor nutritional status and QOL exists.

Several medications have been shown to influence chemosensory perceptions [42, 48, 49]. We did not investigate the influence of concurrent medications as this information was not always available (*e.g.* medications prescribed by the family physician or non-prescription medications) and the list of known medications was often extensive due to co-morbid conditions and varied greatly among subjects. Thus an investigation of the influence of concurrent medications would be interesting, but beyond the scope of this paper. We acknowledge that medications such as non-steroidal anti-inflammatory drugs, ACE inhibitors, antibiotics, and opiates are associated with a loss of chemosensation [41, 50]. Further research is needed to determine the influence of concurrent medications on taste and smell alterations in cancer.

In summary, both stronger and weaker chemosensory perceptions for the four basic tastes and sense of smell were observed, with the greatest number of subjects perceiving chemosensation to be stronger as compared to before the onset of cancer. It appears that the nature of chemosensory alterations is not as influential on food intake behaviour as the number and severity of perceived alterations. Severe chemosensory alterations were associated with lower caloric intakes, higher weight loss, and poorer QOL. The self-assessment tool which allowed subjects to describe their chemosensory alterations as well as their influence on food choice and QOL was useful for capturing all aspects of food

intake behaviour. Future research should determine if the perceived chemosensory alterations are altered detection capabilities, a neurological disorder, or hedonic changes. Once this is understood, determining the cause and identifying potential treatments for chemosensory alterations in cancer may be feasible.

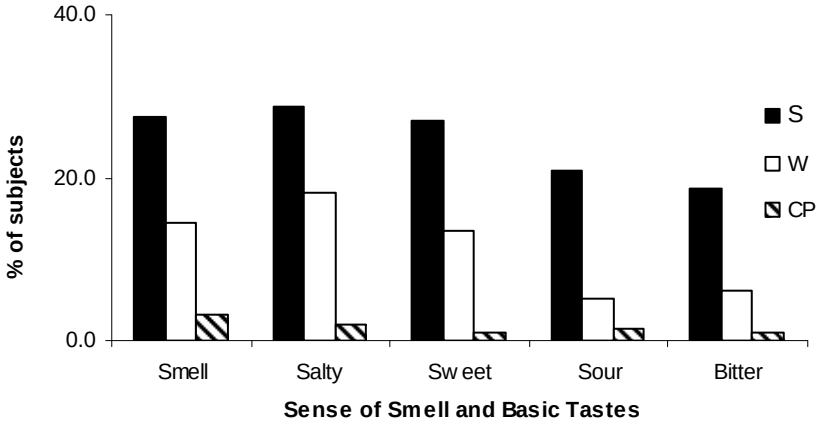

Figure 3.1. Frequencies of intensity ratings of individual sensations expressed as a % of the study population. A greater proportion of subjects described their perception of the individual 4 basic tastes and sense of smell to be stronger rather than weaker (Salty ($p=0.0350$) Sweet ($p=0.0032$) Sour ($p<0.0001$) Bitter ($p=0.0005$) Smell ($p=0.0055$)). S = stronger; W = weaker; CP = can't perceive.

Table 3.1 Characteristics of study population

Study Population	**N=192**
Male [n (%)]	97 (51)
Age (y) [mean ± SD]	64.3 ± 12.4
Mean survival (months) [mean ± SD]	8.6 ± 8.6
Cancer Diagnosis [n (%)]	
Lung	48 (25)
Breast	36 (19)
Genitourinary (*including bladder, renal, female genital: vaginal, ovarian, peritoneal, cervical, and male genital: testicular, prostate*)	27 (14)
Gastrointestinal *(including liver, pancreas, colorectal, stomach, esophageal)*	62 (32)
Neuroendocrine system/skin/hematologic system *(including melanoma, leukemia, myeloma, neuro-endocrine, lymphoma)*	10 (5)
Other *(including unknown primary)*	9 (5)

Abbreviations: SD=standard deviation

Table 3.2 Nutrition and Quality of Life scores based on 4 perceived chemosensory intensity groups

	Chemosensory Intensity Groups				
	No Change *n = 49*	Stronger *n = 81*	Weaker *n = 35*	Mixed *n = 27*	*p*-value
Energy Intake					
kcal/day	2208 ± 714[a]	1776 ± 721[b]	1770 ± 578[b]	1643± 827[b]	0.0018
kcal/kg BW/day	30.6 ± 10.5[a]	26.1± 11.6[b]	25.7 ± 12.6[b]	25.0 ± 11.8[b]	0.0286
Weight Loss (%)	4.6 ± 7.8[a]	7.9 ± 10.6[ab]	10.2 ± 10.0[bc]	11.7 ± 9.3[c]	0.0036
Age (yrs)	66.6 ± 11.1	62.8± 13.8	65.0± 10.0	64.0± 12.6	0.4035
Quality of Life Subscale (FAACT)					
Global quality of life	115.2 ± 27.7[a]	104.0 ± 25.1[b]	101.3± 25.7[b]	101.5 ± 23.5[b]	0.0176
Physical well-being	21.5 ± 6.0[a]	17.6 ± 6.9[b]	18.0 ± 5.8[b]	17.1 ± 6.3[b]	0.0065
Anorexia-cachexia-related nutritional well-being	37.0 ± 9.0[a]	32.0 ± 9.6[b]	28.4 ± 10.8[b]	28.8 ± 10.0[b]	0.0004

All data are means (± SD). Means in a row with different subscript letters are significantly different, $p < 0.05$.
Abbreviations: kcal, kilocalories; BW, body weight; FAACT, Functional Assessment of Anorexia/Cachexia Therapy

Table 3.3 Energy intake, age, and nausea scores (ESAS) based on subjects' perceived intensity changes since the onset of cancer for the 4 basic tastes and sense of smell

	Perceived intensity changes since the onset of cancer			
	As Strong	**Stronger**	**Weaker**	*p*-value
Salty	***n=98***	***n = 55***	***n=35***	
Energy Intake (kcal/day)	1979 ± 711	1854 ± 825	1658 ± 587	0.0968
Age (yrs)	65.7 ± 12.5	62.6 ± 12.5	63.9 ± 10.9	0.1857
Nausea score	0.7 ± 1.6[a]	1.7 ± 2.7[b]	0.5 ± 1.1[a]	0.0219
Sweet	***n=112***	***n=52***	***n=26***	
Energy Intake (kcal/day)	1941 ± 668	1798 ± 885	1640± 635	0.0787
Age (yrs)	66.6 ± 11.6[a]	59.7 ± 13.4[b]	63.4 ± 10.9[ab]	0.0032
Nausea score	0.6 ± 1.3	1.7 ± 2.9	1.1 ± 1.9	0.0705
Sour	***n=139***	***n=40***	***n=10***	
Energy Intake (kcal/day)	1970 ± 725[a]	1599 ± 738[b]	1399 ± 420[b]	0.0021
Age (yrs)	64.5 ± 12.3	63.7 ± 11.9	62.8 ± 16.3	0.7583
Nausea score	0.8 ± 1.9	1.3 ± 2.3	1.0 ± 1.6	0.3312
Bitter	***n=142***	***n=36***	***n=12***	
Energy Intake (kcal/day)	1892 ± 744	1843 ± 739	1560 ± 554	0.2418
Age (yrs)	65.2 ± 12.1	60.6 ± 13.1	63.9 ± 12.1	0.1486
Nausea score	0.9 ± 2.0	0.9 ± 1.6	0.9 ± 3.0	0.2983
Smell	***n=105***	***n=53***	***n=28***	
Energy Intake (kcal/day)	1986 ± 684[a]	1688 ± 787[b]	1767± 763[b]	0.0241
Age (yrs)	67.0 ± 12.0[a]	58.3 ± 12.7[b]	64.7 ± 9.0[a]	<.0001
Nausea score	0.6 ± 1.2[a]	1.7 ± 2.7[b]	0.9 ± 2.4[ab]	0.0210

All data are means (± SD). Means in a row with different subscript letters are significantly different, $p < 0.05$.
Abbreviations: kcal, kilocalories; ESAS, Edmonton Symptom Assessment Scale

Table 3.4 Nutrition and related indices and QOL scores based on chemosensory complaint groups

	Chemosensory Complaint Group				
	Insignificant	Mild	Moderate	Severe	
	n = 43	*n* = 40	*n* = 66	*n* = 43	*p*-value
Energy Intake					
kcal/day	2239 ± 647 [a]	1903 ± 689 [b]	1802 ± 752 [bc]	1559 ± 691 [c]	0.0002
kcal/kg BW/day	30.3 ± 9.7 [a]	27.1 ± 11.0 [ab]	27.0 ± 11.8 [ab]	23.6 ± 13.2 [b]	0.0184
Protein Intake					
g/day	89 ± 32 [a]	77 ± 31 [b]	72 ± 31 [b]	62 ± 31 [b]	0.0024
g/kg BW/day	1.2 ± 0.4 [a]	1.1 ± 0.5 [ab]	1.1 ± 0.6 [ab]	0.9 ± 0.5 [b]	0.0398
% of daily calories consumed as nutritional supplement drinks	1.5 ± 4.7 [a]	1.7 ± 4.7 [a]	6.1 ± 10.9 [b]	11.3 ± 19.8 [b]	0.0014
Weight Loss (%)	4.3 ± 7.1 [a]	5.5 ± 10.8 [ab]	9.0 ± 9.2 [bc]	12.3 ± 10.4 [c]	0.0012
Age (yrs)	67.4 ± 10.6	65.5 ± 12.5	63.3 ± 13.4	61.8 ± 11.7	0.1002
Nausea scores (ESAS)	0.1 ± 0.3 [a]	0.9 ± 1.6 [b]	0.9 ± 1.6 [b]	1.9 ± 3.1 [b]	0.0156
Months to death	14.4 ± 12 [a]	9.8 ± 8.3 [a]	6.0 ± 5.5 [b]	5.7 ± 6.2 [b]	0.0003
Quality of Life Subscale (FAACT)					
Global quality of life	124.7 ± 20.1 [a]	109.1 ± 23.3 [b]	100.4 ± 27.6 [bc]	92.3 ± 20.7 [c]	<0.0001
Physical well-being	23.6 ± 4.6 [a]	20.4 ± 5.1 [b]	17.0 ± 6.7 [c]	14.4 ± 5.6 [d]	<0.0001
Functional well-being	20.1 ± 6.0 [a]	16.1 ± 6.7 [b]	15.7 ± 6.9 [b]	13.8 ± 5.0 [b]	0.0001
Social/family well-being	22.3 ± 5.5	22.1 ± 4.7	22.3 ± 5.1	21.3 ± 5.0	0.5382
Emotional well-being	18.9 ± 3.7 [a]	16.9 ± 4.8 [ab]	15.9 ± 5.5 [b]	16.5 ± 4.7 [b]	0.0232
Anorexia-cachexia-related nutritional well-being	39.8 ± 6.5 [a]	34.3 ± 7.7 [b]	29.8 ± 10.8 [b]	26.1 ± 9.2 [c]	<0.0001

All data are means (± SD). Means in a row with different subscript letters are significantly different, p< 0.05.
Abbreviations: kcal, kilocalories; BW, body weight; ESAS, Edmonton Symptom Assessment Scale FAACT, Functional Assessment of Anorexia/Cachexia Therapy

Table 3.5 Logistic regression to predict energy intake and global quality of life scores of advanced cancer patients

Dependent Variable	Parameter	Estimate	SE	Wald Chi-square	P>Chi-square
Energy Intake (Kcal/day)	Intercept	-4.51	1.18	14.62	0.0001
	Age (yrs)	0.06	0.02	12.57	0.0004
	Chemosensory complaint score	0.12	0.05	6.10	0.014
	Nausea scores (ESAS)	0.09	0.10	0.93	0.335
Global quality of life (FAACT)	Intercept	-0.53	0.54	0.96	0.328
	Chemosensory complaint score	0.18	0.07	7.64	0.006
	Months to death	-0.05	0.04	1.59	0.207
	Nausea scores (ESAS)	0.28	0.16	3.07	0.101

Results are based on low energy intake (< 1820kcal/day) and low global quality of life scores (<105). Abbreviations: kcal, kilocalories; ESAS, Edmonton Symptom Assessment Scale FAACT, Functional Assessment of Anorexia/Cachexia Therapy

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Chapter 4

Delta-9-tetrahydrocannabinol may be useful to palliate altered chemosensory perception and improve food enjoyment for cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial[4]

4.1 Introduction

Anorexia and weight loss are common among advanced cancer patients, contributing to functional loss, decreased survival, and poor quality of life (QOL) [1, 2]. The potential of cannabinoids (*e.g.* delta-9-tetrahydrocannabinol, THC) to palliate loss of appetite in cancer has been investigated. However, the efficacy of THC to palliate cancer – associated loss of weight and appetite is difficult to interpret as only 7 published studies exist [3-9]; 2 of which were anti-emetic studies assessing appetite as a side effect [3, 4], 2 were uncontrolled [5, 6], and 1 of the 2 placebo controlled studies used weight gain as an outcome following just 1 week of treatment [8]. Earlier work held promise for THC therapy [3-6, 8], but recent controlled clinical trials have dampened enthusiasm [7, 9].

THC stimulates appetite through endocannabinoid receptors (CB1r) stimulating homeostatic controls of appetite (Figure 1.2); this is well documented in animals [10, 11] and in human healthy [12-15] and AIDS populations [16-18]. Research to date has overlooked other potential benefits of THC-therapy. Specifically, taste and smell (chemosensory) alterations are common and distressing among advanced cancer patients contributing to decreased food intake and enjoyment and diminished QOL [19, 20]. Patients frequently report the loss of food ideation and desire to eat [21, 22]. THC has been suggested to increase food intake by stimulating the brain's orosensory reward pathway, increasing the motivation to eat energy dense foods and enhancing food enjoyment and potentially the taste of food [23-25]. CB1r are located in reward-related areas of the brain [26] illustrating this potential. Moreover, CB1r are also located in the olfactory epithelium and bulb [26, 27] and recent studies have shown CB1r to be involved in peripheral odour processing [27] and potentially taste function [28]. We hypothesized that the ability of THC to stimulate food intake was related to its ability to help overcome perceived chemosensory abnormalities. We therefore undertook this randomized, double-blind, placebo-controlled pilot trial to determine the therapeutic potential of THC for cancer patients with self-reported chemosensory abnormalities. Our innovative approach included the use of food intake based outcomes for a more complete understanding of the effects of THC compared to placebo than has previously been evaluated in appetite stimulation trials. These outcomes included chemosensory perception, food enjoyment, food preferences and aversions, caloric intake, appetite, and QOL. The safety and tolerability of THC were also assessed.

[4] A version of this chapter will be submitted to *Journal of Clinical Oncology*, 2009 (authors Tristin Brisbois Clarkson, Ingrid de Kock, Sharon Watanabe, Mehrnoush Mirhosseini, Daena Lamoureux, Martin Chasen, Neil MacDonald, Vickie Baracos, Wendy Wismer)

4.2 Patients and methods

This 2-centre, phase II, randomized, double-blind, placebo-controlled 22-day pilot study was approved by Health Canada and the Research Ethics Boards of the Alberta Cancer Board, University of Alberta, and McGill University. The clinical trial was sponsored by the University of Alberta.

4.2.1 Eligibility Criteria

Adult advanced cancer patients (defined as locally recurrent, locally advanced, or metastatic) with self-reported chemosensory alteration(s), decreased food intake for at least 2 weeks (reported by subject or physician) and a life expectancy of > 2 months (as determined by physician) were eligible. All patients spoke English and provided informed consent. Use of chemotherapy and radiation therapy other than to the head and neck area was permitted during the trial provided no therapy-related adverse events ensued.

4.2.2 Exclusion Criteria

Exclusion criteria included receiving enteral or parenteral feedings; allergies or sensitivity to THC and/or sesame seed oil; history of substance abuse or psychotic episodes; mechanical obstruction of alimentary tract, mouth, or nose; radiation therapy to the head/neck area; primary brain tumour; nausea score > 5 on 11-point scale; history of tachyarrhythmias, angina pectoris, or uncontrolled hypertension within the last 6 months; current diagnosis of liver impairment; use of marijuana within 30 days prior to start of trial.

Patients on treatments that potentially increase appetite, such as corticosteroids, were able to participate provided their dose for the other appetite stimulant remained constant for the duration of the trial. Patients were screened for mouth infections (*i.e.* thrush) and were only entered into the trial once the infection was successfully treated.

4.2.3 Random Treatment Assignment, Blinding, and Intervention

After baseline assessments, eligible patients were randomly assigned in a double-blinded manner to either receive THC (Marinol®, dronabinol 2.5mg capsules, Solvay Pharma Inc.) or placebo. Randomization scheme was created (computer generated) by a third party and administered by the pharmacy. Patients started on a dose of 2.5mg capsule of THC or placebo once daily for the first 3 days (before bedtime for first 2 days, before supper on 3rd day). The dose increased to 2.5mg of THC/ placebo twice daily (1 capsule before lunch and supper) on the 4th day (Figure 4.1).

4.2.4 Outcome Measures

Patients completed questionnaires at the times indicated in Figure 4.1; *i.e.* baseline (day 0) and following 16-18 days of treatment (post-treatment, days 19-21) allowing 1 day latitude due to weekends or patient not feeling well. The validated Taste and Smell Survey [29] assesses the severity and intensity (*i.e.* heightened or loss of sensation) of self-reported chemosensory complaints as well as any shift in chemosensory perception following study treatment. The survey consists of 8 questions related to taste and 6 questions pertaining to smell. A point is awarded for each complaint. Scores range from

0-16, 0 indicating no chemosensory change and 16 indicating the greatest number and severity of changes [20]. The Taste and Smell Survey also includes open-ended questions for subjects to elaborate on chemosensory change(s) [30].

The 100mm Satiety Labelled Intensity Magnitude (SLIM) scale [31] was completed 10-15 minutes prior to each meal for an assessment of appetite throughout the day over the course of the trial. The SLIM scale is anchored with greatest imaginable fullness = 0 and greatest imaginable hunger = 100 (neither hungry nor full = 50). The Macronutrient Preference Checklist (MPC) [32] was completed at the same times as the SLIM to assess objective momentary shifts in macronutrient and flavour preferences. The MPC is scored based on the number of food items selected (0-8) in each of the four macronutrient categories of high protein, high fat, high carbohydrate, and low energy. A 3-day dietary record [33] was used to determine changes in caloric intake and shifts in macronutrient intake following study treatment using the Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR).

QOL was assessed with the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire [34]. Interviews were conducted to determine patients' food preferences and study treatment-related changes in chemosensory alterations. The 11-point Edmonton Symptom Assessment Scale (ESAS) [35] was used to assess patients' nausea. Finally, patients completed a Side Effect Survey [36] to document the tolerability of the study drug.

4.2.5 Statistical Analyses

All statistical analyses were performed on a per protocol analysis basis [37] using SAS [38]. Descriptive statistics were used to describe the prevalence, nature, and severity of chemosensory complaints. Chi-Squared and Fisher's Exact test analyses were used to evaluate patient characteristics, *yes/no* responses, treatment side effects, and adverse events. Time series analysis of variance [39] with baseline assessments as covariates where significant [40], were used to assess differences in chemosensory complaints, caloric intake, appetite, macronutrient preferences, QOL, and nausea between and within treatment groups. Pair-wise differences of Least Squares Means (pdiff) were used for post hoc comparisons.

4.3 Results

4.3.1 Patients

Advanced cancer patients were recruited from either the palliative home care program or outpatient clinics at local cancer clinics in Edmonton, Alberta and Montreal, Quebec, Canada over 2.5 years (2006-2008). There were no differences for any outcomes between study sites ($p<0.05$). Patient characteristics (Table 4.1) and dropout rates (Figure 4.2) were similar for THC and placebo groups. With respect to factors that could affect chemosensory perception, 33% of patients were receiving chemotherapy at the time of data collection; 19% had taste and smell problems predating the cancer diagnosis; less than 10% were currently bothered by hay fever, allergies, or sinusitis; 76% were current or former smokers; and 52% wore dentures. Patients were living at home and were assumed to make their own food choices based on personal preference.

Patients were able to increase their drug dose during the trial. In the THC group, 8 patients followed the dosing protocol (*i.e.* 2.5mg twice daily) and 3 patients increased their dose to 7.5 mg THC per day by taking an additional 2.5mg before supper.

4.3.2 Taste and smell perception

Taste and smell perception improved with THC treatment compared to placebo. When asked if the study medication made food taste better, significantly more patients in the THC group responded *yes* (n=6) compared to placebo (n=1) (p=0.04). On the Taste and Smell Survey, patients more frequently reported their sense of taste and/or smell and the taste and/or smell of food to be better with THC treatment compared to placebo (p=0.026). Taste and smell scores reflected enhanced chemosensory perception with THC treatment compared to baseline and placebo groups (Table 4.2). Similarly, THC-treated patients reported in open-ended questions and interview enhanced chemosensory perception (n=7) and overall appreciation of food (n=6). One patient compared the restoration of his taste and smell function to smoking cessation. Patients claimed they could *now discriminate tastes, flavours,* and *food odours*. Smells were reported to be of *better quality* and foods were reported to taste and smell *more appealing* / *better* with THC treatment. Half the patients who reported odours to be unpleasant at baseline no longer found odours offensive with THC treatment (p=0.083). By contrast, the majority of patients in the placebo group reported their taste and smell function to be the *same as before* (n=6) or *worse* (n=2) compared to before study treatment. No patient in the placebo group reported an enhanced chemosensory perception.

Total chemosensory complaint scores decreased with THC treatment compared to baseline, but were not different from placebo (Table 4.2).

4.3.3 Appetite

For the THC group, SLIM appetite scores improved relative to baseline and placebo (Table 4.2). The majority of THC-treated patients (64%) had increased appetite, 3 patients (27%) showed no change, and 1 patient's data was incomplete. No THC-treated patients showed a decrease in appetite. By contrast, the majority of patients receiving placebo had either decreased appetite (50%) or showed no change (20%).

4.3.4 Food preferences and caloric intake

Compared to placebo, THC-treated patients increased their protein intake in proportion to total caloric intake. Accordingly, there was a trend for THC-treated patients to choose more high protein foods on the MPC compared to placebo (Table 4.2). When asked about changes in food preferences since the study treatment, patients in the THC group commonly reported savoury foods and meats (*e.g. hamburgers, chicken, fish, baked beans, and mushrooms*) to *taste better* and to be *more appealing*. No patients in the placebo group reported an increased liking of meats.

Caloric intake did not significantly differ between treatment groups for average total caloric intake (Table 4.2) or average caloric intake as a proportion of body weight (p=0.557). However, 8 of the 11 THC-treated patients increased their caloric intake from baseline (range 100-775 kcal/day), while 5 patients in the placebo group increased their calorie count (100-965 kcal/day).

4.3.5 QOL

FAACT QOL scores showed a placebo effect as global FAACT QOL scores improved similarly for both THC and placebo groups (Table 4.2). Anorexia-cachexia related nutritional well-being improved in the THC group, but was not different from placebo. One patient reported to be no longer depressed after THC treatment; no changes in depression were reported in the placebo group. Nausea scores were unaffected by THC treatment ($p=0.532$).

4.3.6 Treatment side effects and adverse events

Quality of sleep and relaxation were both more frequently reported to be *pleasant* by THC-treated patients compared to placebo on the Side Effect Survey (Table 4.2). There were no other significant differences in survey responses between treatment groups ($p>0.05$, Table 4.3).

THC was well tolerated. No differences were reported during the trial or within the 30-day follow-up period between THC and placebo groups for the number of adverse events (AE) or serious AE (SAE) ($p=0.622$ and $p=0.244$ respectively). The majority of AE were unrelated to THC therapy, 6 were unclear (*nausea, headache, unsteady feet, shortness of breath, seizure*), and 4 were possibly related to treatment (*nausea/vomiting (2), hives/rash, irregular heart beat*, Table 4.4). The majority of SAE were also unrelated to THC therapy, 4 were unclear *(nausea, headache, shortness of breath, seizure*), and 1 was possibly related to treatment (*irregular heart beat*).

4.4 Discussion

4.4.1 Main findings

Our pilot study is the first to determine the efficacy of THC treatment to improve self-reported taste and smell alterations in addition to appetite stimulation. We argue that THC's effect on food intake behaviour is complex, involving chemosensory perception, reward-related pathways), and appetite. As such, we opted to use an array of questionnaires to capture THC-related effects not previously explored. Our results demonstrate that THC compared to placebo improved and enhanced chemosensory perception, food enjoyment, preferences and intake of high protein foods, appetite, relaxation, and quality of sleep for advanced cancer patients with self-reported chemosensory alterations.

Our findings are important as there is no accepted treatment for taste and smell perception alterations, which are prevalent in cancer [19, 20] We, along with Bartoshuk, speculate that taste and smell alterations in cancer are not solely physiological changes, but also involve the loss of food enjoyment [22, 30]. As such we opted to measure self-reported chemosensory perception in lieu of clinical measures of chemosensory function as a more appropriate predictor of food intake and enjoyment among advanced cancer patients.

In addition to statistical significance, results are clinically significant as effort and cost associated with THC-treatment are low. A 0.113 improvement in SLIM appetite score

yields a number needed to treat of 8.85 and an associated cost of $743[5] for 18 days of THC treatment; meaning for every 9 patients treated with THC, appetite loss would be completely alleviated for one patient, costing a total of $743 ($84 / patient) [41]. These calculations do not account for the number of patients screened or drop-out rates as both would vary among recruitment sites. Still, with public costs for a cancer patient's last year of life being ~$36, 600 [42] and the side effect profile of THC shown to be low, we feel these results are clinically significant.

Our findings parallel earlier surveys of healthy marijuana users reporting THC to enhance sensory perception, specifically the taste of food, improving food enjoyment [43-45]. Jarrett *et al* reported THC to reduce the unpleasantness of a bitter taste solution in animals [25]. Similarly, our THC-treated patients reported odours and the taste of meat to be less offensive, most likely contributing to the increase in calories ingested as protein and increased preferences for high protein foods among THC-treated patients. These results suggest that THC improved chemosensory perception through reward systems; however, the possibility of THC improving chemosensory function should not be ruled out as studies investigating this possibility in humans are limited [46]. Improved sleep may be due to the presence of cannabinoid receptors in the basal forebrain [26] or related to increased relaxation noted in various populations including cancer [8, 47]. Improved quality of sleep and relaxation may have contributed to increased appetite and even improved chemosensory perception as patients' mood likely also improved, encouraging a positive outlook on food [48].

Limitations of this study were the short duration of the trial and small sample size. We did not measure weight gain as study duration (18 days of treatment) was insufficient for weight gain to be a feasible measure [49]. However, improvements to appetite and food enjoyment are arguably as important to patients as weight gain. Our sample size and length were sufficient to show statistical significance for several outcomes, clearly demonstrating the potential of THC to improve self-reported chemosensory perception, food enjoyment, appetite, relaxation, and quality of sleep in advanced cancer. However, generalization of the results to the advanced cancer population is limited given the small sample size and preliminary nature of the findings (*e.g.* first to demonstrate improved perceived chemosensory perception with THC treatment in cancer). A larger clinical trial is needed to verify these outcomes. Sample size calculations indicate that certain outcomes, such as total chemosensory complaint scores and preferences for high protein foods, require ~50-60 patients in each treatment group while other parameters, such as caloric intake, require over 300 patients in each group. Indeed, variances would likely be higher with a greater number patient participants and thus these estimates are likely low. Still it is evident that certain outcomes are useful to power a study around, while others are not. Global QOL scores would likely never be differentiated given the prominent placebo effect. Very few studies in cancer anorexia have successfully shown improvements in QOL as participation in a study appears sufficient to improve QOL and questionnaires may be too insensitive to detect changes [50] and are clearly susceptible to placebo effects.

[5] Based on Canadian retail price (including dispensing fee) of a 60 capsule (2.5mg THC) bottle

4.4.2 Evaluation of prior and future clinical trials of THC

THC reputedly stimulates appetite in healthy volunteers [12-15] and AIDS patients [16-18], but its orexigenic efficacy in cancer varies. THC has been reported to increase appetite for 34-72% of cancer patients with doses ranging from 5 to 45mg THC per day [4-9, 47]. Nelson *et al* [5] showed promising THC effects for appetite loss in cancer, but were criticized for their lack of control group. It is notable that 6 of the 18 patients opted to remain on THC treatment for improved appetite and food intake [51]. Jatoi *et al* [7] reported THC to stimulate appetite in 50% of patients, but concluded THC to be inferior to megestrol acetate despite negligible differences in weight gain and no differences in QOL. Strasser *et al* [9] noted no differences between THC or THC + cannabidiol and placebo for appetite or QOL; however assessments were susceptible to placebo effects. In our study, 64% of THC-treated patients showed improved SLIM appetite scores that were not susceptible to placebo effect, suggesting the SLIM scale which includes word indicators and was completed prior to each meal, may better quantify appetite compared to previously used questionnaires.

The dose of 5mg THC daily used by Jatoi *et al* [7] and Strasser *et al* [9] has been criticized[52] as Nelson *et al* [5] showed more promising results with 7.5mg THC daily. Both authors stated 5mg THC daily was chosen to decrease side effects [7, 9]. A recent study of AIDS patients reported doses as high as 40mg THC daily to be well tolerated [18]. We started patients at a low dose to build-up tolerance and minimize negative psychoactive effects [53, 54] and allowed patients to titrate their dose upwards. Our dosing regimen was well tolerated, even among the elderly, as few AE were potentially related to THC treatment. We noted numerous drop-outs and withdrawn consents due to changes in health status, which were unrelated to study treatment. Clinical trials in advanced cancer have the added complexity of co-morbidities and imminent death. The exclusion of data that are confounded by poor prognosis is critical for interpretable results, which may be a criticism of previous work [9].

Considering the potential of cannabinoids to palliate an array of symptoms that burden advanced cancer patients, such as self-reported chemosensory alterations, loss of appetite and food enjoyment, pain, nausea, depression, anxiety, poor quality of sleep, and inflammation [55], the use of THC in cancer holds promise. For the design of future trials it seems important to 1) include a placebo group as outcomes may appear more favourable when compared to drug alone; 2) include assessments able to capture all aspects of food intake behaviour, such as chemosensory changes and food preferences and aversions; and 3) power studies around differentiable outcomes, such as chemosensory complaint scores, rather than placebo susceptible outcomes such as QOL. As absorption of oral THC varies greatly between individuals [46, 53], and given the controversy surrounding the appropriate dose in cancer, future trials should allow patients to titrate their dose.

In conclusion, THC was well tolerated and improved taste and smell perception, food enjoyment, and appetite among advanced cancer patients with self-reported chemosensory alterations. THC merits further investigation as a therapy for patients who suffer from self-reported chemosensory alterations and loss of food enjoyment.

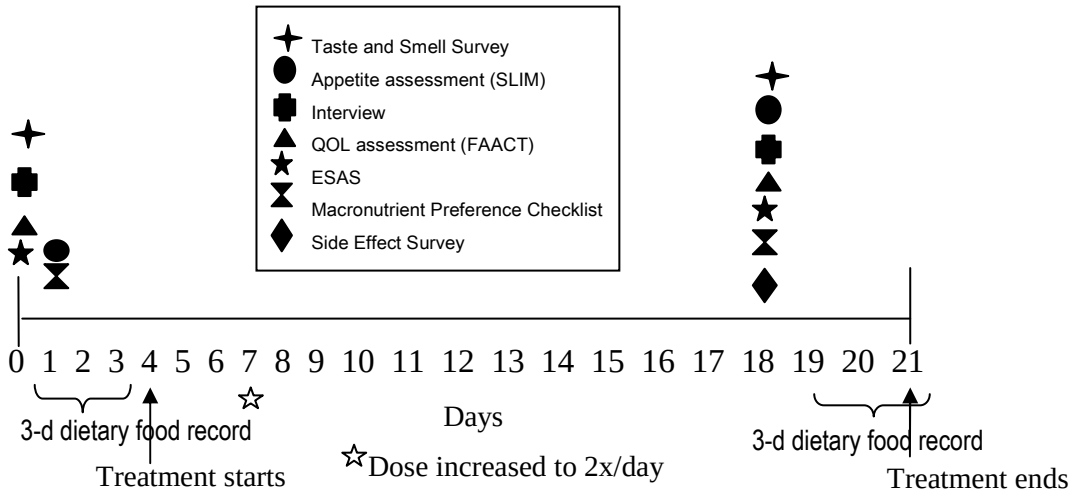

Figure 4.1 Experimental timeline for a double blind, randomized, placebo-controlled THC trial in advanced cancer patients. Abbreviations: SLIM, Satiety Labeled Intensity Magnitude scale; QOL, quality of life; FAACT, Functional Assessment of Anorexia/Cachexia Therapy questionnaire; ESAS; Edmonton Symptom Assessment Scale.

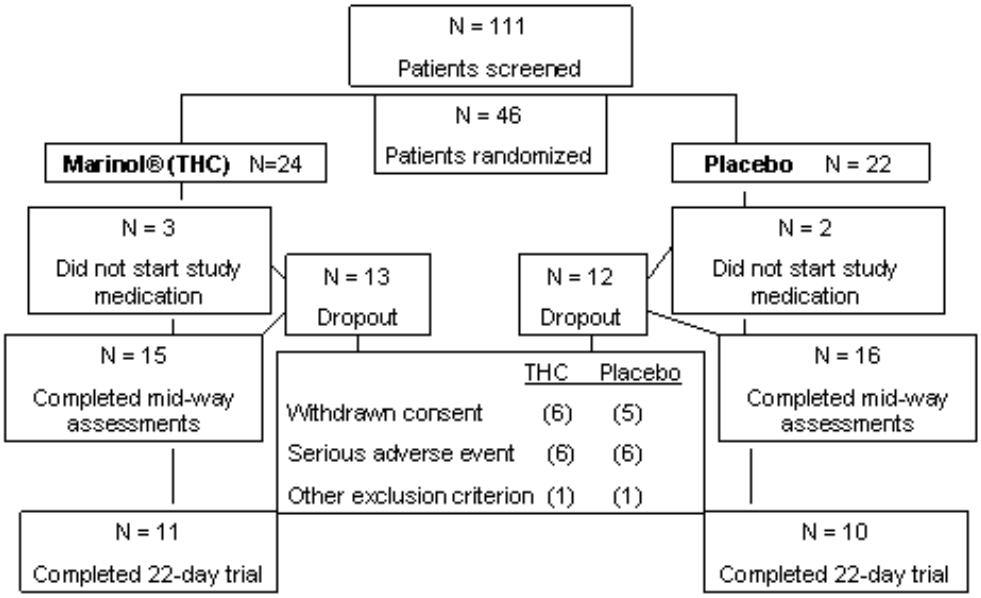

Figure 4.2 Patient flow. N=number; THC, delta-9-tetrahydrocannabinol.

Table 4.1 Baseline Patient Characteristics

Characteristic	THC (n=11)	Placebo (n=10)
Male [n (%)]	7 (64)	5 (50)
Age (y) [mean ± SD]	67.0 ± 10.9	65.5 ± 8.0
Survival (months) [median ± SD][6]	7.5 ± 5.5	6.0 ± 4.6
Chemotherapy* [n (%)]	3 (27)	4 (40)
Nausea, *11-point scale* [mean ± SD]	1.5 ± 2.0	0.9 ± 1.0
Cancer Diagnosis [n (%)]		
Lung	5 (45)	5 (50)
Breast	1 (10)	0 (0)
Genitourinary (*including bladder, renal, female genital: vaginal, ovarian, peritoneal, cervical, and male genital: testicular, prostate*)	3 (27)	2 (20)
Gastrointestinal *(including liver, pancreas, colorectal, stomach, esophageal)*	2 (18)	2 (20)
Other *(including unknown primary)*	0 (0)	1 (10)

Abbreviations: THC, delta-9-tetrahydrocannabinol; SE, standard deviation
*Patients received chemotherapy in the 2 weeks prior to baseline assessments. Types of chemotherapy included gemcitabine, capacitabine, erlotinib, cisplatin, carboplatin, oxaliplatin, etoposide, vincristine, cycylophosphamide, vinorelbine and fluorouracil as sole agent or in combination therapy.

[6] Four patients are still alive and thus median survival data is currently incomplete

Table 4.2 Baseline and Post-Treatment Assessments for Advanced Cancer Patients Receiving either THC or Placebo Treatment for 18 Days

	THC (n=11)				Placebo (n=10)					
	Baseline		Post-treatment		Baseline		Post-treatment		Between post treatment groups	Within THC group
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	p-value	p-value
Major THC-related outcomes										
Taste and Smell Survey Scores										
Chemosensory enhancement	1.3 [a]	0.2	2.5 [b]	0.2	1.3 [a]	0.2	1.8 [a]	0.2	0.018	<0.001
Total chemosensory complaints	7.3 [a]	0.4	5.7 [b]	0.4	7.3 [a]	0.4	6.4 [ab]	0.4	0.225	0.008
Appetite										
Avg pre-meal SLIM appetite score	49.4 [a]	3.3	60.7 [b]	3.4	51.7 [a]	3.4	50.9 [a]	3.4	0.05	0.03
Protein intake										
Avg protein(kcal)/ avg Kcal	0.16 [ab]	0.01	0.18 [a]	0.01	0.17 [ab]	0.01	0.15 [b]	0.01	0.008	0.217
Avg protein(g)/ day	65	9	82	9	62	9	62	9	0.121	0.179
Food preferences (MPC)										
Avg pre-meal high protein preference	1.6	0.3	2.1	0.3	1.4	0.3	1.2	0.3	0.063	0.341
Number of subjects responding change was "pleasant" on Side Effect Survey¥			**n=**				**n=**			
Quality of sleep			6				1		0.043	
Relaxation			5				1		0.046	
Placebo-susceptible outcomes										
Caloric intake										
Avg Kcal/ day	1594	114	1726	114	1543	120	1647	120	0.637	0.425
Quality of life (FAACT)										
Global quality of life	76.2 [a]	5.8	98.5 [b]	6.1	76.6 [a]	6.1	101.8 [b]	6.1	0.704	0.026
Anorexia-cachexia related nutritional well-being subscale	23.9 [a]	1.9	29.6 [b]	2.0	23.4 [a]	2.1	28.5 [ab]	2.1	0.700	0.05

All data (unless otherwise specified) are means (± SE) analyzed using time series ANOVA with baseline values as covariates where significant. Means in a row with different subscript letters are significantly different, $p \leq 0.05$. ¥ Data are frequencies analyzed using Fisher exact test.
Abbreviations: THC, delta-9-tetrahydrocannabinol; SE, standard error; avg, average; Kcal, kilocalories; g, grams; MPC, macronutrient preference checklist; SLIM, satiety labeled intensity magnitude scale; FAACT, Functional Assessment of Anorexia/Cachexia Therapy.

Table 4.3 Patient Responses to Side Effect Survey* Post Study Treatment

	Pleasant (n)	Neutral (n)	Unpleasant (n)
THC	quality of sleep has changed (6), relaxation (5), feeling sleepy (3) reduced anxiety (1)	feeling "high" (2), relaxation (2), unsteady feet (1)	fast heart rate (1), unsteady feet (1), dizziness (1), abdominal pain (2), nausea (1), heaviness in limbs (1), noises seem louder (1)
Placebo	quality of sleep has changed (1), relaxation (1)	quality of sleep has changed (1), relaxation (1), feeling sleepy (2), dizziness (1), abdominal pain (1),	

Abbreviations: THC, delta-9-tetrahydrocannabinol

Table 4.4 Patient-Reported Toxicities

	THC n (%)	Placebo n (%)
nausea/vomiting	5 (45)	2 (20)
hives/rash	3 (27)	3 (30)
bowel obstruction/constipation	0	3 (30)
shortness of breath/fluid on lungs	3 (27)	1 (10)
stomach cramps	1 (9)	2 (20)
tired/drowsy	1 (9)	2 (20)
pain	2 (18)	1 (10)
c. difficile/diarrhea	2 (18)	0
headache	2 (18)	0
dehydration	1 (9)	1 (10)
pneumonia	1 (9)	1 (10)
seizure	1 (9)	0
unsteady feet	1 (9)	0
low blood count	1 (9)	0
irregular heart beat	1 (9)	0
thrush	1 (9)	0
confusion	0	1 (10)
fever	0	1 (10)
edema	1 (9)	0
vaginal discharge	1 (9)	0
troubles sleeping	1 (9)	0

Abbreviations: n, number; THC, delta-9-tetrahydrocannabinol

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Chapter 5

Altered response to palatable high energy diet and Δ-9-tetrahydrocannabinol in anorexic tumor-bearing rats[7]

5.1 Introduction

Loss of appetite is an important behavioural adaptation following infection or injury. For an animal in a compromised state, limiting the incentive to forage for food may serve the purpose to reduce exposure to risk of predation or injury. The loss-of-appetite adaptation also occurs in the tumour-bearing state and is a common feature of animals and humans with cancer [1]. The specific nature and site(s) of cancer-related anorexia remain poorly understood. The prominent regulators of appetite neuropeptide-Y (NPY) and melanocortins have been the focus of earlier research and there is evidence for dampened NPY responses and increased signalling via melanocortin receptors during cancer anorexia [2-4]. As food intake is regulated by both appetite and orosensory reward systems [5], malfunctioning control of appetite may be only partially responsible for the prevailing level of food intake in cancer anorexia. The brain's orosensory reward pathway mediates food intake motivation and hedonic responses to food [6]. Cancer patients frequently report loss of food enjoyment [7-9] suggesting the possibility of suppressed orosensory reward systems in cancer anorexia. Our working hypothesis is that cancer anorexia may involve loss of activity of the orosensory reward pathway, a system that normally motivates the consumption of palatable high fat and/or sweet foods. The reward pathway is suggested to be a factor in obesity [10-12]. However, it is unknown how this pathway influences cancer anorexia and if tumour-bearing animals respond to rewarding stimuli via this pathway.

The participation of the orosensory reward pathway in the regulation of food intake can be explored by the use of stimuli, including palatable high fat sweet (HFS) diet [13] and cannabinoid receptor (CB1r) agonists. Following intake of a HFS diet before and throughout the disease trajectory may help to illustrate the role of the orosensory reward system in cancer-induced anorexia. It is generally accepted that the endocannabinoid system is involved in both appetite and reward related systems of food intake [14-16]. Specific exogenous CB1r agonists (*e.g.* Δ-9-tetrahydrocannabinol, Δ-9-THC) may be used to investigate the role of appetite and reward pathways. Δ-9-THC has been shown to increase palatable food intake to a greater degree compared to a less palatable diet in healthy animals [17, 18], but this effect has not been investigated in tumour-bearing animals. The purpose of this study was threefold, to determine if 1) tumour-bearing rats are responsive to a palatable HFS diet (*i.e.* food reward); 2) Δ-9-THC can increase food intake in tumour-bearing rats; 3) Δ-9-THC can increase intake of palatable HFS diet to a greater degree than chow in tumour-bearing rats.

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[7] A version of this Chapter will be submitted to *Physiology and Behavior*, 2009 (authors Tristin Brisbois Clarkson, Ingrid de Kock, Spencer Proctor, Wendy Wismer, Vickie Baracos)

5.2 Materials and Methods

5.2.1 Animals

The study was conducted in accordance with the Canadian Council on Animal Care Guidelines and was approved by the Alberta Cancer Board Animal Care Committee. Forty male Sprague-Dawley rats (8 weeks old, weighing 290-350g at start of test procedures) were housed individually in metabolic cages (Nalgene® metabolic cages for rats over 300 g, Techniplast no. 3701M081) and maintained on a reversed light-dark cycle (lights off at 0900h) throughout the study period. The room temperature ($21 \pm 1\ ^{o}C$) and humidity were controlled. Food (chow or palatable high fat sweet diet) and water was available ad libitum. All tests commenced in the dark part of the cycle under low-intensity light (*i.e.* a 40W lamp).

5.2.2 Drugs

Δ-9-THC (Lipomed, Switzerland) was prepared in a solution of 1 ml ethanol, 1ml Cremaphor (Sigma), and 18 ml saline, at a concentration of 1mg/ml. Rats were injected subcutaneously (s.c.) at a volume of 1ml/kg body weight. Fresh solutions of drugs were prepared on each test day. A single dose of Δ-9-THC (1mg/kg) was chosen as it has been shown to optimally increase food intake without inducing potentially harmful side effects such as sedation or ataxia (*i.e.* motor-related side effects) [17, 19].

5.2.3 Diets

The HFS diet (Research Diets, Inc. no. D12266B) and was chosen as it was similar to the diet used in Koch's study [17]. The HFS diet contained 51% of calories as carbohydrates (corn starch and sucrose), 32% as fat (butter fat and corn oil), and 17% as protein (4.41 kcal/g). The control diet (AIN-93M formula, Research Diets, Inc. no. D10012M) contained 76% of calories as carbohydrates (corn starch), 9% as fat (soy bean oil), and 15% as protein (3.85 kcal/g).

5.2.4 Tumours

Yoshida Ascites Hepatoma AH130 (YAH) was used as a model of cancer-induced anorexia. Animals were injected intraperitoneally (i.p.) with 50µl YAH ascites fluid [20]. The YAH was chosen due to its well-characterized anorexic effects which have a rapid onset [21] and established use as a model of cancer-induced anorexia [22-24].

5.2.5 Experimental Procedures

5.2.5.1 Food intake and body weight

Rats were randomly assigned to one of the two diets and maintained on the diet for the duration of the trial (Figure 5.1). Animals were acclimatized to light cycle, metabolic cages, diet, handling, and drug administration techniques prior to the test phase. Daily food intake (accounting for spillage) was measured (~30 minutes after lights out) for 12

days. Rats were weighed at the start of the test phase (study day 0), on the day of tumour/sham injection (day 5), and 4 days post tumour/sham injection (day 9).

5.2.5.2 Tumour transfer and inoculation

Frozen YAH tumour cells were injected initially into non-study rats for tumour passage (n=2). After 6 days of tumour growth, ascites fluid was harvested and passed immediately into 2 more rats. Ascites fluid was harvested following 7 days of tumour growth and injected (50µl i.p.) immediately into study rats (n=20) 6 days after the start of the test phase (study day 0). Non-tumour bearing (control) animals (n=20) received a sham injection (50µl i.p. of saline) on study day 5.

5.2.5.3 Δ-9-THC response

On study day 9, approximately 1 hr after the onset of the dark cycle, animals were injected s.c. with either vehicle or Δ-9-THC (1mg/kg). Food intake was measured at 0, 1, 2, 3, 4, 6, and 24 hrs after injection. Drug injections were s.c. instead of i.p. to avoid injection into the tumour. Rats were killed on either study day 10 or 11 by CO2 asphyxia followed immediately by exsanguination by cardiac puncture.

5.2.6 Statistical analysis

Food intake was converted from grams to kilocalories consumed and adjusted for body weight in analyses. Data were analyzed by analysis of variance with treatment effects considered fixed and rats considered random using the Mixed Procedure of SAS [25]. All data over time (*e.g.* food intake, body weight, hourly food intake post Δ-9-THC/vehicle injections, and magnitude of Δ-9-THC response) were analyzed employing a repeated measures design within the same Procedure using initial body weight as a covariate and time as the repeated variable. Magnitude of Δ-9-THC response was the difference in caloric intake between vehicle-treated and Δ-9-THC-treated animals. Pair-wise differences of Least Squares Means (pdiff) were used for post hoc comparisons. Bayesian Schwarz information criterion was used to determine the model of best fit.

5.3 Results

5.3.1 Food intake and body weight

Food intake of tumour-bearing rats significantly declined starting 4 days post tumour inoculation (Figure 5.2). The tumour-induced anorexic effect was apparent for both diets (chow: day 9 $p=0.047$, day 10 $p<0.001$, day 11 $p<0.0001$; HFS: day 9 $p=0.04$, day 10 and 11 $p<0.001$). Mean food intake was computed for days before and after the anorexic effect of tumour (*i.e.* before and after day 9, Figure 5.3). Mean food intake for days 9-11 was significantly lower for tumour-bearing compared to non-tumour bearing rats ($p<0.001$). For the effect of diet, prior to the onset of the anorexic effect of the tumour (days 0-9), HFS fed animals consumed more calories compared to chow fed rats ($p<0.001$) with no difference in caloric intake between non-tumour and tumour-bearing

animals (p=0.276). After day 9, anorexic tumour-bearing rats showed no difference in caloric intake between the two diets (p=0.792), whereas non-tumour bearing animals continued to consume more calories on the HFS diet compared to chow (p=0.007).

HFS fed rats had significantly higher body weight compared to chow fed rats by day 5 ($p<0.001$, Figure 5.4). This differential was maintained for both tumour ($p<0.001$) and non-tumour bearing rats (p=0.008) 4 days following YAH/sham injection despite the anorexic effect of the tumour. Tumour-bearing rats were significantly heavier than non-tumour bearing rats on day 9 ($p<0.001$), which was most likely due to tumour weight.

5.3.2 Δ-9-THC response

Δ-9-THC significantly increased food intake in both tumour and non-tumour bearing rats (Figure 5.5). The orexigenic effect of Δ-9-THC was delayed and prolonged in tumour-bearing animals compared to non-tumour bearing with significant increases in food intake for 2-6 hrs for tumour-bearing animals and 1-4 hrs for non-tumour bearing rats post Δ-9-THC injection. There was a trend for vehicle treated non-tumour bearing animals to have higher intakes compared to Δ-9-THC after 24 hrs (p= 0.057). Accordingly, non-tumour bearing animals showed a reversal in Δ-9-THC hyperphagic response in the 6^{th} and 24^{th} hour following test injections, a trend not shared by tumour-bearing rats (Figure 5.6). Consequently, the magnitude of Δ-9-THC response was greater for tumour-bearing compared to non-tumour bearing animals for the 6^{th} and 24^{th} hour post injection (p=0.004 and p=0.014, respectively).

HFS diet did not influence Δ-9-THC's orexigenic effect for tumour-bearing animals (p=0.246), but did show an acute effect in non-tumour bearing rats with Δ-9-THC increasing HFS diet intake to a greater degree than chow in the first hour only (p=0.003 Figure 5.5). This was the only diet and drug interaction noted.

5.4 Discussion

It is accepted that the orosensory reward system is involved in food intake behaviour [26, 27]. However, literature surrounding the role of the orosensory reward system in anorexia is scant. Our study is the first to consider the potential role of the orosensory reward system in a tumour-bearing model. Our results are preliminary in nature in that this was a behavioural study, observing changes in food intake following tumour injection and THC administration to help understand the potential role of the orosensory reward system in cancer anorexia. Our results suggest that the orosensory reward system is malfunctioning in our tumour-bearing animal model of cancer-anorexia. Rats responded to palatable HFS diet upon initial exposure with higher average daily food intake and body weights compared to chow fed rats. The diet-rewarding effect persisted in non-tumour bearing animals throughout the study, but was lost in tumour-bearing rats with tumour progression. Further, the rewarding HFS diet produced no additional Δ-9-THC hyperphagic effect in tumour-bearing animals, whereas this additional hyperphagic response was observed in non-tumour bearing animals one hour post Δ-9-THC injection.

Previous studies have investigated orosensory reward response by introducing palatable diets (*e.g.* high sugar and/or fat) in healthy or obese animals and humans [17, 27-31] and in these studies diet exposed animals show a persistently increased intake of the order of 10-30 kcal/day [31]. When we exposed rats to such HFS diets they showed a clear increase in food intake with weight gain. However, the incremental intake was not persistent during tumour progression (*i.e.* HFS diet did not displace the food intake curve to the right compared with tumour-bearing animals on chow) and was abruptly lost at the onset of the cancer-associated fall in food intake.

The loss of the diet-rewarding effect may be considered to be related to a loss or alteration of orosensory reward. By contrast, the mode of action of Δ-9-THC is both within and outside the reward system. Cannabinoid receptors (CB1r) are located throughout the body and brain, including areas involved in appetite, such as the hypothalamus and areas involved in orosensory reward, such as the neocortex (which includes the orbitofrontal cortex), nucleus accumbens, and ventral tegmentum [32]. As such, cannabinoids are involved in both appetite and orosensory reward systems to influence food intake behaviour [14]. Previous animal studies have used CB1r agonists or antagonists in combination with palatable and non-palatable diets to determine their role in the orosensory reward system [17, 18, 33]. The use of Δ-9-THC with both chow and palatable HFS diet allowed for the comparison of appetite and additional reward response (or lack thereof) in this model of cancer anorexia. Cannabinoid therapy has been investigated in humans with cancer anorexia, but these clinical trials are complex due to numerous co-morbidities of patients, the influence of various food intake behaviour factors, and unknown optimal Δ-9-THC dose for food intake stimulation [34-36]. The use of an established animal model of cancer-anorexia, known optimal Δ-9-THC dose for food intake, and set diets created a controlled environment necessary to answer our fundamental objectives.

Our results confirm Δ-9-THC to induce an acute additional rewarding response in non-tumour bearing rats, by increasing caloric intake to a greater degree for HFS fed rats compared to chow fed rats after the first hour only. Both Koch [17] and Brown *et al* [18] similarly reported in healthy rats Δ-9-THC to increase the intake of sweet food to a greater degree than less palatable diets 1 hr post injection. By contrast we did not observe any drug and diet interactions in our tumour-bearing model, suggesting the orosensory reward pathway may be malfunctioning or suppressed in disease-induced reduction of food intake. The current obesity epidemic is suggested to be potentially related to overstimulation of reward system by constant exposure to HFS diet [11, 12]. If the reward system has the potential to cause large surfeits in caloric intake resulting in obesity, it is plausible that lack of reward response may also cause deficit in the tumour-bearing state. Together, the loss of appetite and loss of orosensory reward may be part of an adaptive response to limit foraging for food, after injury or disease.

Little research exists investigating the possible impairment of orosensory reward in wasting diseases in humans, but a few results support such a possibility. Cancer patients frequently report a loss of food ideation and hedonic response to food [7, 8]. The orbitofrontal cortex (secondary gustatory cortex) determines desire for and pleasantness

of food and thus is involved with reward systems [37, 38]. A recent study employing single-photon emission computed tomography in Alzheimer's patients revealed hypoperfusion in brain regions involved in motivational and reward pathways (*e.g.* orbitofrontal cortex) in patients with reduced food intake compared to patients without this problem [39].

Our results demonstrate Δ-9-THC's ability to increase food intake in anorexic animals. Since the tumour bearing animals lacked hedonic responses to diet and did not show a diet and Δ-9-THC interaction, our results suggest that appetite systems (*i.e.* non-reward systems) mediated by endocannabinoids remain responsive in this tumour model. The shape of the Δ-9-THC response for caloric intake in tumour-bearing rats was however markedly different from healthy animals. Specifically, non-tumour bearing animals compensated for their Δ-9-THC-induced hyperphagia by eating less than normal starting 6 hours post-injection. Compensatory behaviour was not demonstrated by tumour-bearing animals, suggesting Δ-9-THC to increase overall daily caloric intake. However, it remains unknown whether this hyperphagic response would persist with repeated drug administration. The absence of compensatory behaviour in tumour-bearing rats suggests a different homeostatic response than that of healthy rats.

The altered kinetics of the Δ-9-THC response in tumour-bearing animals may reside in the sensitivity of hypothalamic neurons and/ or in the systemic metabolism of this drug. Appetite is mainly regulated by two sets of neurons in the arcuate nucleus, NPY/Agouti-related protein (AgRP) neurons and pro-opiomelanocortin (POMC) neurons [5]. Hypothalamic NPY levels are suppressed in cancer-induced anorexia [40]. Cannabinoids are suggested to increase NPY/AgRP neuronal activity by increasing NPY and decreasing leptin levels [33, 41-43] and more recently are suggested to modulate presynaptic and postsynaptic actions on POMC neurons [44], all of which stimulate appetite. New neurobiology studies are required to investigate Δ-9-THC's effect on hypothalamic neurons in the tumour-bearing state to explain the altered food intake response. The metabolism of Δ-9-THC in tumour-bearing rats is unknown, thus an impaired metabolism of the drug and its metabolites (*e.g.* 11-hydroxy-Δ-9-THC, 11-OH-THC and 11-nor-Δ-9-THC-9-carboxylic acid, THC-COOH) may have contributed to the extended hyperhagic effect in tumour-bearing rats. 11-OH-THC behaves similarly to Δ-9-THC and has been suggested to be involved in food intake [45], whereas THC-COOH exhibits analgesic and anti-inflammatory properties [46] which may have contributed to the delayed and prolonged hyperphagic response in the tumour-bearing rats [47, 48].

The mechanism in which the YAH tumour decreases food intake is not known and it is important to understand the overall context in which these changes occur. The detailed progression of food intake, weight loss, alterations in protein and lipid metabolism and hormones and other humoral factors has been quite well characterized during tumour progression [24]. The time of decreased food intake and Δ-9-THC injections in our study corresponds to a period of exponential tumour growth accompanied by significant decreases in plasma total amino acids, insulin, triiodothyronine (T3), thyroxine (T4), as well as increases in cholesterol, triglycerides, glucagon, corticosterone, epinephrine and norepinephrine. Elevated plasma prostaglandin (PGE) E_2 and tumour necrosis factor α

levels in this model are attributed to tumour production of these mediators as well as an enhanced production by host monocytes [24].

These results suggest several previously unknown complexities of reduced food intake in the tumour bearing state; the loss of orosensory reward and altered response to Δ-9-THC. These results have several implications related to attempts to reverse cancer anorexia by various approaches. Lack of hedonic response may be a considerable barrier to the restoration of food intake, and it remains to be determined whether this response may be restored by some means. There seems to be some potential for Δ-9-THC-mediated stimulation of overall intake, however a persistent response to Δ-9-THC would be required for a meaningful net increase in food intake.

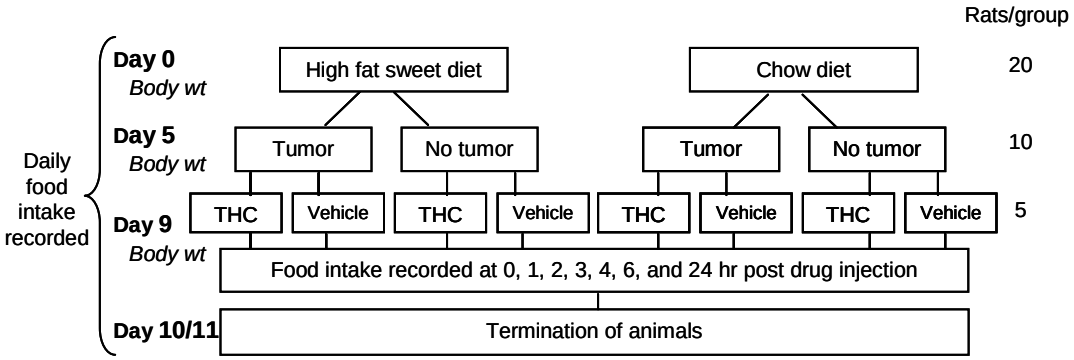

Figure 5.1 Flow diagram of experimental procedures (40 rats). Rats/group signifies number of animals per variation, *e.g.* 20 rats received high fat sweet (HFS) diet, 10 rats received HFS diet and tumor, 5 rats received HFS diet, tumor, and THC. Abbreviations: wt, weight; THC, Δ-9-tetrahydrocannabinol (drug).

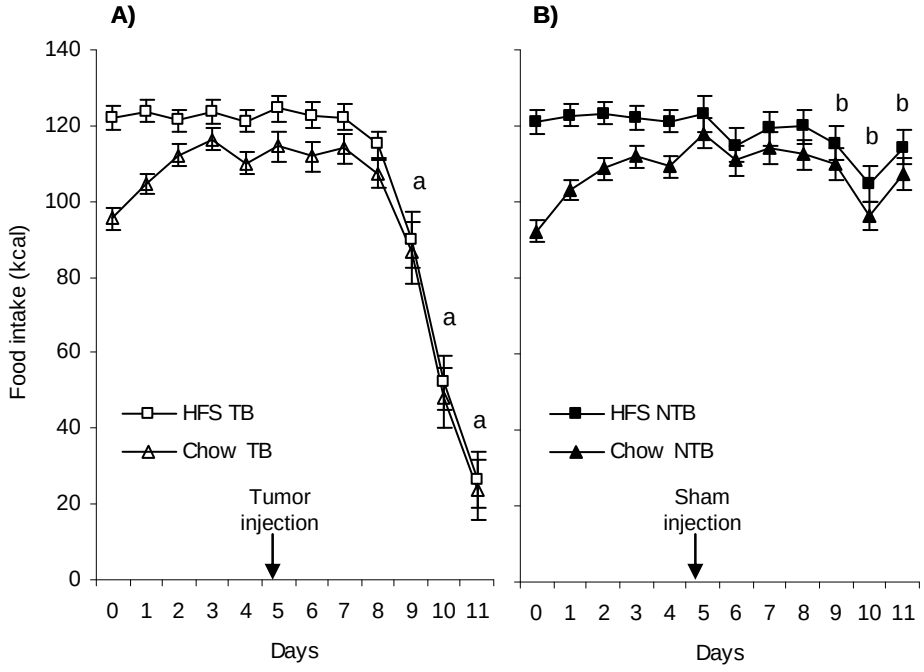

Figure 5.2 Daily food intake (kcal) for A) tumor-bearing (TB) and B) non-tumor bearing (NTB) rats. Values are means ± SE adjusted for body weight, 10 rats/group. Letters indicate significant differences in food intake between TB and NTB animals, day 9 $p=0.005$, day 10 $p<0.001$, day 11 $p<0.001$. Abbreviations: HFS, high fat sweet (diet); Kcal, kilocalories.

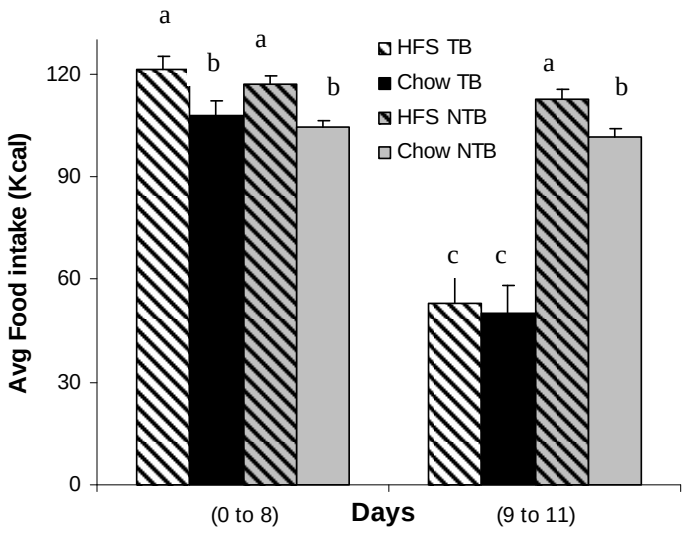

Figure 5.3 Average food intake (kcal) for tumor-bearing (TB) and non-tumor bearing (NTB) rats receiving either HFS or chow diet for periods before (days 0 to 8) and after (days 9 to 11) anorexic effect of tumor. Food intake values were adjusted for body weight. Values are means ± SE, 10 rats/group. Letters indicate significant difference in food intake $p<0.05$. Abbreviations: HFS, high fat sweet (diet); avg, average; Kcal, kilocalories.

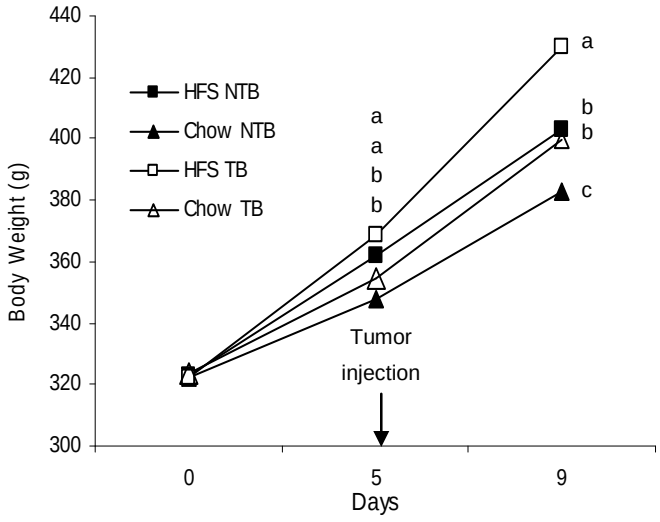

Figure 5.4 Average body weight (BW, g) for tumor-bearing (TB) and non-tumor bearing (NTB) rats receiving either HFS or chow diet for periods before and after tumor or sham injection. Values are means ± SE adjusted for initial BW, 10 rats/group. Tumor was injected on Day 5. Letters indicate significant difference in BW $p<0.05$. Abbreviations: HFS, high fat sweet (diet); g, gram.

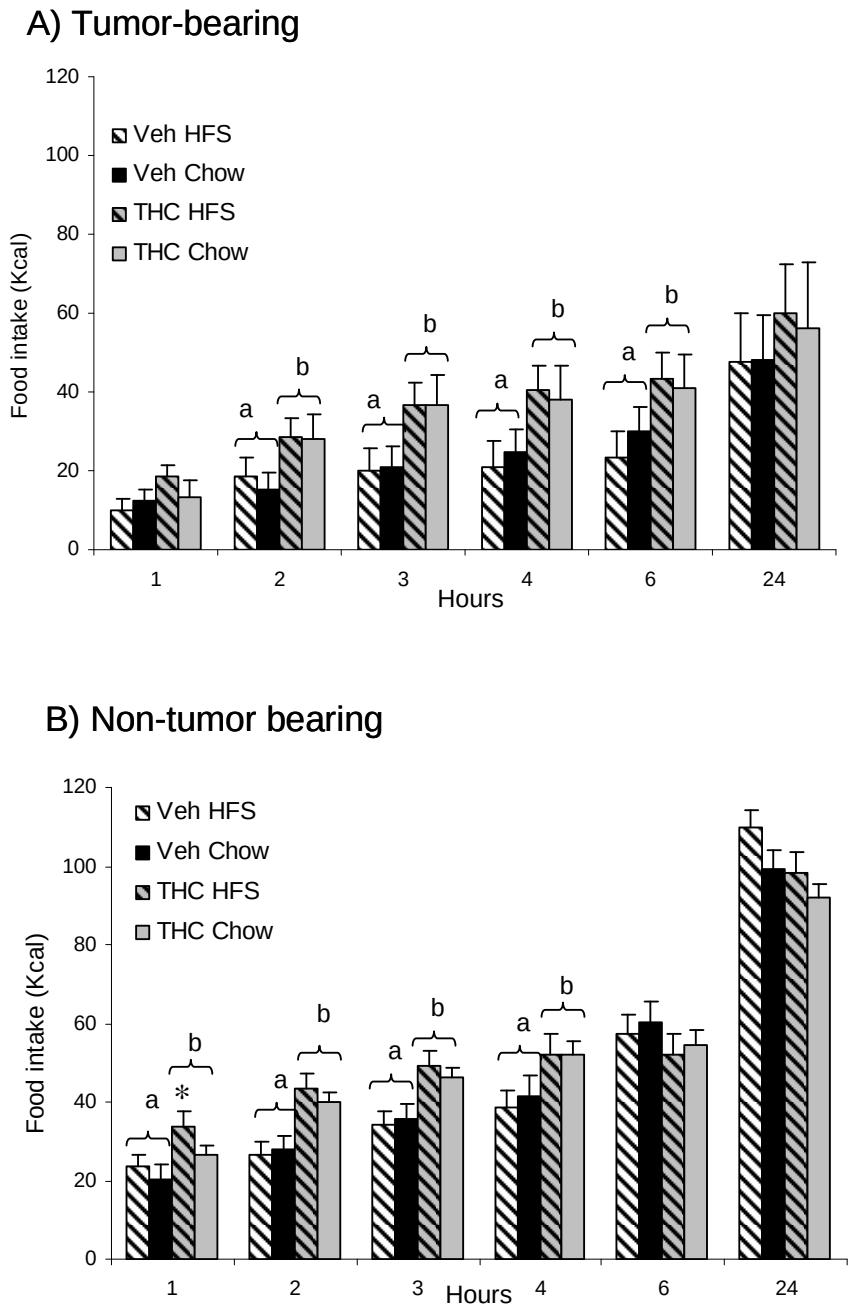

Figure 5.5 Food intake post drug injection (THC or vehicle) in A) tumor-bearing and B) non-tumor bearing rats 4 days after tumor or sham injection. Values are means ± SE, 5 rats/group. Letters indicate significant difference in food intake between drugs independent of diet type: **A)** p=0.041, p=0.015, p=0.028, p=0.047, and p=0.057 for 2, 3, 4, 6, 24 hrs post drug injection; **B)** p=0.026, p<0.001, p=0.004, and p=0.02 for 1, 2, 3, 4hrs post drug injection. ***** Indicates significant difference in food intake between diets within drug type; p=0.004 for THC. Abbreviations: HFS, high fat sweet (diet); Veh, vehicle (drug); THC, Δ-9-tetrahydrocannabinol (drug); Kcal, kilocalories.

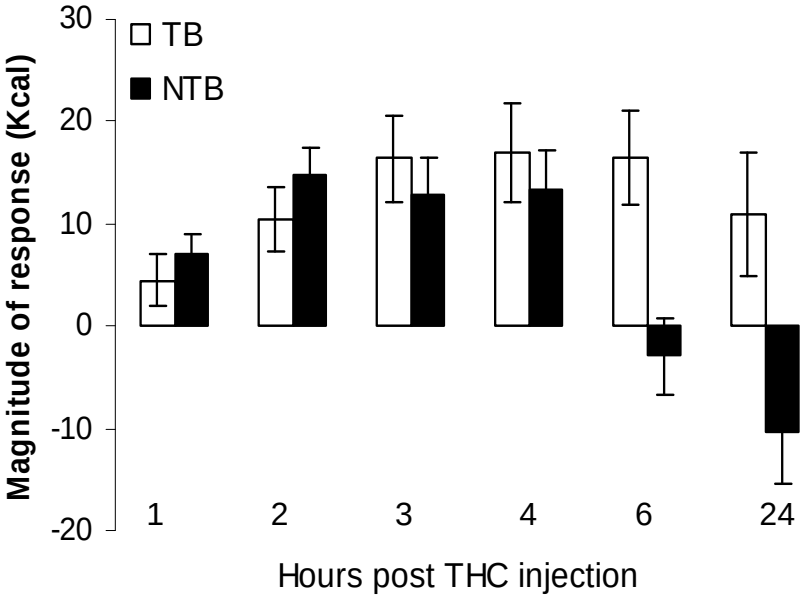

Figure 5.6 Magnitude of THC response for tumor (TB) and non-tumor bearing (NTB) rats. Values are mean difference in caloric intake between vehicle-treated and Δ-9-THC-treated animals ± SE, 10 rats/group. Magnitude of THC responses was greater for TB compared NTB animals for 6 and 24hrs post drug injection ($p=0.004$ and $p=0.014$, respectively). Magnitude of response was not different between TB and NTB animals at 1, 2, 3, and 4hrs post drug injection, $p>0.05$. Abbreviations: THC, Δ-9-tetrahydrocannabinol (drug); Kcal, kilocalories.

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Chapter 6
Discussion

"Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess"
Dr. J. Reynolds (*Queen Victoria's physician*), Lancet, 1890(i): p. 637-8

6.1 Main Findings

Regulation of food intake is complex, involving both appetite and orosensory reward systems. Appetite systems stimulate or reduce hunger, while orosensory reward motivates consumption of high fat and sweet foods, resulting in food enjoyment [1]. Our senses, specifically taste and smell, serve as a link between the two systems such that a positive sensory experience results in reward and perpetuates eating [2]. By contrast, a negative sensory experience likely reduces orosensory reward and appetite; the negative impact of taste and smell alterations on food intake behaviour is palpable in advanced cancer [3, 4]. Understanding the nature of these alterations may help to explain food intake behaviours and further our understanding of the physiology of these alterations. Our investigation of the intensity of chemosensory alterations in advanced cancer patients and their relationship with ingestive behaviour and quality of life (QOL) revealed heightened perception to be dominant, potentially leading to decreased food enjoyment (Chapter 3). Both a heightened and loss of sensation were equally associated with caloric intake; the number of perceived chemosensory alterations as measured by a chemosensory complaint score was found to be a better predictor of decreased caloric intake, weight loss, and poor QOL. Perceived chemosensory alterations in advanced cancer are likely a combination of physiological and hedonic changes.

Possible interventions to palliate chemosensory alterations include seasonings or flavour enhancers [5] and micronutrient supplementation (*e.g.* zinc) [6] (Chapter 2). However, success of these agents is limited and likely to be ineffective for patients with heightened chemosensory perception. As loss of appetite is also associated with perceived chemosensory alterations, appetite stimulants, such as megestrol acetate and glucocorticoids are commonly prescribed. However, these appetite stimulants are unable to palliate chemosensory alterations or improve food enjoyment and thus influence only one dimension of food intake behaviour, limiting their efficacy [7]. Cannabinoids (*e.g.* Δ-9-tetrahydrocannabinol, THC) however are accepted to stimulate both appetite and reward systems [8-12] and potentially enhance taste and smell function [13, 14]. Consequently, cannabinoids, such as medicinal marijuana and THC (dronabinol, Marinol®) or synthetic cannabinoids (nabilone, Cesamet®) are used off-label to improve food intake. There is currently no indicated or suggested use for cannabinoids and appetite stimulation in cancer. For the AIDS population however, THC has a suggested use as an appetite stimulant as results from multiple studies concur including those of a well-powered placebo controlled trial [15], indisputably demonstrating the ability of THC to improve appetite compared to placebo.

By contrast, only 5 published studies report the use of THC for appetite loss in cancer [16-20], of which only 2 were controlled trials [17, 20]. No studies have previously

investigated the use of THC in cancer to palliate perceived chemosensory alterations and loss of food enjoyment. The lack of studies investigating the orexigenic capabilities of THC in cancer make it impossible to assign such an indication. Further, the only two large randomized controlled trials suggested THC to have little merit as an appetite stimulant, despite positive [20] and un-interpretable results [17]. Jatoi *et al* [20] reported THC to stimulate appetite in 50% of patients, but concluded THC to be inferior to megestrol acetate despite negligible differences between the two treatment groups for weight gain and no differences between groups for QOL. Strasser *et al* [17] noted no differences between THC or THC + cannabidiol and placebo for appetite or QOL; however assessments were susceptible to placebo effects and results were arguably confounded by patients' poor health status, illustrated by the numerous unrelated adverse events and high number of deaths that occurred during the 6 week trial. It is not possible to interpret the results of a trial when the patient population is imminently dying. These two trials [17, 20] likely created doubt and perhaps discouraged future research involving cannabinoids and cancer anorexia, illustrating the importance of our clinical trial, which demonstrates for the first time the ability of THC compared to placebo to improve various aspects of food intake behaviour in cancer (Chapter 4). The objective of the randomized double-blind placebo controlled clinical trial was to determine if THC was able to overcome chemosensory abnormalities in advanced cancer patients to stimulate food intake and re-instate food enjoyment. THC treatment compared to placebo improved and heightened self-reported chemosensory perception, and improved food enjoyment, appetite, preference and intake of high protein foods, quality of sleep, and relaxation for advanced cancer patients with perceived chemosensory alterations. Alteration of chemosensation with THC-treatment was reported to be a positive experience. THC appeared to stimulate orosensory reward systems by increasing food enjoyment; however these improvements may be partially due to improved chemosensory function (Figure 6.1).

Appetite systems have been the focus of cancer anorexia research in animal models. However, malfunctioning control of appetite may be only partially responsible for the prevailing level of food intake in cancer anorexia as reward systems are also involved. The orosensory reward pathway is suggested to be responsible for the current obesity epidemic [21-23]. By contrast, there is little research investigating the role of orosensory reward in cancer anorexia and it is unknown if tumour-bearing animals respond to rewarding stimuli via this pathway. The objective of the animal study was to determine if orosensory reward systems are responsive to a palatable high fat sweet diet and drug (THC) in cancer using a tumour-bearing rat model (Chapter 5). Orosensory reward systems appeared to be impaired in tumour-bearing animals demonstrated by the loss of rewarding effect of high fat sweet diet and no additional rewarding effect of THC treatment combined with high fat sweet diet. THC compared to vehicle significantly increased caloric intake in tumour-bearing rats, suggesting endocannabinoid-mediated appetite systems are still functioning in this tumour model.

The objectives of this thesis were to investigate the role of sensory alterations and orosensory reward on food intake behaviour in advanced cancer as well as the efficacy of cannabinoid therapy for perceived sensory alterations and loss of food enjoyment and appetite. I hypothesized that orosensory reward systems are hindered in advanced cancer. Findings of the studies presented in this thesis appear to support the original hypothesis,

suggesting orosensory reward systems are impaired in advanced cancer, decreasing the liking and motivation to eat. THC treatment may help to palliate perceived chemosensory alterations and loss of appetite in advanced cancer.

6.5 Methodological considerations and study limitations

This thesis is a collection of published and submitted papers addressing a common theme of food intake behaviour in cancer. A limitation of this thesis work was the inability to build on the findings of each study, as the studies were designed and conducted in parallel, rather than sequentially. Knowing the results of the clinical trial (Chapter 4) would have influenced the design and perhaps research question of the animal work (Chapter 5). For instance, the inclusion of a high protein diet in the animal study would have verified the observed THC-induced change in protein preference among patients. It also would have been useful to design an animal trial to attempt to determine if the improved chemosensory perception reported by THC-treated patients was attributed to improved chemosensory function or improved food enjoyment through reward systems.

A limitation of the human studies (Chapters 3 and 4) was the omittance of a question assessing another sensory modality that would not be expected to change with cancer, such as visual perception of line length. This additional assessment would have verified if subjective improvements in chemosensory perception were valid and not the result of a generalized response pattern. It would be prudent to include such an assessment in future studies examining the effect of perceived chemosensory alterations on food intake behaviour. Nausea assessments would have been repeated to capture changes of chronic nausea instead of acute nausea. The QOL questionnaire (FAACT) was not useful given the susceptible placebo effect (Chapter 4). It appears that the FAACT might not capture social aspects of food intake behaviour given the disconnect between patient comments and social/family well-being scores (Chapter 3). Patients reported perceived taste and smell alterations to impact social aspects of eating, but no differences were noted among chemosensory complaint groups for social/family well-being scores. Other QOL questionnaires have been used in the advanced cancer population, such as the European Organization for Research and Treatment of Cancer QOL questionnaire (EORTC-QLC-C30, 1995 version 3), the Spitzer Quality of Life Index [24], and the McGill QOL questionnaire [25]. However the sensitivity of these questionnaires is also questionable and the nutrition-anorexia QOL component is often missing (e.g. EORTC-QLC-C30 and the McGill QOL questionnaire). In-depth qualitative interviews may be better able to capture all aspects of QOL. However this methodology is time-consuming and impractical for a clinical trial.

The 3-day food record was also susceptible to placebo effect (Chapter 4). There was no clear over or under-reporting by patients (Chapter 3), but the accuracy of these records has been questioned [26]. Other intake assessments, such as food frequency questionnaires (FFQ) or 24hr recalls also have their limitations and rely heavily on memory; 24hr dietary recalls have proven to be ineffective in the advanced cancer population as subjects could not recall what they ate the previous day [27]. A recent comparison of the 3 methods revealed the FFQ to be the most unreliable [28]; however

other studies have reported the opposite to be true [26]. Like the QOL questionnaires, a more reliable dietary assessment is needed.

The work presented in this thesis aimed to determine the influence of perceived chemosensory alterations on food intake behaviour (e.g. reward) and psychosocial parameters as well as to determine the efficacy of THC treatment to improve perceived chemosensory alterations. Subjective measures of chemosensation were appropriate for these studies rather than traditional clinical measures of chemosensation used to characterise taste and smell. However, subjective measures of chemosensation do have several limitations. Technical sensory terms are not well understood by the general population. For instance, the taste "bitter" is not as easily identified as salty or sweet. Patients might associate an unpleasant GI experience such as gastric reflux with the word "bitter", and as a result report a change in bitter taste sensation. Examples of bitter foods, such as black coffee or tea or tonic water were given to patients to help them better understand the taste modality and answer the question appropriately. It is unknown if all patients answered the question in terms of perceived changes to their sense of taste. The 5^{th} basic taste, umami, was not assessed in the studies presented in this thesis as it is highly unlikely that patients would know what umami meant. Thus description of changes in umami sensation would be limited. There were several complications surrounding the meaning of the word "taste". When patients were asked about changes in their sense of taste since the onset of cancer, patients would often indicate a change in taste preference; this was evident in the open-ended responses of the Taste and Smell Survey (Chapter 3). The general population does not associate smell with food, but rather with garbage or body odour. Thus patients may also have underestimated the contribution of their sense of smell to food flavour, and used the term 'flavour' interchangeably with 'taste'. Further research of perceived and objective measures of chemosensory alterations is warranted to better understand and palliate this symptom.

This thesis focused on the biological regulation of food intake (*i.e.* appetite and reward). However, social, cultural and contextual factors, such as mood, social settings and norms, tradition and values, habit, price, and income and education levels also influence food intake behaviour [29-31]. In cancer, food intake behaviour becomes even more complicated with patients often motivating themselves to eat in the absence of appetite [32]. Shragge *et al* [32] noted patients feeling that they had to eat to survive and thus made the conscious decision to eat even in the absence of hunger. Improved quality of sleep and relaxation (Chapter 4) likely improved patients' mood, creating a positive outlook on food, which in turn may have increased patients' appetite and even improved chemosensory perception. Eating alone, depression and having a caregiver prepare meals could all influence food intake behaviour. Moreover patients experience "good" days and "bad" days, which can affect mood and a variety of symptoms [33]. Understanding the implications of these external factors would help identify the influence of perceived chemosensory alterations and should be considered in future research investigating food intake behaviour in cancer.

6.3 Cannabinoids and food intake behaviour

Figures 1.1 and 1.2 outlined the various areas in which cannabinoids are involved in food intake behaviour. Results presented in this thesis suggest appetite systems and potentially reward and sensory function to be responsive to THC stimulation in cancer. Other factors (*e.g.* quality of sleep and relaxation) may have also been responsive to THC treatment and involved in improved food enjoyment.

6.3.1 Chemosensory function

The literature suggests THC improves food enjoyment through orosensory reward systems [34-42]. However, as cannabinoids are also involved in chemosensory function, the perceived heightened chemosensation reported in the clinical trial may have been due to improved chemosensory function instead of or in addition to improved food enjoyment (Chapter 4). As cannabinoid receptors are located in the olfactory bulb and have been shown to be involved in odour processing [13], it is possible that THC increased afferent input to the olfactory bulb enhancing smell perception, resulting in increased chemosensory acuity. The role of cannabinoids in taste function is less studied, but it has been suggested that cannabinoids are involved in the activation of the transient receptor potential M5 (TRPM5) ion channel. TRPM5 is specifically expressed in taste receptor cells and is involved in the perception of sweet, bitter, and umami tastes [43, 44]. Umami is a Japanese word meaning savoury, brothy, or meaty and is generally now accepted as one of the 5 basic tastes [45, 46]. Results from Oike *et al* [14] strongly suggested arachidonic acid to modulate TRPM5 channel activity. As endocananbinoids (*i.e.* N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG)) are synthesized from arachidonic acid [47] it has been suggested that they too may be involved in taste signalling pathways [13]. It is unknown if exogenous cannabinoids, such as THC, also influence TRPM5 channel activity, but if so then the increased preference and intake of savoury high protein foods reported in the clinical trial (Chapter 4) may have been attributed to modulated TRPM5 channel activity resulting in improved umami taste sensation.

There is very little research investigating the role of cannabinoids in chemosensory function, especially in humans. To my knowledge only one study exists; Mattes *et al* [48] investigated clinical taste function in humans and reported no differences in taste function between THC and placebo groups of healthy adults. However, THC compared to placebo increased preference and intake of sweet and salty foods, suggesting stimulation of reward systems. However, olfactory function was not assessed. It is unclear (from our clinical trial results) if THC altered the physiology of taste and smell function or altered hedonic response through reward-related pathways or both. However, it is interesting that THC favourably enhanced chemosensory perception (Chapter 4) for the group of cancer patients who likely already perceived chemosensations to be unpleasantly heightened (Chapter 3). It would be expected that if a patient already complains of heightened sensation, increased acuity would further negatively impact food intake behaviour. All THC-treated patients however claimed the perceived heightened chemosensation to be a positive response improving food enjoyment, which alludes to improved orosensory reward. The apparent decrease in avoidance of meat and other high protein foods also suggests stimulation of orosensory reward with THC-treatment. It

seems likely then that THC improved food enjoyment and chemosensory perception through orosensory reward systems, leading to the perception that food tasted better and odours and meats were less offensive.

6.3.2 Quality of sleep and relaxation

In addition to improved chemosensory perception, appetite, and food enjoyment, the findings of the clinical trial showed THC to improve quality of sleep and relaxation (Chapter 4). Cannabinoids have been previously reported to improve quality of sleep, particularly in multiple sclerosis [49, 50]. Improved sleep may be due to the presence of cannabinoid receptors in the basal forebrain [51] or related to increased relaxation noted in various populations including cancer [18, 52]. As discussed, improved quality of sleep and relaxation may have contributed to the observed positive food intake behaviour-related outcomes with THC-treatment.

6.3.3 Gastric motility

THC may slow gastric motility [53]. Since constipation is an already troublesome symptom in advanced cancer, Strasser *et al* [17] were concerned with this potential THC-related side effect. It is unclear if 5 - 7.5mg THC/ day would slow gastric motility as evidence in humans is conflicting [54-56]. Doses used for Crohn's and colitis are generally higher than 5mg THC/ day [53], making it unlikely that THC slowed gastric motility in our clinical trial. THC-treated patients did not report side effects related to slowed gastric motility (Chapter 4).

It is recognized that THC potentially influenced a variety of systems related to food intake behaviour (e.g. CCK release, energy and lipid metabolism, Figure 1.2) which were not investigated or discussed here as these were beyond the scope of this thesis.

6.4 Research challenges

6.4.1 The palliative cancer population

Improvement in quality of life and/or alleviation of symptoms of palliative care patients is an important and valuable research endeavour. Food is a source of pleasure and is often the center of social activities for the healthy population. For the advanced cancer population however, the experience is quite different due to nauseating or offensive food odours and tastes [57, 58]. Results of the clinical trial showed clear and immediate benefits; THC-treated patients had improved self-reported sensory perception, food enjoyment, and appetite; potentially re-instating the pleasure of food (Chapter 4). These promising results demonstrate the value of investigating a potential therapy for chemosensory alterations and loss of food enjoyment and appetite in advanced cancer. However, in the fragile advanced cancer population there were several challenges in the recruitment, completion, and interpretation of our randomized, double-blind, placebo controlled 22 day trial.

White *et al* [59] recently surveyed advanced cancer patients and their relatives to determine the interest of participating in randomized controlled trials. The majority of palliative care patients were willing to participate in research studies but willingness declined with increasing complexity of the trial *(i.e.* randomization, double blind, placebo controlled), invasiveness, length of trial, participants' age, and the potential of drug-related side effects. According to the criteria of White *et al* [59], our study design (i.e. randomized, double-blind, placebo controlled) would have deterred approximately half of those approached. From Jordhoy *et al* [60] one could expect 40% of those approached to decline participation based solely on lack of interest or poor health or cognitive status. Overall, patients were generally interested in our clinical trial. However, our relatively strict exclusion criteria limited the participation of a large number of interested patients. The potential of drug-related side effects was also a deterrent, but the length of the trial (22 days) was not excessive for most. According to White *et al* [59], our attrition rate was higher than that of comparable shorter trials, which was likely due to nondrug-related adverse events. Advanced cancer patients are in the end stages of their disease, obviously suffering from numerous cancer-related adverse events. In addition, patients often suffer from sometimes multiple co-morbidities, which also affect their health status. As a consequence, the health of patients was often unstable, changing very rapidly and unexpectedly, impeding them from entering or finishing the trial. Palliative care researchers should be aware of high attrition rates and power clinical trials accordingly.

Co-morbidities, concurrent medications, and nondrug-related changes in health status complicate interpretation of results. Ideally patients participating in a clinical trial would not change the type or dose of concurrent medications. However, symptoms such as pain and nausea often vary in intensity, requiring changes in medications which may affect trial-related outcomes. The variance in health status can also influence trial outcomes as it is difficult to determine if improvements or declines in health status are or are not treatment-related. Results of previous cancer anorexia trials have been confounded by the poor health status of patients, which lead to the potentially incorrect conclusion that the investigated therapies were ineffective [17, 61]. The difficulty of determining when (in terms of patient prognosis) interventions for cancer anorexia would be appropriate and helpful adds to the complexity of palliative care research. The inclusion of a placebo group helps to identify unrelated adverse events and treatment-related outcomes. However, although necessary, the inclusion of a placebo group deterred patients from entering this trial and the perception of being in the placebo-group caused some patients to withdraw from the study.

According to White *et al* [59] aspects of our trial that would have positively influenced patient recruitment and compliance were no cost to subjects for study drug, easy to understand consent form, relatively short questionnaires (~30min to complete), and non-invasive procedures. Family and physician support influenced patients' decision to participate and complete the trial. The majority of patients who entered the trial were accompanied by a relative or friend who encouraged participation. Physician support had the greatest influence on patients' willingness to participate and their compliance. The majority of patients who completed the trial had some type of social support system. Overall, patients were willing to participate in the hopes that the research will help others and the treatment might help palliate their own symptoms.

6.4.2 Societal perceptions and regulations of cannabinoids

Due to cannabinoids' history, negative societal perception, and potential for abuse, investigating the therapeutic benefits of these drugs has proved to be trying for the scientific community [62]. Cannabinoid research requires multiple authorizations from government organizations. Even though Marinol® is a legal prescription drug in Canada, two levels of approvals from Health Canada were required prior to commencing the trials with THC (one for the use of a controlled substance and the other for the use of a drug off-label). The animal studies also required Health Canada approval for the use of a controlled substance. All applications required annual renewal. The paperwork surrounding cannabinoid research is not trivial and likely deters researchers from pursuing investigations involving these drugs. The efficacy of medicinal marijuana for appetite loss and chemosensory alterations would have been interesting and useful to study; however the logistics and requirements surrounding such an undertaking made the research improbable. The consistent and rapid absorption rates of smoked marijuana would be ideal for the investigation of the effect of cannabinoids on chemosensory function (versus perception). Perhaps as the evidence for the clinical uses of cannabinoids continues to grow, the regulations and negative connotations surrounding the drug will dwindle allowing for such research to be possible.

6.5 Future directions and design of future trials

There is virtually no research investigating the role of orosensory reward in cancer. There is however a growing body of research investigating orosensory reward in obesity [23, 63-71]. The implications of the orosensory reward pathway in overeating have drawn the attention and efforts of several scientific communities, including neurology, nutrition, physiology, and psychology. Methodologies from the various obesity studies may be employed in the cancer population to understand the implications of orosensory reward regarding decreased food intake. Approaches may include questionnaires that can be used as part of a clinical trial or instrumental techniques used for investigational research. Davis *et al* [63, 67, 68] have used validated questionnaires to determine subjects' sensitivity to reward; if subjects had high sensitivity to reward they were at greater risk to overeat and become overweight [63]. Such questionnaires may be used to determine if the opposite is true in cancer anorexia. More sophisticated studies have used instrumental techniques, such as brain imaging, to determine activity levels in the brain's reward centres. Geliebter *et al* [71] used functional neuroimaging to observe brain activity following exposure to rewarding stimuli (visual and audio cues of palatable and non-palatable foods and non-food stimuli) in lean and obese women. The authors noted increased activation of the prefrontal cortex in obese binge-eaters following palatable food cues, suggesting obese subjects were more motivated to eat palatable foods compared to lean individuals. This methodology may be useful to determine if cancer patients with perceived chemosensory alterations and/or loss of appetite are less motivated to consume palatable foods compared to patients without these symptoms and/or age matched controls.

To my knowledge, only one study has investigated the role of orosensory reward on decreased food intake, which was that of Ismail *et al* [72] in Alzheimer's patients. Single-photon emission computed tomography was used to identify areas of hypoperfusion (and thus impairment) of brain reward and appetite centres. The orbitofrontal cortex is involved with orosensory reward as it determines desire for and pleasantness of food [73, 74]. Ismail *et al* [72] noted higher levels of hypoperfusion for patients with low appetite scores (determined by 100mm visual analogue scale) in the orbitofrontal cortex, but not in appetite regions (*e.g*. thalamus-hypothalamus). The results of Ismail *et al* [72] suggest an impaired orosensory reward system to be correlated with appetite loss, which concur with the findings presented in this thesis. Repeating Ismail *et al* [72] study with cancer patients would be useful to verify our results and my thesis hypothesis. Employing this methodology would enable the comparison of patients with perceived chemosensory alterations to those without alterations to determine the role of perceived chemosensory alterations on brain appetite and reward centres.

Animal models of cancer anorexia may be useful to investigate specific mechanisms, using techniques such as a taste reactivity test or conditioned place preference paradigm. A taste reactivity test may be used to compare the pleasantness of sweet and aversiveness of bitter solutions between tumour-bearing and healthy animals, as well as the effect of THC on the palatability of these solutions for both healthy and tumour-bearing animals [75]. A conditioned place preference paradigm may also be useful to determine if anorexic tumour-bearing animals are still willing to work for palatable food to receive the reward. However, results may be difficult to interpret as tumour-bearing animals may still *like* and *want* palatable food, but are unable to work for it due to decreased mobility and fatigue from tumour burden. Consumption of a novel palatable food item induces reward [66, 76]. To build on the findings of the animal study (Chapter 5), presentation of novel palatable food item at the onset of anorexia would clarify the influence of cancer anorexia on orosensory reward; meaning impairment of orosensory reward in our tumour model of cancer anorexia would be confirmed if tumour-bearing animals did not consume more of the novel palatable food item compared to regular chow. Further, brain slices of tumour-bearing animals may be taken to investigate dopamine levels in reward areas following palatable food and/or THC stimuli. As mentioned in Chapter 1, the implications of chronic opioid use (*e.g.* for pain) on reward systems and cannabinoid receptors in advanced cancer have yet to be studied, but are of interest as chronic opioid use likely down-regulates reward response [77]. Animal models may be appropriate to determine the effect of chronic opioid use on reward systems.

It is also unknown if cannabinoids improve food enjoyment by stimulating orosensory reward systems or by improving chemosensory function, or both. Mattes *et al* [48] is the only study to my knowledge to have attempted to tease apart these functions. The authors investigated both intensity and liking of taste attributes. For clinical assessments of taste, authors used a 13-point category scale with word descriptors to assess intensity ratings of varying concentrations of tastants (i.e. salty, sweet, sour, and bitter) in solution. Healthy adult subjects were also asked to rate the liking of these solutions on a 9-point hedonic scale. It would be interesting to repeat a similar study, but with the addition of clinical olfactory assessments, such as threshold testing (n-butanol odour detection [78]) or smell identification tests [79] given the evidence of cannabinoid involvement in olfactory processing [13]. Patients could complete the Brief Smell Identification Test (BSIT) [80]

and in addition to identifying the correct odour, patients could also rate the intensity and liking of each odour. These additional assessments could help clarify the role of THC in chemosensory function versus orosensory reward. However, discriminating whether THC improves chemosensory acuity or orosensory reward may not be so simple to dissect. Like cannabinoids, dopamine receptors are also located in the olfactory bulb [81]. Low dopamine levels in the olfactory bulb impairs olfactory discrimination [82], while stimulating dopamine receptors improves both odour discrimination and odour detection thresholds in animals [83-85]. As cannabinoid and dopaminergic reward systems are positively related [86], it is likely that the two systems also influence one another in terms of olfactory function; this too has yet to be studied.

There is a common misconception that chemosensory alterations recover once active therapy (either chemotherapy or radiation therapy) has finished [4]. A recent longitudinal study examined clinical taste and smell function of breast cancer patients and reported a loss of chemosensation during treatment with chemosensory function recovering completely 3 months after the completion of chemotherapy [87]. Conversely, *perceived* chemosensory alterations were found to persist well after completion of chemotherapy, beyond the time required for taste and smell receptors to rejuvenate (Chapter 3). Further, patients more often reported tastes and smells to be heightened rather than diminished. As discussed in Chapter 3, perceived chemosensory alterations are likely both physiological and hedonic in nature [88], which may not result in clinically assessed altered chemosensory thresholds. Clinical assessments of chemosensory function (*e.g.* detection and recognition threshold testing) do not capture changes, such as food tasting *off* or *not like it used to* or food to be no longer appealing or odours to be offensive or repulsive; all of which encompass perceived chemosensory alterations. Thus future research should incorporate assessments able to capture both clinically evaluated and self-assessed chemosensory alterations. As perceived chemosensory alterations and loss of food enjoyment in advanced cancer are chronic and distressing, therapeutic approaches to palliate these symptoms are needed.

Methods of improving food enjoyment have been outlined in Chapter 2, such as altering the taste, smell, texture, or even color of food to re-instate reward and increase overall caloric intake [89, 90]. However, these tactics may be ineffective for patients with perceived chemosensory alterations as these tactics are intended for populations experiencing a loss of sensation, such as the elderly. Advanced cancer patients were shown to perceive chemosensations to be heightened, or diminished, or a combination of both (Chapter 3). In the clinical trial (Chapter 4), THC was shown to pleasantly enhance chemosensory perception and improve other nutrition impact factors, such as appetite, food enjoyment, and quality of sleep and increased food variety for advanced cancer patients; thus a larger randomized placebo controlled follow-up trial is warranted. Future trials should include assessments similar to our study that capture various aspects of food intake behaviour. These assessments should be short and easy to complete for optimal compliance [59]. To date, clinical trials in cancer have used appetite, weight gain, and QOL as outcomes, which provided limited results. Assessing changes in weight gain requires longer study durations, which increases the already high attrition rates. Further, weight gain results can be difficult to interpret as fluid retention or fat mass is often not differentiated from fat free mass. Moreover, other outcomes such as improved food enjoyment and increased liking of a variety of foods are arguably more important to

patients than weight gain. Changes in QOL are rarely detected in trials for appetite loss in cancer [7], which may be due to prominent placebo effect.

From our results it is clear that QOL and caloric intake are susceptible to placebo effect and thus researchers should not power studies around such outcomes. Powering a trial around chemosensory complaint scores from the Taste and Smell Survey [91] would be reasonable; our data suggest 50-60 patients in each treatment group would be acceptable. Placebo controlled designs are unfortunately necessary for clear interpretation of results as many assessments are susceptible to placebo-related effects. However, researchers should be aware of the ethical issues surrounding the use of placebo in advanced cancer. A cross-over design or open-label design (upon study completion) would ensure all patients received treatment, which would encourage patients to participate and complete the study. However, with cannabinoid treatment a cross-over design would require a lengthy washout period of ~30 days. As poor health status can greatly influence trial results, a method of either determining appropriate candidates or screening for inappropriate candidates would be useful. Arkeneau *et al* [92] recently developed a prognostic score paradigm for patients with disease progression treated within the context of a phase I study. The paradigm awarded 1 point for each of the 3 factors found to significantly affect survival rates. These factors were high lactate dehydrogenase levels (> upper normal limit), low albumin levels ($<35\ gl^{-1}$), and 2 or more sites of metastasis. Patients with a score of 2-3 had a median survival rate of 25 weeks, which was significantly lower than patients scoring 0-1 (median survival of 74 weeks). Generally, the inclusion of patients with a life expectancy of > 2 months is acceptable, although studies have collected useable data 1 month before death [60].

Future trials may consider alternative routes of cannabinoid administration (*e.g.* vaporizers or sublingual sprays) and sources (*e.g.* plant extracts) as these may be easier to titrate and have better and more consistent absorption rates compared to oral THC [20, 93-95]. Routes of administration, such as inhalation or sublingual application are absorbed faster than oral THC [96], which may allow for shorter trial durations, reducing attrition rates and patient burden. However, the potential of patient impairment should be considered for data collection and interpretation of results. The optimal dose for THC and appetite stimulation in cancer is still unknown, thus permitting patients to titrate their dose would be beneficial. Patients would benefit from studies aimed to determine an optimal dose for appetite stimulation in cancer.

There is currently no consensus as to what the primary outcome should be for cancer anorexia cachexia trials. The 2 large randomized clinical trials investigating the use of THC for cancer anorexia had different primary outcomes: $\geq$10% weight gain [20] and improved appetite (reported on a visual analogue scale) [17]. As there are multiple causes of cancer anorexia cachexia, the primary outcome would depend on the primary symptom of the target patient population. For instance, we targeted patients with taste and smell alterations and therefore the primary outcome should be changes in these symptoms. Thus If another clinical trial using THC were to be designed, I would recommend perceived chemosensory alterations (assessed by the Taste and Smell Survey [91]) to be the primary outcome. The response is as similar for what should be the basis for an indication. A global basis for cancer anorexia cachexia should be something that is accepted by the medical community; meaning a tangible outcome, such as weight gain.

However as previously discussed weight gain might be water gain or fat mass. Appetite is arbitrary and difficult to effectively measure. Further, improvements in appetite may not determine food intake as seen in our clinical trial (appetite was shown to increase with THC treatment, but caloric intake did not (Chapter 4)). For THC, given the results of the clinical trial (Chapter 4) perhaps a new indication would be for the palliation of perceived taste and smell alterations. However, would we be able to convince the medical community that this is an important and distressing symptom that if palliated would improve food intake behaviour and food enjoyment? Again, larger randomized placebo controlled clinical trials are needed to make this argument as well as a reasonable price of treatment. It appears that anorexia cachexia is not as high of a priority as some symptoms, such as pain, and thus the price tag associated with treatment for anorexia cachexia is also lower. The end of life care costs for a cancer patient's last year of life is ~$36, 600 [97]. The cost of THC treatment for 1 year is $1,700 or 5% of the total end of life care cost. As THC appears to be able to palliate a variety of symptoms associated with food intake behaviour the cost of the drug is reasonable.

6.6 Concluding remarks

The importance of the reward system is striking; sensitivity to reward has been related to over-eating and food addiction and an absence of dopamine in brain reward centres results in death from starvation. The research studies described in this thesis are the first to consider the implications of orosensory reward impairment in advanced cancer and to employ cannabinoids as a therapeutic solution. Findings of these studies strongly suggest perceived chemosensory alterations hinder orosensory reward, reflected by low food enjoyment and resulting decreased caloric intake. Currently there is no accepted treatment for perceived chemosensory alterations and loss of food enjoyment in cancer despite their high prevalence and obvious impact on food intake and quality of life. THC-treatment was found to be useful in the palliation of perceived chemosensory alterations and loss of food enjoyment and appetite in advanced cancer; these results set the platform for the design of future clinical trials further investigating the therapeutic uses of cannabinoids in advanced cancer. The findings presented in this thesis are the starting point for future research investigating the role of orosensory reward in advanced cancer to better understand and improve food intake behaviour in this population.

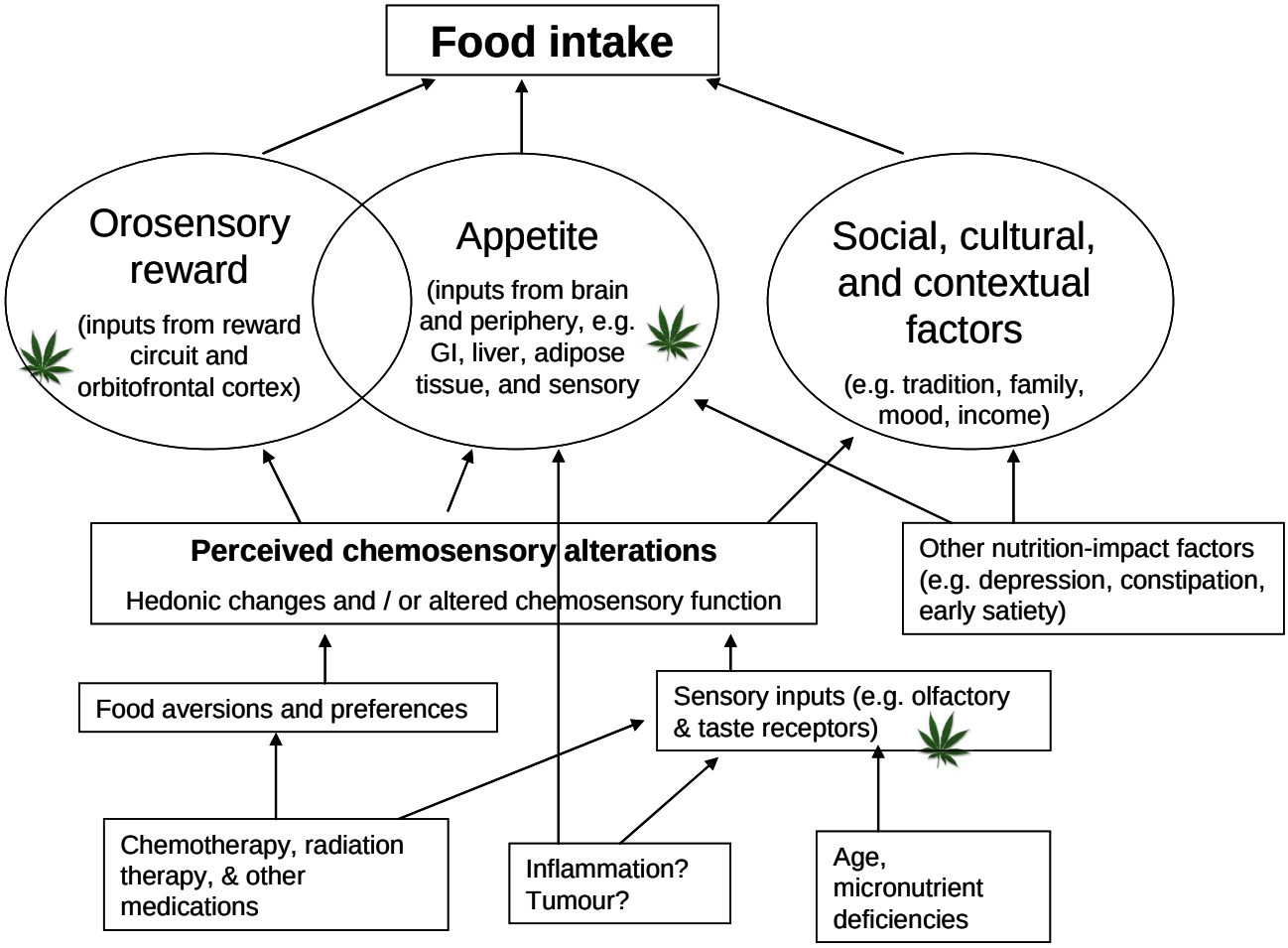

Figure 6.1 Basic conceptual model of potential influence of perceived chemosensory alterations on food intake in advanced cancer. In normal food intake behaviour, appetite, orosensory reward, and environmental factors (e.g. social, cultural, and contextual factors) all influence food intake. Both central (e.g. hypothalamus) and peripheral (e.g. GI tract, liver, adipose tissue and sensory inputs) systems are involved in appetite regulation. Cannabinoid receptors are located in areas involved in appetite (e.g. GI tract, liver, adipose tissue, and hypothalamus), orosensory reward (e.g. orbitofrontal cortex and nucleus accumbens) and sensory, which are depicted with the marijuana leaf. The overlapping circles of appetite and orosensory reward signify substantial cross-talk between these two systems.

In cancer, additional nutrition-impact factors (e.g. depression, early satiety, and perceived taste and smell changes) and potentially the illness itself (e.g. tumour and inflammation) further complicate the already complex picture of food intake behaviour by influencing various intake-related systems. The model highlights the potential of perceived taste and smell alterations to impact appetite and reward systems as well as environmental factors (e.g. social aspects of eating and mood). The cause of perceived chemosensory alterations is unknown, but may be due to altered chemosensory function or hedonic changes. A variety of factors in cancer could alter chemosensory function such as age, inflammation, medications, or anti-neoplastic treatment, all of which could affect sensory inputs and consequently food intake. Hedonic changes may occur from learned aversions following chemotherapy altering food preferences, affecting the orosensory reward system. Patients may misreport these altered food preferences (hedonic response) as perceived chemosensory alterations. Cancer patients likely suffer from both altered chemosensory function and hedonic changes, which are not mutually exclusive as changes in chemosensory

function likely alter the pleasantness of food. As cannabinoid receptors are located in both olfactory receptors and reward centres the observed improved chemosensory perception (Chapter 4) may be due to improved chemosensory function and / or improved hedonics.

Missing are specific hormones and neuropeptides such as ghrelin and NPY as the model (and thesis) focus on the potential impact of perceived chemosensory alterations and impaired orosensory reward on food intake behaviour.

6.7 References

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Appendix I Marinol® Clinical Trial Protocol[8]

A double-blind, randomized, placebo controlled clinical trial to evaluate the efficacy of orexigenic therapy with delta-9-tetrahydrocannabinol in advanced cancer patients with chemosensory abnormalities – a pilot study

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Introduction

Various medicinal uses of delta-9-tetrahydrocannabinol have been observed in recent research. Delta-9-tetrahydrocannabinol (THC) has numerous benefits, such as decreasing chemotherapy-induced nausea and vomiting, alleviating pain and depression, and improving sleep [1-3]. Delta-9-tetrahydrocannabinol also stimulates appetite in the healthy [4-7] and AIDS [8-10] populations. Previous studies have had some positive results regarding THC's ability to stimulate appetite in cancer populations [3, 11, 12], but evidence is not conclusive. Marinol®, a synthetic derivative of THC, was approved in 1985 for treating chemotherapy-induced nausea. In 1992, the US Food and Drug Administration approved Marinol® as an appetite stimulant (orexigenic aid) for AIDS patients.

Background

Cancer Anorexia-Cachexia Syndrome

Cancer Anorexia-Cachexia Syndrome is a condition of advanced protein calorie malnutrition [13], comprising of a loss of appetite (anorexia) with a state of involuntary weight loss that leads eventually to cachexia (emaciation) [14]. Approximately 80% of advanced cancer patients suffer from malnutrition and wasting and a large percentage also experience chemosensory abnormalities, both of which contribute to decreased survival and quality of life (QOL) [15]. Anorexia may occur from a loss of appetite because of psychological distress (*e.g.* depression and anxiety) [13] or from impediments to eating because of chemotherapy-induced symptoms (*e.g.* pain, vomiting, nausea, *etc*) or **taste and smell (chemosensory) changes** [16-18].

Rationale for assessing chemosensory changes

Glasses and hearing aids correct visual and auditory distortions or deteriorations, but no treatment is generally applied for chemosensory dysfunction [19] even though interventional strategies are available. Masking agents can block bitter and sour flavors [20]. Flavor enhancers, such as monosodium glutamate (MSG), can be used to improve the taste of food when a loss of taste is experienced. Flavor enhancers and spices were shown to improve grip strength, food intake, food enjoyment and immune function in the elderly population [21, 22]. Thus, improving chemosensory alterations have been shown to have positive effects on nutritional status and food related QOL. However, these methods of intervention are for loss of taste or smell and are somewhat trivial especially for someone who is repulsed by the taste or smell of food.

Lack of chemosensory treatments is most likely because of the current limited understanding of the cause of chemosensory abnormalities. Taste and smell alterations are not commonly measured. Clinical tests such as butanol threshold testing [23] for smell and taste threshold testing with the four basic modalities (*i.e.* sweet, sour, bitter and salty) [24] exist, but are not commonly used to

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assess cancer patient's chemosensory alterations. Moreover, these tests effectively assess taste and smell thresholds, but miss any chemosensory distortions and food aversions. Interviews and surveys can be used to identify and differentiate between decreased thresholds and chemosensory distortions [25], but are rarely administered in the cancer population. Therefore, the recognition of chemosensory disturbance as a symptom contributing to anorexia (and therefore nutrition) is rare, and as such, unlike the other symptoms mentioned (*i.e.* depression, nausea, *etc*), no effective clinical intervention has been applied for chemosensory alterations.
The senses of olfaction and gustation are subject to distortions and deteriorations (Table I.1). Taste and smell disorders are ignored and left untreated because they are not fatal, nor are they considered serious handicaps [26], however they are senses with both a physiological function and they contribute to our QOL. Olfaction and gustation allow us to enjoy the aroma and taste of foods [18] and help us to recognize spoiled foods and warn us of poisonous substances [19]. Both senses are involved in sensual and emotional life [27].

A. Consequences of Chemosensory disorders
Chemosensory disorders can cause modification of food choices and preferences that can lead to a decrease in nutritional status and aggravate the disease state [26]. Alterations in digestion can occur, since salivary and pancreatic flow rates, gastric contractions, and intestinal motility are affected by taste stimuli [28]. These distortions induce stress, depression and **anorexia** [26].

I. Decreased caloric intake
"Change in food appreciation can be one of the causes of poor dietary intake and thereby contributes to a deterioration of the cancer patient's general condition" [16]

Cancer patients are reported to experience chemosensory abnormalities. Common complaints of cancer patients are that food tastes metallic, bitter, distorted or bland, and smells are unpleasant or different [18, 25]. Patients with chemosensory disorders commonly alter their eating patterns and frequency [29, 30]. For example, certain foods are avoided because of their altered or unpleasant taste, such as protein rich foods, tea and coffee [31, 32]. Other foods may be avoided because they have induced an unpleasant experience (*i.e.* digestive disorder) after food consumption. When a patient becomes nauseated or vomits after eating a food, an unfavorable association with that food develops known as a "conditioned taste aversion" [33] or "learned food aversion" [34]. Food odors alone commonly cause food aversions, as the smell can induce nausea [19].

Such aversions cause a decrease in caloric intake and lead to weight loss [29]. The patient does not eat, in fear of having another unpleasant experience. Nielsen *et al* [19] noted that 70% of patients with food aversions consumed less calories than those without food aversions. Dewys and Walters [17] reported 50% of the cancer patients in their study claimed to have a taste alteration, half of which also experienced an aversion to meat. The participants ate less than they did prior to the taste disorder because food had either lost its appeal or it tasted bitter. The authors also noted that 75% of advanced cancer patients (*i.e.* patients not undergoing active therapy) experienced taste and smell abnormalities. Thus it appears that chemosensory alterations are even more prevalent in the advanced cancer population (*i.e.* metastatic) compared to cancer patients still undergoing active therapy. Recent work in our lab revealed that ~90% of advanced cancer patients had experienced a change in either their sense of taste or smell since the onset of cancer [35]. It was revealed using the validated tool of Heald *et al* [36] that individuals who rated their abnormal sense of taste as "severe" ingested significantly fewer calories (21.6 kcal/kg body weight / day) than those who rated their chemosensory problem as "insignificant" or "mild" (27.5 kcal/kg body

weight/ day) (P=.0055). Significant chemosensory changes were also associated with the highest rates of weight loss.

II. Decreased food enjoyment and food-related QOL

Chemosensory abnormalities hinder the patient's ability to enjoy food [30]. Decreased food enjoyment not only leads to a decrease in caloric intake [29, 30], but also lowers QOL [16]. Wickham *et al* [18] found 68% of cancer patients reported taste changes, of which 75% rated these taste changes as distressing. Several patients stated that chemosensory changes affected their lives and were depressing. Taste changes were also associated with lower QOL, especially the QOL dimensions of physical and functional well-being [18]. Similarly, our lab noted a negative correlation between the frequency of chemosensory complaints and QOL (assessed by the Functional Assessment of Anorexia/Cachexia Therapy questionnaire [37]) for advanced cancer patients (P=.0064); particularly for physical well-being (R^2=.2680, P=.0001) and anorexia-cachexia-related nutritional well-being (R^2=.3491, P<.0001) [35]. Taste changes are often rated as one of the most distressing symptoms in cancer [18, 38, 39].

B. Causes of chemosensory alterations

Why do so many cancer patients experience chemosensory changes? There are several potential causes of taste abnormalities. Chemotherapy and radiation therapy can destroy taste buds and salivary glands [40]. Wickham *et al* [18] noted that vomiting and nausea were associated with taste changes. Medications (*e.g.* cisplatin, doxorubicin, *etc*), consist of organic substances that create a bitter, unpleasant or metallic taste [18].

However, as mentioned above, chemosensory alterations seem to be more prevalent in advanced cancer patients. Thus other factors besides active therapy must also contribute to chemosensory alterations. Taste and smell abilities decrease with age [22, 41]. At around the age of 60, taste and smell abilities start to decline, and these changes are severe by the age of 70 [42]. As the majority of the advanced cancer population is elderly, they will suffer from normal chemosensory losses in addition to the chemosensory abnormalities related to their disease.

Deficiencies in vitamin A [43], copper, nickel [44], zinc, or niacin are thought to alter taste [15, 45], but empirical evidence is lacking. Davidson *et al* [46] reported that patients with hypogeusia also had Fe deficiencies, which lead to elevated taste thresholds for bitterness. Other medications such as antibiotics, analgesics, bisphosphonates, cardiac medications, muscle relaxants, antidepressants, anticonvulsants, *etc*, can also produce unpleasant, bitter, or metallic tastes [18]. The common cold, infections, poor oral hygiene, smoking, dentures, hormonal fluctuations (menstruation, pregnancy), heredity, and depression can influence taste and smell perception [44]. Dry mouth or sticky saliva can reduce or alter taste as taste molecules must be dissolved in solution to be detected by the taste buds [18]. Chemosensory disorders can occur because of nerve damage from head or neck trauma, surgery or malignancies. This damage can result in the perception of phantom tastes and odors [46]. Alterations in the receptor renewal cycle because of malnutrition, disease, drugs, metabolic disturbances, age, radiation, *etc,* will also affect taste and smell abilities [26].

Causes of chemosensory changes are most likely multifaceted, which makes treatment difficult. Interviews that consist largely of demographic questions associated with chemosensory deficits (*e.g. "Are you taking any herbal medications? If yes which ones?" "Are you a smoker*?" "*Are you*

currently bothered by your sinuses?") can help to determine potential causes of the observed chemosensory disorders [25, 47].

Rationale for the use of orexigenic therapy

C. Suggestions for coping with chemosensory disorders

Several suggestions to cope with taste and smell disorders are found in the literature. Patients with chemosensory disorders are encouraged to increase/decrease seasonings and salt, eat small frequent meals, add flavor enhancers to foods, eat bland foods, drink water, eat cold foods to avoid nausea-inducing food odours, avoid exotic foods, use mouthwash, and increase salivary flow rate by chewing or sucking on a candy, as dry mouth can cause taste alterations. Varying foods by changing a sensory specific quality (*e.g.* flavor, texture, and appearance) increases food intake and palatability [48]. Odors are linked to memories, so foods that trigger unpleasant past experiences (such as vomiting) should be avoided [21]. Zinc [34], vitamin A and B3 supplements may decrease chemosensory alterations [20], however, there is no compelling proof that these supplements can improve chemosensory abnormalities. The preceding suggestions are generally ineffective for reducing chemosensory complaints or to increase a patient's caloric intake over the long term. Appetite stimulants are therefore administered in attempt to increase caloric intake.

D. Appetite stimulants

Eating is a source of pleasure for the healthy population [49], but absence of appetite is a common complaint and is ranked as one of the most distressing symptoms in the advanced cancer population [50]. Appetite stimulants have become popular treatments in terminal disease because loss of appetite, unlike chemosensory alterations, is commonly identified.

There are two classes of orexigenic aids; primary and secondary. Primary appetite stimulants are those that affect the central nervous system (CNS)'s ability to regulate appetite. Among the primary orexigenic aids are, glucocorticoids, progestational agents (*e.g.* megestrol acetate), delta-9-tetrahydrocannabinol (THC) (*e.g.* Marinol®), neuropepetide Y (NPY), and ghrelin [13, 15, 51, 52]. Secondary orexigenic aids act by improving gastric motility and by decreasing satiety. Such appetite stimulants include, prokinetic agents, metoclopramide, and constipation control agents [13, 15, 51, 52]. None of these appetite stimulants have been linked to the improvement of food enjoyment, with the exception of THC.

Currently, the most prescribed treatment for cancer-associated anorexia is megestrol acetate (MA), a synthetic progestational agent. Megestrol acetate has been shown to increase appetite, caloric intake, and weight gain in humans [see 53], but with an overall low rate of success. Megestrol acetate improves appetite for less than 30% of advanced cancer patients [54]. Moreover, nutritional status is not improved because patients gain fat or retain water rather than increase muscle mass [51, 52]. A prominent side effect of MA is impotence [12, 55], so it is suggested that men be administered testosterone in combination [51]. Other side effects include fluid retention, flushing, vaginal bleeding, edema and possibly adrenal insufficiencies [15]. Deep vein thrombosis is also common [53, 56], so bed-bound patients should not be administered MA.

Appetite stimulants have a relatively high failure rate, as the most investigated and prescribed orexigenic aid (*i.e.* MA) is only effective for 1/3 of cancer patients to whom it is prescribed [54]. Orexigenic aids may be potentially ineffective because of the patient's chemosensory abnormalities. For instance, if the patient becomes nauseated from the smell of food or repulsed the taste of food, then they will not eat, even if they feel hungry. Inducing hunger is one feat;

getting the patients to eat is another. Delta-9-tetrahydrocannabinol is an appetite stimulant that may be capable of re-instating the enjoyment of food by improving chemosensory perception. The proposed study will examine THC's efficacy and tolerability as a treatment for cancer-induced anorexia by assessing its potential to overcome chemosensory disorders.

Rationale for using delta-9-tetrahydrocannabinol

A. Appetite stimulation and caloric intake

Delta-9-tetrahydrocannabinol has been suggested to induce appetite and increase caloric intake at a low chronic dose [6, 8, 9, 11, 12]. Mattes *et al* [6] observed THC to induce eating in healthy individuals. Nelson *et al* [11] reported three-quarters of the cancer patients who were given THC and completed the trial experienced an increase in appetite and 90% of the patients that kept a food diary recorded an increase in calories consumed over 4 weeks. In an AIDS-induced wasting population, Beal *et al* [8] found appetite to be greater in the THC-treatment group compared to the placebo group after 2 weeks. Similar results were noted in studies involving an advanced cancer population [3, 12, 57].

Haney *et al* [5] observed that THC increased caloric intake, especially in afternoons and evenings. Participants consumed the same amount of food each time they ate, but the number of eating occasions increased. Hollister noted similar results in that subjects ate more frequently even in a satiated state [4]. Mattes *et al* [6] also reported THC to induce eating even in a satiated state. By increasing eating frequency and hyperphagia, THC is a promising treatment for cancer-induced anorexia, as cancer patients commonly suffer from early satiety [38] and snacking drastically increases overall caloric intake [58].

I. Biochemical pathway for appetite stimulation

It is thought that cannabinoids stimulate appetite in two ways:

1) Inhibiting prostaglandin synthesis or interleukin-1 (IL-1) secretion
2) Through activation of the endogenous cannabinoid system [13].

The endocannabinoid system consists of endogenous cannabinoid receptors (CB1 and CB2) [59] and endogenous agonists, such as anandamide [59], arachidonyl-glycerol (2AG) [60], and noladin ether [61]. The central receptor (CB1) is primarily found in the brain (cortex, basal ganglia, cerebellum, hippocampus, entopeduncular nucleus and nucleus accumbens), but is also found in nerve terminals innervating the gastro-intestinal tract.

The CB1 receptor promotes eating by decreasing the release of leptin [62-64] and satiety-associated neurotransmitters (*e.g.* dopamine, norepinephrine, and serotonin) [65, 66]. Leptin is secreted by adipose tissues and acts within the hypothalamus, suppressing appetite-stimulating peptides, such as neuropeptide-Y (NPY)and agouti-related protein, and stimulates appetite-reducing peptides, such as alpha–melanocyte-stimulating hormone and cocaine- and amphetamine-regulated transcript [67]. There is speculation that cannabinoid and NPY neurochemical systems are interrelated, since NPY orexigenic properties have been ceased with SR 141716 (CB1 antagonist) [68]. In rodents, knocking out or blocking the CB1 receptors decreases caloric intake [63, 69] and lowers body weight and fat mass [64]. This indicates that the endocannabinoid system is an independent pathway capable of controlling appetite, which will not be affected by any hormonal, catabolic, or other changes [70] commonly experienced by cancer patients.

THC's ability to induce hyperphagia may not be solely due to the reduction of satiety signals. There is speculation that the cannabinoid system induces eating by increasing the incentive to eat and the reward of food [71], which is a unique property among appetite stimulants.

B. Effects on senses and food-related QOL

Cannabinoids are thought to enhance sensory perception, including taste and smell, but empirical proof is lacking [62]. Hollister (1971) assessed the pleasantness of food in healthy individuals and found that THC increased the subjective appreciation of food. However, only one study thoroughly assessed the effect of THC on taste in humans. Mattes *et al* [72] studied the effects of THC on taste intensity, hedonic (liking) responses, and caloric intake over three days. They reported that the desire for sweet and other palatable foods increased after administration of THC. Mattes *et al* (1994) noted that the most popular snack items overall for the healthy individuals given THC were sweet solid foods, such as pastries and chocolates. Two to four hours after drug administration there was a preference for salty foods. The effects of THC on chemosensory perception in cancer patients remain unknown as there is currently no published literature that addresses this subject.

Koch [73] observed THC to increase food intake for chow, high fat (HF) food and high fat sweetened (HFS) food in rats, where HF and HFS food was consumed to the greatest degree. The CB1 antagonist, SR 141716, reduced sucrose and ethanol intake as well as NPY-induced sucrose drinking in rats [68]. Harrold and Williams [62] also reported that by inhibiting the CB1 receptor the consumption of palatable food in rats decreased, especially foods high in sucrose and alcohol, but had little effect on bland food intake. Simiand *et al* [74] observed similar results in marmosets.

Delta-9-tetrahydrocannabinol induces reward (*i.e.* sense of satisfaction or gratification) through the incentive and motivation to eat [75]. The dopaminergic and opioid systems are primarily involved in the rewarding and dependence effects of cannabinoids [see 76]. The goal in understanding these systems and how they interact is to obtain beneficial therapeutic effects while minimizing adverse events. However the reward pathway of THC has not been clearly elucidated.

I. <u>Biochemical pathway of the reward system</u>

The reward circuit involves the ventral tegmental area (VTA), nucleus accumbens (NAc), ventral pallidum (VP) and medial prefrontal cortex (MPFC) [77]. These areas of the brain are linked together by synaptically interconnected neurons to form the circuit. Stimulation of this circuit induces pleasure in humans [77].

Wiiliams and Kirkham [71] suggested that the cannabinoid system and opioid reward pathways (involving the motivation and hedonic aspects of eating) are related. Naloxone (an opioid antagonist) decreases the hyperphagic effects of cannabinoids, especially the consumption of palatable foods [71, 78]. It is speculated that cannabinoids increase the synthesis and/or release of endogenous opioids [79]. Studies suggest that cannabinoid-induced up-regulation of opioid gene expression occurs in pain-related systems, motor behavior regulators, pituitary hormone secretion and reward pathways. How they interact is unknown. However, opioid, cannabinoid and dopamine reward pathways seem to work in congruence.

Natural rewards, such as the pleasure of eating, cause the nucleus accumbens to release dopamine. Delta-9-tetrahydrocannabinol mimics this effect, inducing hyperphagia [see 71, 78] and satisfaction from eating [49]. Delta-9-tetrahydrocannabinol and select other cannabinoids affect the VTA-NAc dopamine neurons by increasing the neuronal firing in the forebrain reward loci. Thus THC enhances dopamine synthesis and inhibits dopamine neuronal uptake [see 77]. It appears that the cannabinoid, central opioidergic and dopaminergic reward systems are interrelated, but the endogenous cannabinoid pathway works independently in certain aspects of reward, such as inducing the firing of VTA-NAc dopamine neurons[77].

If cannabinoids can manipulate the endocannabinoid system to induce appetite and amplify the taste of food, THC may increase the satisfaction of eating and overcome the problem of lost or distorted senses exhibited by advanced cancer patients. No one, to our knowledge, has investigated the capability of THC to improve the food-related quality of life of palliative care patients by reinstating the enjoyment of food.

Moreover, if THC can increase the palatability of food by stimulating the reward pathway, more food will be eaten as palatable meals have been reported to be greater in size and duration compared to less preferred meals [80]. Consuming preferred meals hastens the desire to eat again and quickens the return of hunger [81]. It is suspected that eating good tasting food will induce salient food cues, leading to an increase in inter-meal snacking. Following this logic, if THC induces the consumption of palatable foods then patients should eat good tasting snacks, which will increase their appetite and energy intake of their next meal. However, a person who finds food repulsive due to chemosensory distortion may be refractory to appetite stimulation, which may account for the relatively high proportion of treatment failures with appetite stimulants.

Research Methodology

Hypothesis

We hypothesize that the ability of THC to stimulate food intake will be related to its ability to help overcome chemosensory abnormalities.

Objectives

Primary - To determine if THC can increase total macronutrient intake for advanced cancer patients with chemosensory abnormalities. *Secondary* - To determine if THC can: 1) improve self-perceived chemosensory ability; 2) increase intake of palatable foods; 3) improve self-perceived appetite; and 4) to determine the effect of THC on participants' nausea; and 5) to assess the safety and the tolerability of THC when used by the advanced cancer population.

Research approach

A 22-day, double blind[9], randomized, placebo-controlled trial will be conducted. A detailed medication history will be obtained from each patient prior to commencing the trial. Participants will be screened for mouth infections, *i.e.* thrush, prior to entering the trial. If the participant has thrush, the date that the thrush was treated will be recorded and the participant may enter the study once the infection has cleared. For those patients receiving chemotherapy, the type, date and dose and

[9] The researchers will be blinded to the treatments administered and the participants will not be informed of which treatment they are receiving. However participants may discern which treatment they received from the presence of drug effects.

number of prior cycles of treatment will be recorded at the beginning and throughout the trial. Participants will complete the survey tools at the times indicated in Figure I.1. On day 0, the validated tool of Heald *et al* [36] (Taste and Smell Survey, Appendix I.A1) will be used to assess the severity of the patients chemosensory complaints (*i.e.* mild/moderate or severe). This tool will also be administered on day 18 to assess the change in chemosensory complaint scores after 2 weeks of treatment. The 3-day dietary record [82] will be completed on days 1-3 and 19-21 to determine the change in caloric intake and shift in food pereference by macronutrient analysis using the Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR). Participants will be asked to complete two 24-hour urine collections on days 3 and 21 to validate the 3-day dietary record [83]. The Satiety Labeled Intensity Magnitude scale (SLIM) [84] (Appendix I.B) will be completed 15 minutes prior to breakfast, lunch and supper on days 1, 11 and 18 for an assessment of appetite throughout the day over the course of the trial. The Food Preference Checklist (FPC) [85] (Appendices I.E and II) will be completed at the same times as the SLIM to assess objective shifts in macronutrient and flavor preferences. The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire [37] will be administered on days 0 and 18 to assess participant's QOL. An interview will be administered on days 0, 11 and 18 (Appendices I.C1 and I.C2) to determine the cause and affect of chemosensory alterations. The Edmonton Symptom Assessment Scale (ESAS)[86] will be administered on days 0 and 18 to assess participant's symptoms that may influence food intake, *e.g.* nausea. On day 18 of the study, the Side Effect Survey[87] (Appendix I.D) will be administered to document the tolerability of the drug. On days 0 and 18, the participants will complete the survey tools with the aid of the researcher. All tools are short and easy to complete, which minimizes patient burden. We anticipate reading aloud the majority of the survey questions based on past experience in our lab and from suggestions in the literature [47]. The questions are structured to allow for this adjustment if necessary.

Participants will be randomized into either the THC or placebo arm by a randomization scheme provided by the statistician at the Epidemiology Coordinating and Research (EPICORE) centre. The randomization scheme will be prepared for 80 participants using a computerized statistical program and it will be "blocked" at low even numbers to avoid uneven numbers in the two arms if the trial is terminated early. To ensure the integrity of the double-blinded study, the randomization scheme will not be seen by any of the investigators as it will be sent directly from EPICORE to the pharmacy that is distributing the study drug.

Participants will start on a dose of 2.5mg of THC once daily (before bedtime) for the first 2 days, on the 3rd day they will take the drug before supper, and then increase to 2.5mg of THC twice daily before lunch and supper on the 4th day (Figure I.1). Participants will record their daily dose (time and quantity taken) on the provided dose record sheet. Participants will be asked to authorize access to their medical charts for the list of current and previous drugs taken, description of their malignancy, and record of their weight loss history.

Anticipated Outcomes

For the treatment group we anticipate: a) an increased caloric intake and subjective appetite rating; b) a decreased number of chemosensory complaints; and c) a shift in food preference towards sweet and other palatable foods, especially for those participants with mild/moderate chemosensory complaints (as determined by the Taste and Smell Survey). The results for participants with severe chemosensory complaints will be novel and are hard to predict. The severe nature of the complaints may be intractable to THC action, making this population unable to respond with increased food intake; a person who finds food repulsive would be refractory to

appetite stimulation, which may account for the relatively high proportion of treatment failures with appetite stimulants in general [54]. Alternatively, since THC is involved in perception alteration, it is plausible that this agent could overcome some degree of chemosensory complaints to promote increased intake. We anticipate participants with higher levels of nausea (*i.e.* scores of 3-5 on the ESAS) to have lower caloric intake and to be less responsive to THC treatment. However, since Marinol®'s indication is an antiemetic it is plausible that nausea will be reduced in these participants (even at this low dose) causing an increase in food intake. Changes in nausea and their influence on food intake will therefore be reported as another outcome.

It is possible that the dose of THC will be inconsistent between the chemosensory complaint sub-groups, *i.e.* the "severe" (*i.e.* score >9) chemosensory complaint sub-group may need higher doses compared to the "mild/moderate" (*i.e.* score 2-9) sub-group. Such a difference in dose will be reported as an outcome.

Recruitment

Advanced cancer patients will be recruited from the Cross Cancer Institute (Metastatic Clinics and Pain and Symptom Clinic), Palliative Home Care, three hospices, and Tertiary Palliative Care Unit in Edmonton, AB. Home care and research nurses from several cancer care facilities in Edmonton, AB will recruit palliative care patients based on pre-defined inclusion and exclusion criteria. After eligibility is determined, participants' written consent will be obtained by completing the approved consent forms by tenable cancer board facilities. We anticipate 80 patients will be recruited and evaluated over 18 months.

Inclusion Criteria

Inclusion criteria includes: (1) advanced cancer patients (defined as locally recurrent, locally advanced, or metastatic) over 18 years old with a decreased food intake for at least 2 weeks (reported by subject or physician) (2) able to complete questionnaires in English (3) able to provide informed consent (4) life expectancy of greater than 2 months (as determined by physician) (5) chemosensory complaint score >1.

Exclusion Criteria

Exclusion criteria includes: (1) receiving enteral or parenteral feedings (2) allergies or sensitivity to THC and /or sesame seed oil (3) history of substance abuse or psychotic episodes (4) mechanical obstruction of alimentary tract, mouth or nose (5) received radiation therapy to the head/neck area (6) brain tumor (7) nausea score greater than 5 on ESAS (8) history of tachyarrhythmias, angina pectoris, or hypertension (9) current diagnosis of liver impairment (10) use of marijuana within 30 days prior to start of trial.

Participants on treatments that potentially increase appetite, such as corticosteroids (*e.g.* dexamethasone), may participate in the study if their dose for this other orexigenic aid remains constant for the duration of the trial.

Drug interactions

Clinical trials in the AIDS and cancer populations have co-administered Marinol® (THC) with various drugs (*e.g.* cytotoxic agents, anti-infective agents, sedatives, or opioid analgesics) and no significant drug/drug interactions were reported [70]. Solvay (Unimed) Pharmaceutical suggest that special precautions should be taken when Marinol® (THC) is administered in combination with the following concomitant drugs: 1) sympathomimetic agents (*e.g.* amphetamines and cocaine); 2)

anticholinergic agents (*e.g.* atrophine, scopolamine, antihistamines); 3) CNS depressants (*e.g.* barbiturates, benzodiazepines, ethanol, opioids, lithium, buspirone, anthinistamines, and muscle relaxants); 4) tricyclic antidepressants (*e.g.* amitriptyline, amoxapine, and desipramine) 5) disulfiram; 6) fluoxetine and 7) anthipyrine; as drug/drug interactions involving THC and the above drugs has been reported [70]. However, these drug/drug interactions are rare (*i.e.* case reports) and the majority were reported with the use of smoked marijuana, not oral THC (*i.e.* Marinol®). Beal *et al* [9] noted that Marinol® did not interfere with other medications.

Marinol® is highly bound to plasma proteins and therefore might displace other protein-bound drugs [70]. Drugs which are used in palliative care and which are highly protein bound are: coumadin: 99% protein bound; fentanyl: 80-86% protein bound; methadone: 71-88% protein bound; tricyclic antidepressants: 86-98% (amitriptyline and desipramine no information available on protein bound %); diphenhydrinate: 76%; and lorazepam: 85-91% protein bound [88, 89]. However, the likelihood of THC interfering with these drugs is remote, especially at the low doses we are proposing for this study.

Special precautions will be taken for patients who are on coumadin. These patients will be monitored by serial blood work [partial thromboplastin time (PTT) and international normalized ratio (INR)] on days 0, 5, and 8 (Figure I.2) and any time the dose of THC is increased. The dose of coumadin will be adjusted according to laboratory results.

All patients taking any of the above drugs will be carefully monitored for any additional side effects.

Monitoring of patient safety

Participants are given the pager numbers of the clinical research team, *i.e.* the research physician for the Cross Cancer Institute and the Regional Palliative Care Program as well as the research nurse. Patients can call the appropriate number 24 h a day to convey any concerns or side effects.

Participants will be forewarned that it will take 3 days to develop tolerance to the drug. If participants experience unpleasant side effects after taking the pill before supper rather than before bed as per protocol on day 3, then patients should resume taking the medication at bedtime on days 4 and 5. On day 6, participants should attempt to take the dose before supper rather than at bedtime. If they are still experiencing unpleasant side effects in spite of this action, they will contact the clinical research team. The research physician will then decide in conjunction with the patient whether to continue or cease treatment.

If the participants start to experience moderate or severe side effects after day 6 of the trial they should contact the clinical research team. For participants in palliative home care who experience severe palpitations and/or tachycardia, delirium, ataxia, and psychotic reactions they will be referred to the nearest emergency room. The research physician will then notify the applicable emergency room. For patients in health care facilities the clinical research team will arrange for an assessment. For patients with other severe side effects advice will be offered by phone and follow-up will be provided. Participants will be offered the option of decreasing treatment to the previous dose. If side effects persist withdrawing from the study will be discussed with the participant. With this combination of low dose and careful follow-up, we feel that any side effects in the oldest participants will be minimized and rapid action will be taken to adjust dose if necessary.

Drug distribution and storage

Participants will record their daily dose (time and quantity taken) on the provided dose record sheet. All Marinol® (THC) capsules will be kept at the Cross Cancer Institute research pharmacy. The drugs will be distributed to the participants by the research team or the participant can pick up the drugs directly from the pharmacy if the latter is more convenient for the subject. The participants will receive capsules for the full18 days of treatment assuming a dose of 2.5mg twice daily (*i.e.* 40 capsules). If participants choose to increase their dose, they must first consult one of the research physicians at which time the physician will determine if an increase in dosage is necessary (assessment may be done by phone). If it is determined that subjects might benefit from an increased dose, the research physician will notify the pharmacy. The participants may then receive more capsules from the pharmacy by either picking the pills up themselves or the researcher will bring the subjects the capsules after the first week of treatment.

Patient confidentiality

For confidentiality, random numbers will be assigned to each participant as they enter the study. Names will not be used; only the participation number will appear on the questionnaires. All information pertaining to this study will be securely stored at the Cross Cancer Institute, room 4022.

Rationale for research methodology

A. Rationale for selecting the oral route of administration

Absorption of THC is affected by the method of drug administration. The efficacy of three major routes has been documented; inhalation, rectal, and oral administration. Inhalation has a quick onset (within minutes) and a high THC bioavailability (18-23%), but a short duration of action (2-4 hrs) [1]. Smoking is extremely hard to control. It depends on the amount inhaled and overall time of ingestion. Also, the elderly population, characteristic of patients with advanced cancer, may be apprehensive about smoking a marijuana cigarette and may be more comfortable with alternative routes.

Suppositories of a THC hemisuccinate ester formulation increase THC absorption and promote a more consistent increase in food intake over other methods [6]. The onset is quicker than that of oral capsules, except after fasting [6, 90]. This route appears to be the most effective (highest THC bioavailability) and reliable [91]. However, the rectal route is not a preferred route for most patients.

The rate of absorption of oral THC varies greatly among individuals [6, 12, 70]. After oral administration, 90 – 95% of THC is absorbed [1]. However, due to first-pass metabolism, high lipid solubility, and rapid degradation in stomach acid [91], THC bioavailability is only 5-20% [70, 92]. Thus the required amount of THC will depend on the amount of the drug absorbed by the individual, which is the reasons we will allow patients to titrate their dose upwards if required. We will use oral THC (*i.e.* Marinol®) for this study because of its simplicity of administration and availability by prescription in Canada. Marinol® is approved by the American Food and Drug Administration for its use of as an antiemetic in the cancer population and as an appetite stimulant in the AIDS population. Therefore, a letter of approval from Health Canada is required for this trial for the use of THC as an appetite stimulant in the cancer population.

B. Rationale for chosen dosage and time of administration
It appears that the higher the dose of THC the lower the reward effects [93]. Previous studies have shown that low doses of THC lower brain-reward thresholds in the VTA-NAc reward axis to enhance brain reward processes in animals [see 77]. Moreover, smaller doses of THC, such as 2.5mg–5mg b.i.d. or t.i.d. are optimal for stimulating appetite [3, 6, 8, 57]. Nelson *et al* [11] reported THC to effectively increase appetite in cancer patients when taken one hour after meals. The drug was administered after meals to slow absorption, decrease the 'bolus effect' and reduce neuropsychiatric side effects [94]. However, the onset effect of THC is faster (0.5-1hr) when capsules are taken on an empty stomach [6]. Drug administration in early morning causes an increase in adverse events [57] and is not recommended [70]. Unimed Pharmaceuticals, a division of Solvay Pharmaceuticals (Marietta, GA) [70] suggest taking Marinol® 1 hr before lunch and supper. Several clinical trials support this time of administration [8-10].

The dose of THC administered must result in optimal appetite stimulation with minimal side effects. Previous THC studies have shown that dose and side effects are positively associated [8, 11, 12]. Currently, a dose of 2.5mg before lunch and supper is recommended for appetite stimulation based on clinical trials in the AIDS population [70]. However, some populations (*e.g.* the elderly) have reported sensitivity to psychoactive effects [95] thus doses should be further modified to avoid side effects. We are starting participants at 2.5mg of THC before bedtime because THC will induce sleep [1, 13]; negative psychoactive effects will be minimized [1, 13]; and absorption will be optimized as the patient's stomach is nearly empty at bedtime [6]. The participants should become tolerant to side effects within 1-3 days of drug treatment [70]. Thus, we will increase their dose after the 3rd day (Figure I.1) to the recommended 2.5mg twice a day.

The recommended dose of 2.5mg b.i.d. has been administered in cancer populations with promising results (*i.e.* 49% reported an increase in appetite) [12, 57]. However, Nelson [11] believes that higher doses may produce greater benefits if side effects can be tolerated [94] as the level of psychotropic activity is positively correlated with therapeutic effects [96]. Slightly higher doses (*e.g.* 2.5 mg t.i.d.) have successfully increased appetite in both cancer [3, 11] and healthy populations [4]. Since discrepancies regarding the optimal dose of THC still exist, patients will be allowed to titrate their dose upwards (up to 20mg THC/day) if they feel necessary.

<u>I. Genetics of endocannabinoid, dopamine and opioid systems</u>
Genetics related to the endocannabinoid, dopamine and opioid systems may affect pharmacological actions of THC and the cannabinoid reward-related pathway. Differences may exist in synthesis, transport, and release as well as receptor and second messengers of dopamine neurons involved in the reward pathway (delta-9-tetrahydrocannabinol elevates dopamine levels in the reward related limbic and forebrain dopaminergic loci[77]). Lepore *et al* [97] reported Lewis rats to be most affected by THC followed by Sprague-Dawley rats. Fischer rats were unaffected, but authors speculated that these rats may have shown THC-related effects with an elevated dose. From this and similar studies [98] it appears that genetics may play a role in drug effect, which could explain the variance in absorption seen in previous clinical trials [6]. Thus allowing participants to titrate their dose upwards also avoids this possible problem of genetics on reduced drug efficacy.

C. Rationale for length of treatment.
Cannabinoid levels appear to buildup gradually to an effective level in the blood [6, 8]. From previous studies, it appears that optimal results for appetite stimulation occur 2 weeks after

initiation of treatment [8, 11, 12, 70]. Therefore, we will encourage participants to stay on the treatment for at least 2 weeks. In our trial, participants will have 18 days of THC-treatment. This is the least number of days in which appetite stimulation is likely to be observed and the standard protocol for the completion of the 3-day dietary food record will be followed [82] (*i.e.* completed over two week days and one weekend day).

The onset time for THC-induced chemosensory responses is unknown. There are no studies that have evaluated chemosensory perception at either the THC dose we propose to use or in the advanced cancer population. Mattes *et al* [72] studied the effects of THC on taste intensity, hedonic responses, and caloric intake over 3 days in a healthy population and at relatively higher doses (*e.g.* 10-15mg THC/day). Thus, the effects of THC on chemosensory perception in cancer patients remain unknown. Therefore, we are proposing to ask questions (*i.e.* interview, Appendix I.C2) pertaining to THC effects on chemosensory perception after 1 week of treatment (Figure I.1). If chemosensory changes are present after one week then future clinical trials assessing THC's effect on chemosensory perception and food enjoyment can be conducted after one week of treatment. The reduced trial duration would potentially increase patient compliance.

D. Rationale for inclusion and exclusion criteria

Life expectancy is required to be longer than 2 months as patients' nutritional status and functional status decrease significantly near the end of life [15]. Participants must have at least 2 complaints (*i.e.* score >1 on the Taste and Smell Survey) because we are trying to determine THC's effects on advanced cancer patients with taste and smell abnormalities. Marinol® (THC) contains sesame seed oil, therefore subjects with allergies or insensitivities to THC or sesame seed oil will be excluded. We are excluding patients who are physically unable to eat (*i.e.* receiving enteral or parenteral feedings; mechanical obstructions of alimentary tract, mouth or nose).

We are excluding patients with brain tumors, since the hypothalamus (and thus appetite) can be affected [99]. We are excluding patients who have had radiation therapy to the head/neck because of the incidence of xerostomia [100, 101]. Xerostomia induces severe long-term chemosensory dysfunction due to radiation damage to salivary glands [100] - hyposalivation is normally irreversible [101]. We are excluding participants with an ESAS score greater than 5 as nausea at this level would be too much of a confounding factor on food intake and that patients with higher nausea scores would likely be embarking on a first or second line treatment for nausea at the time. We are excluding any patients with a concurrent diagnosis of liver impairment because THC is metabolized chiefly in the liver and the biliary excretion is the major route of elimination [70]. However THC is not expected to decrease liver functions (especially at the low dose used in this study) and any prolonged side effects can be reversed with the cessation of treatment.

Since THC is a narcotic we are excluding any subjects with a history of substance abuse or psychotic episodes. Delta-9-tetrahydricannabinol has been noted to increase heart rate, therefore subjects with a history of tachyarrhythmia, angina pectoris, or hypertension will be excluded. Cannabinoids gradually build up in the blood and remain in the system for up to month [1], therefore we are excluding individuals who have smoked marijuana within the past 30 days. We are not excluding participants who are taking potential appetite stimulants such as corticosteroids, as these subjects may be taking these drugs for other symptoms such as pain. By not allowing participants to change their corticosteroid dose for the duration of the study will ensure that the potential appetite stimulating effects of the corticosteroids do not affect the study results.

Rationale for tools selected for this study

A. Nutrient intake and Appetite

I. Three-day dietary record

To evaluate nutrient intake, subjects will be asked to complete a 3-day dietary record on days 1-3 and days 19-21. Other methods that evaluate caloric intake, such as 24hr dietary recalls, have been proven to be ineffective in the advanced cancer population, as subjects could not recall what they ate the day before [102]. Therefore, food records are the superior method and three days is the minimum duration that provides adequate assessments [82]. The recording days will include 2 weekdays and 1 weekend day, as this is the standard method that provides the most reliable assessments [82]. The Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR) will be used to analyze caloric intake and macronutrient composition of the diet. From these data we will be able to quantify anticipated increases in caloric intake to assess THC's appetite stimulating ability for cancer patients with and without chemosensory abnormalities. From previous studies we anticipate that THC will shift food preference towards palatable foods (*i.e.* sweet and salty foods). The three-day dietary record will allow us to see if the patients change their eating patterns to consume a greater quantity of palatable foods. However, food preferences and food consumed are not always highly correlated [81].

II. Food Preference Checklist

A North American 32-item Food Preference Checklist (FPC, Appendices I.E and II) [85], which was based on a previously validated Food Preference Checklist developed in the U.K [103] will be used to assess shifts in macronutrient and flavour preferences induced by THC. The foods chosen and thus recorded on the dietary record, may not be based on food preference alone [104]. Other factors influence food choices, such as price, convenience, nutrition, physiological need, culture, social norms, income, marketing, lifestyle, habit, and availability [105-107]. Thus the participants may not be eating what they actually prefer due to these external factors. The FPC asks participants to check off all the items (not accumulative) that they would *like* to eat at that moment. Thus the FPC minimizes the influence of external factors, providing a quick way (takes a maximum 5 minutes to complete) and more accurate assessment of THC's effect on food preferences. The FPC consists of a list of 32 commercially available foods that are either high carbohydrate (HC), high protein (HP), high fat (HF) or low energy (LE). Each of these four nutrient groups consist of 8 foods, 4 of which are predominantly sweet and 4 that are savoury, except for the HP group which consists of 8 savoury foods. Comparing the number of foods checked off in each of these nutrient groups over the course of the trial will demonstrate if THC does shift food preferences towards sweet and high fat foods.

The standard method for determining food preferences is to use a 9-point hedonic scale to rate a list of foods (usually 171-items) from "dislike extremely" to "like extremely" [19, 108-111]. The FPC is far less onerous than this standard method of assessing food preferences and has recently been shown to obtain comparable results [85].

III. Twenty-four hour urine nitrogen analysis

The 24-hr urine nitrogen analysis has been shown to effectively validate dietary records [83]. Twenty-four hour urine nitrogen is a biological marker used to determine the amount of protein consumed. Studies show that urine nitrogen should be ~80% of the dietary intake [112]. The 24-hr urine nitrogen analysis has been tried in the cancer population and was found to effectively validate dietary records [83]. Therefore, the 24-hr urine nitrogen analysis is a simple method to ensure that

no systematic misreporting of caloric intake occurs. We feel that a validation of the dietary records is necessary, as caloric intake is our primary measurable outcome. The 24-hr urine nitrogen analysis is an objective method that will validate the subjective 3-day dietary records.

IV. Satiety Labeled Intensity Magnitude scale

Appetite assessments will be made on a 200mm Satiety Labeled Intensity Magnitude scale (SLIM)[84] (Appendix I.B). Previous THC studies have used visual analogue scales (VAS) to assess subjective appetite [8-10, 57]. However, Cardello *et al* [84] recently determined that a labeled visual analogue scale (*i.e.* scale labeled with verbal indicators) increased the reliability and validity of appetite assessments compared to VAS. The verbal indicators will make it easier for our test population to quantify their appetite, since they most likely will be unfamiliar with line scales. The SLIM scale includes both fullness (0 to 100) and hunger (0 to -100) assessments. Thus we will obtain a more accurate assessment of the patients appetite compared to the VAS as a large majority of advanced cancer patients suffer from a constant perception of satiety[14].

V. Edmonton Symptom Assessment Scale The Edmonton Symptom Assessment Scale (ESAS) will be used to assess changes in nausea induced by THC. Since Marinol® (THC)'s indication is an anti-emetic [70], any changes in nausea should be reported, as a decrease in nausea may account for an increase in food intake. Thus the ESAS will help to clarify if THC is in fact improving taste and smell perception or if changes in nausea are the cause of increased food intake.

B. Chemosensory change

The validated tool of Heald *et al* [36] (Taste and Smell Survey, Appendix I.A1) was developed originally for use in an AIDS population to determine the severity of chemosensory complaints. In our study it will be used as a screening tool (participants must have a score >1 to be eligible for the study) and to separate patients into 2 sub-groups (within each study arm): 1) mild or moderate chemosensory complaints and 2) severe chemosensory complaints. We hypothesize that chemosensory complaints are a significant barrier to appetite stimulation. Thus this tool will allow us to determine for which group THC is a more effective appetite stimulant. The survey consists of 8 questions related to taste and 6 questions pertaining to smell. A point is awarded for each complaint; for two of the questions 2-points are earned if the complaint is severe. The overall chemosensory score is the combined score from the taste and smell sections. Scores range from 0-16, with 0 indicating no chemosensory change and 16 indicating the greatest number and severity of changes. Thus the participants with scores of 2-9 will be part of the mild/moderate chemosensory complaints and scores of 10-16 will comprise the severe chemosensory complaint group [35]. The Taste and Smell Survey will also be used to determine if THC can improve chemosensory perception by comparing pre-treatment scores to scores collected after 2 weeks of THC treatment. This tool was previously adapted and used by our Nutrition and Food Cancer Research Group at the University of Alberta and was found to be an effective self-assessment tool. Further modifications have been made to the Taste and Smell Survey (Appendix I.A2) which is administered after 2 weeks of THC treatment, to assess changes in chemosensory complaints related to the THC treatment. The scoring remains the same as the pre-treatment survey, which is in accordance with the procedures given by the original authors [36].

C. Quality of life

The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire [37] will be administered to assess any changes in quality of life (QOL), by comparing pre-treatment scores and scores after 2 weeks of treatment as well as comparing the mild or moderate chemosensory

complaint group to the severe chemosensory complaint group. The questionnaire consists of 40 questions, which will assess the 4 domains of QOL: physical; functional; social/family; and emotional well-being, as well as the nutritional QOL (anorexia/cachexia). Responses are evaluated on a 5-point Likert-type scale. Scores range from 0-156, with higher scores indicating a better QOL.

D. Cause of chemosensory complaints and food enjoyment

We will conduct a short interview at days 0 (Appendix I.C1), 11 (Appendix I.C2) and 18 (Appendix I.C2) to collect demographic information and to qualitatively document any changes in food enjoyment, food preferences, food aversions and diet that have occurred. The interview has been modified from a previous questionnaire utilized in our Nutrition and Food Cancer Research Group. These questions will explore the changes in food habits, preferences and sensory alterations as a result of the participant's cancer (pre-treatment, Appendix I.C1) and of THC treatment (after 1 or 2 weeks of treatment, Appendix I.C2). Interviews are a recommended method of assessing food enjoyment as patients are unique [18, 47] and there are currently no tools that effectively assess food-related QOL and food enjoyment. Interview questions allow for the flexibility necessary to collect all relevant information [16]. Cohen [113] suggested their use in advanced cancer settings because they can facilitate subjective observations that other survey tools cannot.

E. Drug tolerability and side effects

Delta-9-tetrahydrocannabinol affects the central nervous system. Previously reported common side effects of THC include euphoria, dizziness, somnolence, confusion [3, 8], delirium, abdominal pain, occasional nausea, and at high doses, ataxia [51] (also see Table I.2). It was also noted in these studies that the adverse effects associated with THC are relatively minor at the low doses used to induce appetite.

I. Drug tolerance

Repeated exposure to cannabinoids can result in a tolerance to several behavioral effects [see 76]. This tolerance may be caused by the down-regulation of the CB1 receptors after chronic THC exposure. The body adapts quickly to the cardioacceleration effects of THC [114] and motor coordination tolerance develops after only 24hrs of chronic cannabinoid exposure [see 76]. Thus if the participant experiences side effects, such as tachycardia, heart palpitations or ataxia, they should contact their doctor for instructions on decreasing their dose or ceasing the treatment. Even though tolerance to THC related adverse events occurs after a few days, tolerance to dopamine neuron firing in the VTA and to appetite stimulating effects does not appear to occur [91]. Since VTA neuron firing does not appear to change with prolonged exposure to THC, this suggests that tolerance does not develop to the pleasurable and rewarding experiences induced by the drug, however evidence is not entirely in congruence with this claim [see 76]. The continued stimulation of the reward pathway may explain why Haney, *et al* (1999) observed that even as the study participants no longer experienced psychoactive effects, they continued to demonstrate elevated levels of caloric intake. Therefore, we anticipate that advanced cancer participants will continue to benefit from the drug even over a prolonged period of time.

II. Drug safety

Several studies have investigated the use of THC as an appetite stimulant in varying populations (Table I.3). Not one of these studies had a withdrawal rate greater than 24% due to side effects. Jatoi *et al* [12] investigated 317 cancer patients with an average age of 67 ±10yrs; 152 participants were given Marinol and 159 were given megestrol acetate. Side effects were not found to be

statistically different between the two treatments, except male impotence was more prominent in the megestrol acetate arm.

Studies have shown that THC does not cause neuropsychological damage. Haney *et al* [5] found THC had little effect on task performance, even at extremely high doses of 100mg to 120mg a day. No changes were observed in performance status, intellectual function, and coordination and decreased depression and greater emotional stability were observed in participants in a study by Regelson *et al* [3] (5-20mg p.o. q.i.d.). All participants of the Nelson *et al* [11] study maintained their mini-mental status scores after 28 days of THC use (2.5mg p.o. t.i.d). Marinol has not been found to produce any long term adverse effects [9].

Haney *et al* [5] noted that terminations of drug after 120mg THC/day for 4 days showed increased ratings of anxiety, depression, irritability and restlessness, while decreasing the frequency of eating, and quality and quantity of sleep. Hart *et al* [115] noted in a comparison study of marijuana and oral THC (*i.e.* Marinol®) that withdrawal symptoms such as irritability and feeling miserable were only reported after smoking marijuana, not after taking Marinol® even at 80mg THC/day. Moreover, THC is highly lipophilic and as a result it is readily stored in fat cells and slowly released making withdrawal symptoms rare [76]. Thus we do not anticipate withdrawal symptoms to be an issue in this study.

Cannabinoids' adverse effects on panic attacks and anxiety appear to be greater in the elderly and in women [95]. Marinol® is not recommended for the treatment of anorexia in elderly patients, but it is recommended as an anti-emetic in cancer patients, who are frequently elderly (*i.e.* the mean age of cancer diagnosis in Canada is 65 years and the mean age for cancer-related death is 69 years). Given the demographics of cancer patient populations, one would assume that the indication for Marinol® use would have taken this age distribution into account. In addition, the recommended dose for chemotherapy-induced nausea is 4-6 times greater than the dose that we are proposing (2.5mg b.i.d.) [70]. Thus the adverse effects should be much lower in our trial compared to if Marinol® was administered for its recommended use in this population. Moreover, the adverse effects of THC are as tolerable and acceptable as the side effects of other medications [116]. Marinol® has been proven to be a safe drug. Side effects are usually mild to moderate, are reduced by decreasing the dose, and resolve rapidly after cessation of therapy [70]. Beal *et al* [9] reported that the long-term use of THC is safe. Delta-9-tetrahydrocannabinol did not cause toxicity and continued to increase appetite over the 6-month trial. Researchers agree that THC is a safe and effective appetite stimulant in advanced cancer and AIDS populations [11, 57, 94].

Drug side effects will be tabulated using a modified questionnaire from Ware *et al* [87] (Appendix I.D) developed for marijuana. Our survey includes the side effects of the Ware *et al* [87] questionnaire with additional questions pertaining to the major side effects associated with Marinol® (THC) (*i.e.* abnormal thinking, dizziness, abdominal pain, and nausea). Each side effect is rated by selecting one of the following descriptors: "did not experience", "enjoyable", "neutral", or "unpleasant". The participants will also be asked if they have experienced any other side effects from THC, as rare side effects associated with THC use (*e.g.* myalgias, tinnitus, *etc*) have been previously reported (Table I.2).

Sample size and statistical analyses

Power test

Data from our lab revealed that the energy intakes for an advanced cancer population stratified according to chemosensory ability were 27.4 kcal/kg/day SD=11.0 (mild complaints), 25.9 kcal/kg/day SD=11.2 (moderate complaints), and 19.3kcal/kg/day SD=8.7 (severe complaints) [35]. Since we are considering the two sub-groups (mild/moderate chemosensory complaints and severe chemosensory complaints) within each study arm, we will use an anticipated average caloric intake of 26.7 Kcal/kg/day SD=11.2 for the mild/moderate complaint group. We anticipate the drug to be effective for this group and thus base the power calculations on these data. From previous literature, the expected orexigenic effect of THC, after accounting for placebo effects, ranges from approximately 7.6 kcal/kg/day [7] to 16.4kcal/kg/day [5, 115]. To be conservative we will use 7.6 kcal/kg/day. Using these values with a power of 0.8 and an alpha=0.05, N=27 for each arm. Bruera [117] suggested planning for a withdrawal rate of around 30% for trials lasting over 14 days with advanced cancer patients. Since the study is conducted in a potentially THC-sensitive group (an elderly population), withdrawal rates of 10-15% (in addition to the estimated 30% withdrawal rates above) should be expected due to side effects. Taking these withdrawal rates into consideration we will need a minimum of 40 patients in each arm to avoid non-statistically significant results due to a limiting sample sizes.

Statistical analyses

All statistical analyses will be performed using the Statistical Analysis System (SAS) [118]. Descriptive statistics (PROC UNIVARIATE) [118] will be used to describe the prevalence, nature, and severity of chemosensory complaints and to describe the prevalence and nature of a food preference shift as assessed by the 3-day dietary record and interview. Chi-Squared and Fisher's Exact test analyses will be used for evaluations of patient characteristics and side effects. Regression analyses [119] will be used to assess the relationship between chemosensory complaint scores (Taste and Smell Survey) and 1) caloric intake (3-day dietary record); 2) QOL (FAACT); 3) appetite (SLIM); 4) food preferences (FPC); 5) nausea (ESAS); and 6) chemotherapy (dose and type) at baseline and after 18 days of treatment. Time series analysis of variance [119] will also be used to assess appetite and food preferences over the trial. T-tests of the difference in change [119] will be used to compare the treatment arm to the placebo arm for total caloric intake, QOL, and chemosensory complaints after 2 weeks of treatment. Paired t-tests will be used to compare total caloric intake, QOL, and chemosensory complaints for both arms at pre treatment and after 2 weeks of treatment. Wilcoxon's Rank-Sum test will be used to compare parametric measures (*e.g.* caloric intake) with nonparametric measures (*e.g.* QOL and chemosensory complaints scores, *etc*) as well as to compare chemosensory complaint scores to QOL scores [36]. Both study arms will be evaluated for food intake through analysis of covariance [120], where nausea, appetite, chemosensory complaints, and chemotherapy will be covariant variables. We plan to do an interim analysis at the half-way point of data collection.

Conclusions and benefits

"Experts recognize that for the newborn, the mouth provides the first sensation of pleasure and satisfaction, and for the elderly, eating food can provide one of the last sources of satisfaction" [121]. The number of advanced cancer patients who suffer from both cachexia and chemosensory changes is substantial. Since THC is involved in perception alteration, it is plausible that this agent could overcome some degree of chemosensory complaints to promote increased intake. However, a person who finds food repulsive would be refractory to appetite stimulation, which may account

for the relatively high proportion of treatment failures with orexigenic agents, such as Marinol® or megestrol acetate [54]. If it were possible to confirm a lack of efficacy of THC in certain sub-populations, or a high efficacy in certain cases connected with the chemosensory perception score or problems, this would allow more effective targeting of drug to appropriate patients. This study is the first experiment in a series of clinical trials assessing THC's ability to improve food-related QOL through chemosensory perception. This project is part of the ongoing activity of our unique Food and Cancer Research Group at the University of Alberta.

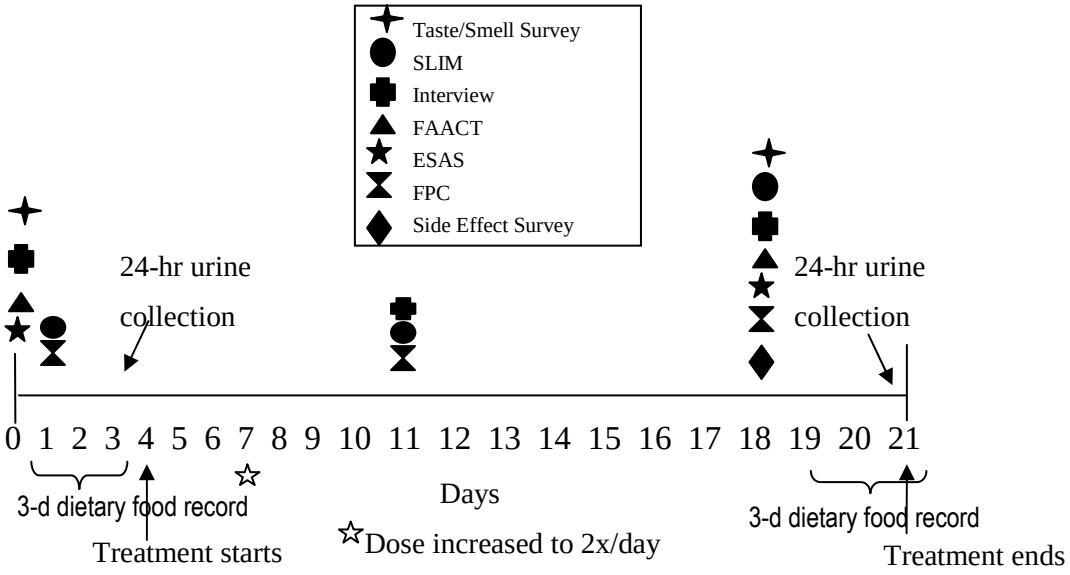

Figure I.1 Experimental timeline for a double blind, randomized, placebo-controlled THC trial in advanced cancer patients

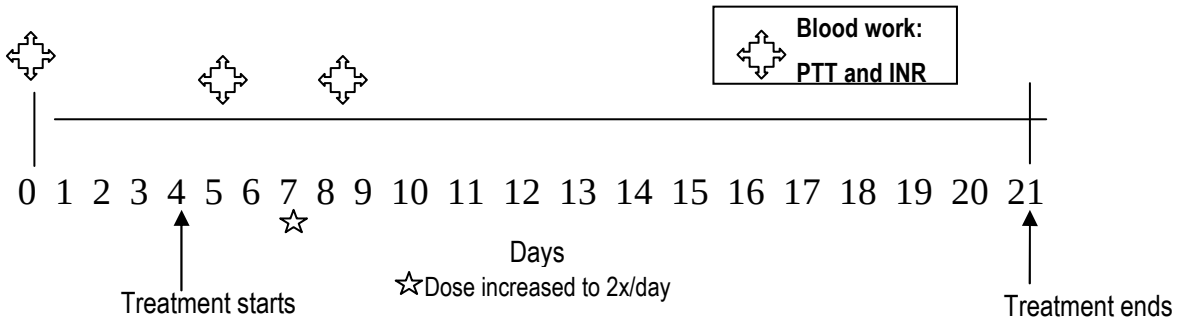

Figure I.2 Additional procedure for patients on coumadin

Table I.1: Nomenclature associated with chemosensory disorders [adapted from 28]

Name	**Meaning**
Normosmia	Normal smell function
Normogeusia	Normal taste function
Hyposmia	Diminished smell
Anosmia	Loss of smell
Hypogeusia	Diminished taste
Ageusia	Loss of taste
Hyperosmia	Heightened smell sensation
Hypergeusia	Heightened smell sensation
Dysosmia	Abnormal/distorted smell
Dysgeusia	Abnormal/distorted taste

Table I.2: Side effects associated with Marinol® (THC) from controlled clinical trials in AIDS population (N=474**)** [69]

Common	***Uncommon/Rare***
Incidence: 3-10%	**Incidence < 1%**
-Nervous system: euphoria, thinking abnormalities, dizziness, paranoid reaction	-Nervous system: depression, nightmares, speech difficulties, tinnitus
-Drowsiness	-Cardiovascular: hypotension, conjunctivitis
-Digestive: abdominal pain, nausea, vomiting	-Myalgias
	-Skin and appendages: flushing
Incidence 1-3%	
-Asthenia	
-Cardiovascular: palpitations, tachycardia, vasodilation/facial flush	
-Nervous system: amnesia, ataxia, dizziness, depersonalization, confusion, delirium, anxiety/nervousness, hallucinations	

Table I.3: Human studies involving administration of cannabinoids (*e.g.* delta-9-tetrahydrocannabinol, marijuana)

Reference	N =	Dose	Duration	Time of Administration	Instruments	Time of Evaluation
Beal (1995)	AIDS: 88 (dronabinol vs placebo)	2.5mg p.o. b.i.d. THC (decreased to 2.5mg/day if needed)	6 weeks	1 hr before lunch and supper	VAS, Karnofsky scale	3 days at baseline, and 3 days weekly
Haney (1999)	Healthy heavy Marijuana users: 12 (6 female, 6 male)	20mg p.o.q.i.d.THC (1st user phase) 30mg p.o.q.i.d.THC (2nd user phase)	20-day period (3 days placebo pre and post drug use, 4 days drug use, 4 days placebo, 4 days drug use)	1000h, 1400h, 1800h, and 2200h	50-item VAS (mood, drug effect, physical symptoms, etc., sleep questionnaire, weight, 3 work periods (learning, memory, vigilance and psychomotor ability), bar codes on food (substance, proportion)	Weight (0800h), sleep questionnaires (0800h), work periods and VAS (0915h, 1015h, 1415h), marijuana withdrawal checklist (2330h)
Nelson (1994)	Cancer anorexia (varying malignancies) 18	2.5mg p.o. t.i.d THC 2.5mg p.o. b.i.d THC (over 65 years, for 3 days, then increased to 2.5mg t.i.d.)	4 weeks	one hour after meals	physical exam (weight, height, etc), Folstein's mini-mental, 24 hr food diary, side effect profile	Food diaries (weekly), side effect profile (weeks 2, 4), physical and mental exams (weeks 0,2,4)
Mattes (1994a)	Healthy, light Marijuana users: 1) 57 (placebo vs THC) 2) 11 (oral vs inhalation vs sublingual) 3) 6 (rectal vs oral) 4) 10 (fasting vs satiated)	•15 mg (males), 10 mg (females) p.o. daily (1) •15 mg (males), 10 mg (females) p.o. daily (2a,c) THC, 710-795mg marijuana cigarette: 2.57% THC (2b) •2.5mg p.r. b.i.d.* (3a) THC, with hemisuccinate ester •2.5mg p.o. b.i.d. (3b) THC •15 mg (males), 10 mg (females) p.o. daily (4) THC	•sessions (0800-2000h) •4 day sessions (2) •3 day sessions (3) •3 weeks between 1st and 2nd session	After breakfast (1,2,4) 0900h After breakfast and 1 hr before supper (3) 1700h	Dietary questionnaires (appetite and food cravings), chemosensory tests, pre-weighed food (60 items), blood, urine, and saliva samples, Nutritionist III Nutrient Database	Dietary questionnaires (hourly), chemosensory tests and blood draws (1100, 1300, and 1500h), self-selected meals and snacks
Mattes (1994b)	Healthy, light marijuana users: 1) 57 (oral vs sublingual vs inhalation) 2) 11 (3 routes + placebo) 3) 6 (oral vs rectal)	•15 mg (males), 10 mg (females) p.o. daily (1) THC •15 mg (males), 10 mg (females) p.o., p.r. THC, 764mg marijuana cigarette: 2.57% THC; placebo: p.r., routes were randomized (2) •2.5mg p.o.b.i.d. (3a) THC •2.5mg p.r.b.i.d. (3b) THC, with hemisuccinate ester	•sessions (0800-2000h) •4 day sessions (2) •3 day sessions (3) •3 weeks between 1st and 2nd session	After breakfast (1,2) 0900h After breakfast and 1 hr before supper (3) 1700h	Appetite and taste questionnaires, chemosensory tests (13-pt category scale response with 5 descriptors), collected saliva, blood and urine samples, pre-weighed foods, hedonic and threshold of different concentrated solutions, foods selected	Taste intensity and hedonic responses [2,4,6 hrs: (1,3) and daily: (2)], chemosensory tests and blood draws (1100, 1300, and 1500h)

*optimal dose VAS = Visual analogue scale

Table 4: Human studies involving administration of cannabinoids (*e.g.* delta-9-tetrahydrocannabinol, marijuana)

Reference	Appetite	Mood	Taste	Weight Gain	Side Effects	Other Outcomes
Beal, (1995)	↑ (P=0.05)	Improved (P=0.06)	Not assessed	↑ (P=0.14)	euphoria, dizziness, thinking abnormalities, and somnolence	•Performance status slightly decreased (2pts, on 100pt scale) for dronabinol arm • decrease nausea for dronabinol arm
Haney (1999)	↑ (drug phase)	↑ quality and quantity of sleep (drug phase)	Not assessed	↑ men ↓ women	•"High" (1st, 2nd phase) •Trouble sleeping, muscle pain, cannot concentrate, clumsy (2nd phase)	•Increased caloric intake and number of eating occasions especially in afternoons and evenings (drug use) •Decreased "stimulated" feeling after 3 or 4 days of drug use •Increased anxiety, depression, irritability and restlessness (placebo phases)
Nelson (1994)	↑	Not assessed	Not assessed	↑	Grade I nausea (n=1), slurred speech (n=1)	•8/9 who kept food diaries had increased caloric intake •Disappearance of the side effects when dose was decreased temporarily •All patients maintained their mini-mental status scores
Mattes (1994a)	↑ (3a,b)	Not assessed	↑ sweet solid foods: pastries and chocolates, followed by salty foods (1,3,4) Salty>sweet (2)	Not assessed	Information not available	•No observable differences due to age •20% claimed to eat after returned home •Plasma levels varied (oral) •Inhalation (2b) had quickest onset followed by oral after fasting (4a) •Snacks accounted for more energy than lunch •No difference between macronutrient intake •Limited significant differences due to low sample numbers
Mattes (1994b)	Not assessed	Not assessed	↑ sweet and salty snacks vs placebo	Not assessed	Information not available	•Consistent identification of intensity proportional to concentrations of solutions •Results are not statistically significant •Increased preference for salty foods 2 hrs post dosing •Increased snack intake compared to placebo
Regelson (1976)	↑	↓ Depression ↑ Emotional stability ↑ Tranquility ↓ Anxiety	Not assessed	↑	•0.1-0.12mg/kg virtually no side-effects (1) •intermediate dose (0.17-0.18mg/kg) and high dose (0.31-0.34 mg/kg) had side effects (1) •25% experienced side effects (2) •Dizziness, somnolence and dissociation	•Antiemetic and analgesic properties •To reduce pain the dose required is usually too high and causes negative side effects
Jatoi (2002)	↑ (1>2)	Not assessed	Not assessed	↑ (1>2)	Male impotence, fluid retention (2>1)	•Objective weighing by the physician resulted in a higher % weight gain, compared to self-reported weight gain (1,2) •No change in QOL (1,2)

↓ = decrease
↑ = increase

Table 4: Human studies involving administration of cannabinoids (*e.g.* delta-9-tetrahydrocannabinol, marijuana)

Reference	N =	Dose	Duration	Time of Administration	Instruments	Time of Evaluation
Regelson (1976)	Advanced cancer: 1) 10 2) 54	0.10 – 0.34mg/kg p.o. q.i.d. THC (1) 0.1mg/kg p.o. t.i.d. THC (2) (Adjusted up or down based on side effects)	•14 days (1,2) •1 week placebo (2)	1 hr before meals (2)	Karnofsky scale, physician records, standard ECOSG flow sheets, 6 psychological tests	weekly
Jatoi (2002)	Advanced cancer: 1) 152 (dronabinol) 2) 159 (megestrol acetate-MA)	2.5 mg p.o. b.i.d. THC (1) 800mg/day p.o. liquid suspension MA (2)	57 days (1) 80 days (2)	Information not available	physical examination, previously validated NCTG questionnaires (appetite and weight), single item Uniscale (QOL), 13-item anorexia-specific FAACT (QOL)	Physical examination (baseline, monthly), NCTG questionnaires [baseline, weekly, monthly (after 4 weeks)], appetite (week 2 & 4)
Beal (1997)	AIDS-anorexia 94 (46 previously received dronabinol)	2.5 mg p.o. b.i.d. THC (90%) 2.5 mg p.o. once daily THC (10%)	12 months	•Before breakfast and dinner or at bedtime •Single dose in evening	VAS (100mm) for appetite, dosing logs, direct questioning, physical examinations	Monthly (appetite, adverse effects, and weight)
Beal (1995)	AIDS: 88 (dronabinol vs placebo)	2.5mg p.o. b.i.d. THC (decreased to 2.5mg/day if needed)	6 weeks	1 hr before lunch and supper (single dose: before supper or bedtime)	VAS (100mm) for appetite, dosing logs, direct questioning, physical examinations	Every 2 weeks (appetite, adverse effects, and weight)
Plasse (1991)	Cancer: 42 (Group 1: chemotherapy Group 2: no chemotherapy)	2.5mg p.o. q.i.d., 2.5mg p.o. b.i.d., 5mg p.o. q.i.d., 5mg p.o. b.i.d	3 weeks (1) 6 weeks (2)	Before meals	VAS for appetite and mood	Before each meal (appetite), before lunch (mood)
Hollister (1970)	Healthy: 12	32mg THC p.o. (1) fed 26mg THC p.o. (2) fasted (vehicle was a flavored non-caloric beverage)	1 day (1 week washout period)	0800am	Hunger questionnaire (8-pt scale), taste questionnaire (5pt scale), blood samples (for glucose and FFA)	Chocolate milkshakes were offered @ 1100, 1130, noon, and 1300hrs, all tests completed at these times
Sallan (1980)	Cancer + chemotherapy: 73 (mean age=32.5yrs)	10mg/m^2 of body surface area THC p.o. t.i.d 10mg THC p.o. t.i.d. (minimum) 15mg THC p.o. t.i.d. (average) 10mg p.o. Prochlorperazine	N=27 completed 1 course; N=8, 2 courses; N=38, 3 courses	•1 hr before chemotherapy, 3 and 7 hrs after chemotherapy •Received THC (T) and Prochlorperazine (P) in 1 of 6 ways: TTP,PPT,TPT,PTP,TPP, PTT	Self-administered questionnaire for nausea, vomiting, food intake, and development of "high"	Daily

*optimal dose VAS = Visual analogue scale MA = Megesterol acetate

Table 4: Human studies involving administration of cannabinoids (*e.g.* delta-9-tetrahydrocannabinol, marijuana)

Reference	Appetite	Mood	Taste	Weight Gain	Side Effects	Other Outcomes
Beal (1997)	↑	Not assessed	Not assessed	↑	Anxiety, confusion, depersonalization, dizziness, euphoria, somnolence, and thinking abnormalities	▪Dosage was modified by 38%, 19% increased (5-10mg daily) and 19% decreased (2.5mg at bedtime) ▪Dronabinol was not found to interfere with other medications
Beal (1995)	↑	↑	Not assessed	↑	•euphoria, dizziness, thinking abnormalities, and somnolence •43% (dronabinol) & 13% (placebo) •Ceased by decreasing dose or stopping treatment	•Decreased nausea (statistically significant) •Stabilized weight in all patients •The 11 patients who decreased their dose to 2.5mg/daily, had the same increase in appetite as those taking 2.5mg THC b.i.d. •Karnofsky performance status slightly decreased in THC group
Plasse (1991)	↑ (2.5mg b.i.d.)	↑ (2.5mg b.i.d.)	Not assessed	Not assessed	Dizziness, memory or concentration difficulties, drowsiness, and mood changes	•Improvement in appetite and mood seen after 3 weeks •Side effects more severe on empty stomach in the morning •Patients could effectively adjust dose to avoid side effects
Hollister (1970)	↑ (1,2)	Not assessed	Not assessed	Not assessed	Euphoria and sleepiness	•THC made subjects eat more frequently •THC appears to induce eating even in a satiated state (those that ate breakfast consumed more milkshakes overall) •Increased appreciation of food, judged by appetite questionnaire
Sallan (1980)	↑ (50%)	Not assessed	Not assessed	Not assessed	"High", i.e. laughing, elation, heightened awareness, mild aberrations of fine motor coordination, or minimal distortion of activities ad interactions with others	•Anti-emetic response with THC was superior and preferred over prochlorperazine •Becoming "high" was correlated with increased food intake and anti-emetic responses
Timpone (1997)	↑ (all arms after 1 week only)	No statistical difference between arms	Not assessed	↑ (2,3)	•THC: confusion, anxiety, emotional lability, euphoria, hallucinations •MA: dyspnea, liver enzyme changes, hyperglycemia •Differences between arms for side effects were not statistically different	•There was no statistical difference between arms for QOL measurements •For study population improvements in social/family QOL were reported

↓ = decrease
↑ = increase

Table 4: Human studies involving administration of cannabinoids (*e.g.* delta-9-tetrahydrocannabinol, marijuana)

Reference	N =	Dose	Duration	Time of Administration	Instruments	Time of Evaluation
Timpone (1997)	AIDS: 52 (mean age=40 ± 8yrs)	1) 2.5mg THC p.o. b.i.d. 2) 750mg MA p.o. daily 3) 750mg MA p.o. daily + 2.5mg THC p.o. b.i.d 4) 250mg MA p.o. daily + 2.5mg THC p.o. b.i.d	12 weeks	1 hr before lunch and supper (THC) 1 hr before lunch (MA)	VAS (100mm) for hunger (VASH), mood (VASM), nausea (VASN); functional assessment questionnaire for HIV (FAHI); Karnofsky (QOL); scale weighing	Karnofsky every 2 weeks; VASH (3 times a day before meals), VASM (at noon), VASN (at noon) 3days/week; FAHI every 4 weeks, weighed every 2 weeks
Walsh (2005)	Cancer: 6 (mean age=65.7yrs, range=52-74yrs)	15mg THC p.o. /day (N=5) 7.5mg THC p.o. /day (N=1) Following 4 week study (Nelson, 1994) of 2.5mg p.o. b.i.d. or t.i.d.	2-30 weeks	Information not available	5 questions regarding efficacy and side effects, weight by scale at pre and post treatment only	During outpatient clinic visits, usually every 2 weeks
Huestis (2001)	Healthy male marijuana users: 63 (age range= 21-45yrs)	1) p. SR141716 + p. marijuana (N=10) 2) p. SR141716 + marijuana (N=10) 3) SR141716 + p. marijuana (N=2 @ 1, 3, 10, 30, 90mg SR141716) 4) SR141716 + marijuana (N=8 @ 1mg; N=7 @ 3mg; N=6 @ 10, 30, 90*mg SR141716) P = placebo; marijuana = 20mg THC in a marijuana cigarette	4 days (1 day of testing)	SR 141716 or placebo @ 9am and marijuana or placebo cigarette @11am	VAS for intoxication and heart rate, M scale (subset of Addiction Research Centre Inventory) for intoxication, heart rate monitor, SR141716 and THC assays from blood samples	Subjective responses: 1hr before SR141716, 1hr before marijuana smoking, and @ 5, 10, 15, 20, 25, 55, and 65 min after marijuana smoking; continuously for heart rate; blood samples 10 min before SR141716, 5 min before marijuana, and @ 2, 5, 10, 15, 20, 40, 60, 80, and 100 min after smoking
Strasser (2006)	Advanced cancer: 1) 100 (THC, extract) 2) 95 (THC + cannabidiol, extract) 3) 48 (placebo)	2.5 mg p.o. b.i.d. THC (1) placebo (2) 2.5mg THC + 1 mg cannabidiol (3) All oral capsules	6 weeks	1 hr before lunch and supper or bedtime, preferably with milk	Word anchored VAS for appetite (0= worst, 100 = best), QOL on VAS 0-100mm transformed from EORTC QLQ-C30, full EORTC QLQ-C30 was completed biweekly (QOL scores were combined 0-100), 3 VAS used for estimation of previous 24hr food intake, current nausea, current mood	Baseline, weeks 2,4,6

*optimal dose VAS = Visual analogue scale MA = Megesterol acetate

Table 4: Human studies involving administration of cannabinoids (*e.g.* delta-9-tetrahydrocannabinol, marijuana)

Reference	Appetite	Mood	Taste	Weight Gain	Side Effects	Other Outcomes
Walsh (2005)	↑ (50%)	↑ (50%)	Not assessed	↑ (67%)	0% - No side effects were reported by participants	▪Stabilized or improved appetite and food intake for all participants ▪Only 1 participant (developed ascites) reported to feel worse and have decreased energy levels ▪None of the participants lost weight on the drug
Huestis (2001)	Not assessed	Not assessed	Not assessed	Not assessed	"High" and heart rates were reduced by SR141716	•Smoked marijuana effects were blocked in part by SR141716 •Higher doses of antagonist may have been more effective •SR141716 did not change THC plasma concentration
Strasser (2006)	↑ (58% ,1) (73% ,2) (69% ,3)	↑ (46% ,1) (60% ,2) (64% ,3)	Not assessed	No differences from baseline for any group	Nausea/vomiting, fatigue, pain, anemia, vertigo, dyspnea, diarrhea, obstipation – no side effects were significantly different among groups	•Trial was stopped due to no differences between THC or CE and placebo groups •No differences in QOL, appetite, mood, or side effects were reported between groups

↓ = decrease
↑ = increase

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Appendix I.A.1 Taste and Smell Survey pre-treatment

TASTE AND SMELL DYSFUNCTION IN CANCER PATIENTS

The purpose of this survey is to see how cancer affects the senses of taste and smell. Please answer the following questions as best you can.

Participant number: _____ Date: ____/____/____

1. Have you noticed any changes in your sense of taste? yes no

   If yes, please describe:

   _____

   _____

2. Have you noticed any changes in your sense of smell? yes no

   If yes, please describe:

   _____

   _____

3. Have you ever noticed that a food tastes different than it used to? yes no

   If yes, please describe:

   _____

   _____

4. Have you ever noticed that a food smells different than it used to? yes no

   If yes, please describe:

   _____

   _____

5. I have a persistent bad taste in my mouth (circle BEST answer)
   1. never
   2. rarely
   3. sometimes
   4. often
   5. always

6. The persistent taste is (circle ALL that apply)
   1. salty
   2. sweet (like sugar)
   3. sour (like lemon or vinegar)
   4. bitter (like black coffee or tonic water)
   5. other (specify)
      _____

7. Do specific drugs interfere with your sense of taste? yes no

   If yes, which ones?

   _____

   _____

8. Do some drugs taste worse than others? yes no

   If yes, which ones?

   _____

   _____

9. Do specific drugs interfere with your sense of smell? yes no

   If yes, which ones?

   _____

   _____

10. Do some drugs smell worse than others? yes no

    If yes, which ones?

    _____

    _____

11. Comparing my sense of taste now to the way it was before I was diagnosed with cancer:

a. Salt tastes (circle BEST answer)
   1) stronger
   2) as strong
   3) weaker
   4) I cannot taste it at all

b. Sweet (sugar) tastes (circle BEST answer)
   1) stronger
   2) as strong
   3) weaker
   4) I cannot taste it at all

c. Sour (lemon or vinegar) tastes (circle BEST answer)
   1) stronger
   2) as strong
   3) weaker
   4) I cannot taste it at all

d. Bitter (black coffee or tonic water) tastes (circle BEST answer)
   1) stronger
   2) as strong
   3) weaker
   4) I cannot taste it at all

12. Comparing my sense of smell now to the way it was before I was diagnosed with cancer,
    odors are
    1) stronger
    2) as strong
    3) weaker
    4) I cannot smell at all

13.Over the past 3 months, I would rate my abnormal sense of taste as: (circle BEST answer)

1. insignificant
2. mild
3. moderate
4. severe
5. incapacitating

14. How has your abnormal sense of taste affected your quality of life?

_____

_____

15. Over the past 3 months, I would rate my abnormal sense of smell as: (circle BEST answer)

1. insignificant
2. mild
3. moderate
4. severe
5. incapacitating

16. How has your abnormal sense of smell affected your quality of life?

_____

_____

Appendix I.A.2 Taste and Smell Survey post-treatment

TASTE AND SMELL DYSFUNCTION IN CANCER PATIENTS

The purpose of this survey is to see how the study treatment has affected the senses of taste and smell. Please answer the following questions as best you can.

Participant number: _____ Date: ____/____/____

Since the study treatment

1. Have you noticed any changes in your sense of taste?

   no, it's the same yes, it's better yes, it's worse

   If yes, please describe:

   _____

   _____

2. Have you noticed any changes in your sense of smell?

   no, it's the same yes, it's better yes, it's worse

   If yes, please describe:

   _____

   _____

3. Within the past 2 weeks, have you ever noticed that a food tastes different than it used to?

   no, it's the same yes, it's better yes, it's worse

   If yes, please describe:

   _____

   _____

4. Within the past 2 weeks, have you ever noticed that a food smells different than it used to?

no, it's the same yes, it's better yes, it's worse

If yes, please describe:

_____

_____

5. I have a persistent bad taste in my mouth (circle BEST answer)
   1. never
   2. rarely
   3. sometimes
   4. often
   5. always

6. The persistent taste is (circle ALL that apply)
   1. salty
   2. sweet (like sugar)
   3. sour (like lemon or vinegar)
   4. bitter (like black coffee or tonic water)
   5. other (specify)

      _____

7. Do specific drugs interfere with your sense of taste? yes no

   If yes, which ones?

   _____

   _____

8. Do some drugs taste worse than others? yes no

   If yes, which ones?

   _____

   _____

9. Do specific drugs interfere with your sense of smell? yes no

   If yes, which ones?

   _____

10. Do some drugs smell worse than others? yes no

If yes, which ones?

_____

_____

11. Comparing my sense of taste now to the way it was before I started the study treatment:

a. Salt tastes (circle BEST answer)
   1) stronger
   2) as strong
   3) weaker
   4) I cannot taste it at all

b. Sweet (sugar) tastes (circle BEST answer)
   1) stronger
   2) as strong
   3) weaker
   4) I cannot taste it at all

c. Sour (lemon or vinegar) tastes (circle BEST answer)
   1) stronger
   2) as strong
   3) weaker
   4) I cannot taste it at all

d. Bitter (black coffee or tonic water) tastes (circle BEST answer)
   1) stronger
   2) as strong
   3) weaker
   4) I cannot taste it at all

12. Comparing my sense of smell now to the way it was before I started the study treatment, odors are
    1) stronger
    2) as strong
    3) weaker
    4) I cannot smell at all

13. Over the past 2 weeks, I would rate my abnormal sense of taste as: (circle BEST answer)
    1. insignificant
    2. mild
    3. moderate
    4. severe
    5. incapacitating

14. How has your abnormal sense of taste affected your quality of life?

_____

_____

15. Over the past 2 weeks, I would rate my abnormal sense of smell as: (circle BEST answer)
    1. insignificant
    2. mild
    3. moderate
    4. severe
    5. incapacitating

16. How has your abnormal sense of smell affected your quality of life?

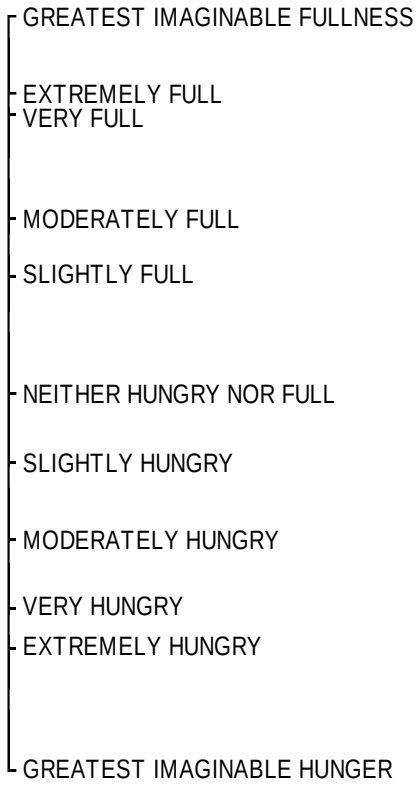
_____

_____

Appendix I.B Satiety Labeled Intensity Magnitude Scale (SLIM)

Participant Number: _____ Date: ____/____/____
Time: _____

Please rate the degree of hunger/fullness you are currently feeling
(Please put a slash (/) mark somewhere on the line below)



Appendix I.C.1 Interview pre-treatment

TASTE AND SMELL PERCEPTION IN CANCER PATIENTS

Participant Number: _____ Date: ____/____/____

There are 3 short sections to this survey.

This part of the survey asks about changes in your food preferences since the onset of your cancer.

1. Since the onset of your cancer, do you avoid or dislike certain foods? yes no

   If yes which ones,

Foods I dislike or avoid	Reason *(e.g. too bland, taste/smells funny, burning sensation, taste too strong, induces nausea…)*	Check (√) if you have always disliked this food

2. Since the onset of your cancer, do you prefer or enjoy certain foods? yes no

   If yes which ones,

Foods I prefer or enjoy	Reason *(e.g. sweet taste, salty taste, fatty, healthy, crunchy, soft, easy to prepare, like the odor/ taste, satisfying, flavorful, bland, spicy…)*	Check (√) if you have always liked this food

3. Are there any odors that are unpleasant to you? yes no

If yes, which ones?

Types of odors that are unpleasant	**Yes**	**No**
Food		
Perfumes		
Hospitals		
Medicines		
Others		

The purpose of this part of the survey is to determine if there are factors other than cancer that influence your sense of taste and smell. Please answer the following questions as best you can.

4.	Do you wear dentures?	Yes	No
5.	Have you had mouth and/or gum infections in the past two years?	Yes	No
6	Are you currently bothered by hay fever and/or allergies?	Yes	No
7	Are you currently bothered by your sinuses?	Yes	No
8	Does your sense of smell change from day to day?	Yes	No
9	Does your sense of taste change from day to day?	Yes	No
10	Has a doctor previously diagnosed you with any taste or smell problems?	Yes	No
11	Before your cancer, did you have any problems with your sense of taste or smell?	Yes	No
12	Do you smell “phantom odours”? (you can smell something but the source of the smell is nowhere near you)	Yes	No
13	Are you taking herbal medicines? If yes, which ones?_____	Yes	No

14	Are you currently a cigarette smoker?	Yes	No
15	If you are not a current smoker, are you a former cigarette smoker?	Yes	No
16	Do you receive acupuncture treatment?	Yes	No
17	Does a caregiver prepare the majority of your meals?	Yes	No
18	Do you prepare the majority of your meals?	Yes	No
19	Do you eat your meals alone?	Yes	No
20	Are you depressed?	Yes	No

Some symptoms or problems can affect your ability to eat. Please indicate the extent to which you experienced these symptoms or problems in the past week, using a scale from one to five, where 1 represents "not at all" and 5 represents "very often".

		Not at all				Very often
21.	Do you have pain or soreness in your mouth, your jaw or your throat?	1	2	3	4	5
22.	Do you have problems swallowing liquids?	1	2	3	4	5
23.	Do you have problems swallowing puréed foods? *E.g. applesauce*	1	2	3	4	5
24.	Do you have problems swallowing solid food?	1	2	3	4	5
25.	Do you have a dry mouth?	1	2	3	4	5
26.	Do you have sticky saliva?	1	2	3	4	5
27.	Do you have trouble eating?	1	2	3	4	5
28.	Do you suffer from constipation?	1	2	3	4	5
29.	Do you enjoy your meals?	1	2	3	4	5

30. Please list all the medications you are currently taking

_____

Appendix I.C.2 Interview post-treatment

TASTE AND SMELL PERCEPTION IN CANCER PATIENTS

Participant Number: _____ Date: ____/____/____

There are 2 short sections to this survey.

The purpose of this part of the survey is to determine if there are factors other than cancer that influence your sense of taste and smell. Please answer the following questions as best you can.

1. Does your sense of smell change from day to day?	Yes	No
2. Does your sense of taste change from day to day?	Yes	No
3. Did the study medication make food taste better?	Yes	No
4. Are you depressed?	Yes	No

		Not at all				Very often
5.	Do you enjoy your meals?	1	2	3	4	5

This part of the survey asks about changes in your food preferences with the study treatment

6. Are there any odors that are unpleasant to you? yes no

If yes, which ones?

Types of odors that are unpleasant	**Yes**	**No**
Food		
Perfumes		
Hospitals		
Medicines		
Others		

7. Since starting the study treatment, do you avoid or dislike certain foods? yes no

If yes, which ones?

Foods I dislike or avoid	Reason *(e.g. too bland, taste/smells funny, burning sensation, taste too strong, induces nausea…)*

8. Since starting the study treatment, do you prefer or enjoy certain foods? yes no

If yes, which ones?

Foods I prefer or enjoy	Reason *(e.g. sweet taste, salty taste, fatty, healthy, crunchy, soft, easy to prepare, like the odor/ taste, satisfying, flavorful, bland, spicy…)*

Appendix I.D Side Effect Survey

Participant Number: _____ Date: ____/____/____

Using the study treatment can make you feel different.
Have you noticed any of the following effects when using the study treatment and how did it affect you?

	Did not experience	Enjoyable	Neutral	Unpleasant
"High" (excessive happiness/laughter)	☐	☐	☐	☐
Increased appetite	☐	☐	☐	☐
Hallucinations	☐	☐	☐	☐
Fear (paranoia)	☐	☐	☐	☐
Relaxation	☐	☐	☐	☐
Anxiety	☐	☐	☐	☐
Sleepiness	☐	☐	☐	☐
Fast heart beat	☐	☐	☐	☐
Unsteady on feet	☐	☐	☐	☐
Abnormal (fuzzy) thinking	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐
Abdominal pain	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Heaviness in limbs	☐	☐	☐	☐
Noises seem louder	☐	☐	☐	☐
Quality of sleep has changed	☐	☐	☐	☐

Other side-effects from the study treatment: _____

Appendix I.E Macronutrient (Food) Preference Checklist

Examine each individual item in turn to make your assessment. If you would like to eat the food ***at this moment*** place a check mark (√) on the line next to it. If not, go on to the next item. Consider each item independently from the others. Do not spend a long time on any item.

_____ A roasted chicken breast
_____ 2 slices of raisin bread with butter or margarine
_____ A milk chocolate bar
_____ A medium sized peach
_____ A baked potato
_____ 2 fried eggs
_____ A grilled cod fillet
_____ 2 average sized tomatoes
_____ A grilled pork chop
_____ A small piece of cheesecake
_____ A mixed green salad
_____ 2 dinner rolls
_____ 2 slices of roast beef lunchmeat
_____ 4 small cookies
_____ A hamburger
_____ A dish of strawberries
_____ 2/3 cup of canned tuna
_____ 2 pickles
_____ A small piece of pie
_____ A slice of baked ham
_____ ¾ cup of ice cream
_____ A medium sized dish of baked beans
_____ A carton of fat-free flavoured yogurt
_____ A small bag of potato chips
_____ 2 slices of turkey breast lunchmeat
_____ A dish of canned fruit salad in syrup
_____ 2 slices of cheddar cheese
_____ A steak
_____ 2 sticks of celery
_____ 2 small brownies
_____ A medium sized bowl of fried rice
_____ A small slice of honeydew melon

Appendix II Modification and validation of a Macronutrient Preference Checklist for use in North America[10]

Introduction

Assessing individual food preferences is useful for tailoring dietary advice as food preferences are an important predictor of food consumption [1]. Food consumption involves inputs from both appetite and reward systems [2]. Food reward is described as both the *liking* (hedonic) and *wanting* (motivation) of foods [3], which have recently been measured in humans as separate entities involved in food consumption [4, 5]. Momentary food preferences describe foods an individual would like to eat *at that moment* and thus capture's the willingness to eat (*wanting*) and potentially the *liking* of the food item as well.

Currently, the most common method for measuring food preference is a 171-item food preference checklist [6], on which participants rate their level of liking or disliking for each food item on a hedonic category scale, usually a 9-pt scale [1, 7, 8]. This method reveals preferences for food groups, including grains, vegetables, fruits, meat, dairy, desserts, fats, sugars, and beverages [9]. The 171-item food preference checklist is useful for able populations; however, for the frail elderly or chronically ill populations this method may be too strenuous and impractical. Moreover, this method only assesses one dimension of food intake; the *liking* not the *wanting* of food items.

A.J. Hill's 32-item Food Preference Checklist [10] reveals momentary preferences for macronutrients rather than food groups and also assesses taste preferences for sweet versus savory foods. In this method participants check off the food items that they would like to eat *at that moment* as individual items, not for a meal. Several studies have used Hill's checklist to assess momentary macronutrient preferences and changes in these preferences following a treatment, such as a test meal [10-12]. Due to its ease of completion and ability to assess momentary macronutrient and taste preferences, Hill's checklist would be particularly useful for the elderly or patients with chronic diseases for whom dietary advice often focuses on macronutrient intake (*e.g.* high protein/high calorie diets) [13] and where changes in macronutrient preferences commonly occur due to age or disease-related treatments (*e.g.* chemotherapy and radiation therapy). However, this tool was developed for use in the United Kingdom (UK) and includes several food items that are not common in North America.

The overall purpose of this study was to modify and validate Hill's European 32-item Macronutrient Preference Checklist (MPC) for use in North America with the goal of generating a simple and quick tool to assess momentary macronutrient and taste preferences. The existing European checklist was modified to meet North American food terminology, brands, and preferences. The MPC was validated for content validity, concurrent validity, test-retest reliability, and internal consistency. The second part of this paper further confirms the validity of the MPC to measure macronutrient preferences

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in a North American population by comparing the results of the MPC to other published works of factors influencing food preferences, such as age, gender, and appetite level.

Methods

This study was approved by the Research Ethics Board of the Faculty of Agriculture, Forestry, and Home Economics at the University of Alberta.

Part 1 - Development and Validation of MPC for use in North America

Subjects

For Part 1, subjects (n=160) were recruited from the University of Alberta campus, a shopping mall, and a local oil company's office in Alberta, Canada (May-August 2005, Table II.1). Subjects were eligible if they were over the age of 18, fluent in English, and able to provide informed consent. Vegetarians were excluded as all high protein items on the MPC are meat products.

Development of the MPC

The North American MPC used in this study was based on a previously validated 32-item food preference checklist developed in the UK by A.J. Hill [10, 14]. The MPC was created by revising 4 names (*e.g.* potato crisps to potato chips) and substituting 13 of the original 32 food items for foods more commonly consumed in North America (Table II.2). The substituted foods were selected by a team of nutrition and food science professionals including a registered dietician.

The checklist consisted of commercially available foods that were either high in 1) carbohydrates (HC); 2) protein (HP); 3) fat (HF); or 4) low in energy (LE). Each category consisted of eight foods, four of which were predominantly sweet and four that were savory, except for the HP category which consisted only of savory foods. The Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR) was used to ensure that each food item was within a 40 kilocalorie (kcal, 0.17 megajoule, MJ) range (185-225kcal, 0.77-0.94MJ) so that energy content did not influence food selection as per the original checklist [10]. The original checklist included portion sizes for most items (*e.g. 2* cookies) to ensure appropriate energy content. Portion sizes which were not included on the original checklist (*e.g.* a steak) were assumed to be based on recommended daily intakes according to USDA food pyramid and Health Canada guidelines. The Food Processor program was also used to ensure that the HF, HP and HC foods contained at least 50% of total energy from their macronutrient category classification (*i.e.* fat content of a HF food item is at least 50% of its total energy content). Additional condiments (*e.g.* margarine or butter) were added to certain items to increase their caloric content to the appropriate range. For the low energy food category the caloric content of each food was less than 80 kcal/item (0.33MJ/item) as per the original checklist [10].

The MPC was scored based on the number of items selected in each category; 0-8 for each of the four macronutrient categories for a total MPC score of 0-32. In each of the HC, HF, and LE categories there were 4 sweet tasting foods and 4 savory tasting foods. Thus for the sweet and savory taste components, scores ranged from 0-4 for each HC, HF, and LE macronutrient categories and 0-12 for total sweet and savory taste scores. As the HP foods were all savory, the HP macronutrient category was not scored in this way.

Procedure
Subjects completed questionnaires on two occasions one week apart at approximately the same time of day after eating a similar meal prior to evaluation [12]. On the first occasion, after providing written informed consent, participants completed a demographic survey, appetite assessment [15], MPC, and liking of the MPC's 32-food items rated on a 9-pt hedonic scale [6]. As per the original checklist [10], participants were instructed to check off all food items that they felt like eating at that moment and to consider each item independent of one another (*i.e.* avoid trying to make a meal). Self-perceived appetite was rated prior to assessing macronutrient preferences as an individual's willingness to eat preferred foods may be influenced by their level of hunger [14]. Appetite was assessed using a 100mm Satiety Labeled Intensity Magnitude scale (SLIM) [15], which assessed *fullness* (score of 10 to 50), or *hunger* (score of -11 to -50), or neither hungry nor full, *i.e. neutral* (score of -10 to 9). In the second session, participants (n=114) completed the appetite assessment (SLIM) and MPC (for test-retest reliability).

After piloting the MPC with 53 participants, two items showed a low average acceptance rating (<6) on the 9-pt hedonic scale [7]. These items, *raisin bread with margarine* and *canned salmon*, were then modified to *raisin bread with butter or margarine* and *canned tuna* for improved preference ratings. After these two modifications, all items on the MPC were rated similarly on the 9-pt hedonic scale (average 6.9, range 6.0-8.0). It is important that the items on the MPC are generally *liked* and have similar acceptance ratings, so that the checklist results reflect macronutrient preferences rather than avoidance of generally disliked food items [14].

Part 2- Influence of age, gender, and appetite on MPC scores
An additional sub-set of older participants (n=79) in good health and who consumed regular meals were recruited from six elderly living facilities in Edmonton, Alberta (Table II.1). The methods used were the same as in Part 1, with subjects participating in the first visit only. Both sets of participants (n=239) were included in further analyses (Part 2).

Data Analysis
Statistical analyses were preformed in either the Statistical Package for the Social Sciences (SPSS) for Windows (version 13, SPSS Inc. Chicago) or Statistical Analysis System (SAS, [16]. All correlations reported were Pearson correlation coefficients. The MPC was validated by comparison with the standard method of measuring food preferences (*i.e.* ratings of food items on a 9-pt hedonic scale) [6] and by verifying its test-retest reliability and internal consistency [17]. Reliability ensures that the test is consistent, dependable, and stable while validity verifies that the test accurately measures what it is meant to measure [17]. To assess concurrent validity the MPC scores were correlated with the 9-pt hedonic scale ratings of the same food items. To assess test-retest reliability of the new MPC, MPC scores from the two sessions were correlated. Partial correlations were used to control for the effects of gender, age, time of day, and differences in appetite ratings. The internal consistency of the MPC was assessed using Cronbach's alpha. To discern if pilot data differed from the test data, the correlation coefficients were compared using a method described elsewhere [18]. This method was

also used to determine if allergies and other special diets affected correlation coefficients. For Part 2, PROC Mixed was used to determine differences in the selection of the macronutrient categories, and differences in age groups, gender, recruitment locations, time of day, and appetite ratings (SLIM scores). A three-way ANOVA was used to determine differences in macronutrient preferences between gender, appetite ratings, age groups, and their interactions. For these analyses, participants were grouped into three age categories: y*oung* subjects aged 18-29 (n=85), *middle aged* subjects aged 30-59 (n=66) and *older* subjects aged 60+ (n=88). SLIM scores (0-100) were grouped into three appetite categories: *full* (10-50), *neutral* (-10 to 9) and *hungry* (-11 to -50) [15]. The frequency with which MPC items were picked was compared using chi-square analysis.

Results

Part 1

Concurrent Validity

MPC scores were significantly correlated with the rating of these items on the 9-pt hedonic scale for all four macronutrient categories and for taste components of sweet and savory items (r=0.34, 0.47, 0.48, 0.36, 0.43, and 0.34 for HC, HC, HF, LE, sweet, and savory respectively, $p<0.001$); meaning if an item was selected on the MPC this item was also rated highly on the 9-pt hedonic scale. These correlations were not significantly different when pilot data were removed or after excluding participants with special diets or allergies ($p>0.05$); therefore pilot data and participants with allergies (N=33), special diets (N=8), and/or dietary restrictions (N=3) were included in analyses. Dietary restrictions most likely did not influence results because the types of allergies/diets were too diverse to affect a single macronutrient category. Partial correlations were performed to control for the effects of age and gender. After controlling for these effects, all correlations remained the same, except for the HP category, for which the correlation significantly improved when controlling for age (r=0.372, $p<0.001$).

Reliability

Reliability analysis revealed the items in the four macronutrient categories to have good internal consistency with Cronbach's alpha values of HP=0.76, HC=0.72, HF=0.64, and LE=0.57. The MPC was highly reproducible. MPC scores for the two test sessions were significantly correlated for all four macronutrient categories as well as for sweet and savory items (r=0.79, 0.73, 0.76, 0.70, 0.79, 0.73, and 0.69 for HC, HC, HF, LE, sweet, and savory respectively, $p<0.001$). PROC Mixed analyses revealed that there was no significant difference in MPC scores between the two visits (p=0.907). HP category correlations significantly improved when controlled for age (r=0.81, $p<0.001$).

Part 2 – Factors influencing macronutrient preferences

Appetite affected macronutrient preferences and thus MPC scores and this effect was influenced by both age and gender. On average, subjects chose fewer items on the MPC, especially savory foods (*i.e.* HP, HF savory, and total savory) when they were *full* compared to a *neutral* or *hungry* state (Table II.3). *Young* and *middle aged* subjects followed this pattern of choosing more items when *hungry* and fewer items when *full*, whereas for *older* subjects, appetite status had no influence on the amount of items chosen on the MPC (Table II.3). There were significantly fewer *older* subjects who reported feeling *hungry* (23%), compared to *middle aged* (65%) and *young* subjects

(52%) ($p<0.0001$). *Older* subjects more often reported feeling neither hungry nor full (*neutral*, 49%) compared to *middle aged* and *young* subjects (12% and 22% respectively, $p<0.0001$). There was a trend for *older* subjects to prefer the LE savory items compared to the other two age groups ($p=0.0893$).

Women also followed the pattern of choosing fewer foods when *full*, whereas men equally preferred HP and HF foods regardless of their appetite level (Table II.3). A greater percentage of men were *hungry* (58%) compared to women (35%) at the time of data collection ($p= 0.0014$). Women preferred LE foods compared to HC, HF, and HP foods ($p=0.0054$) and men showed a similar trend ($p=0.0568$). Men preferred more HP foods compared to women ($p=0.0303$), while women tended to prefer sweet foods more so than men ($p=0.1072$ for total sweet foods, $p=0.1111$ for HF sweet, and $p=0.0788$ for LE sweet foods). Time of day had no influence on food preferences ($p=0.3743$).

Discussion

The modified MPC is a quick and easy tool for evaluating macronutrient and taste preferences. Correlations were moderate between MPC scores and the rating of these items on the 9-pt hedonic scale. These correlations remained unaffected when controlling for gender, but improved for the HP category when controlling for age suggesting that age influenced preferences for this macronutrient. Moderate correlations were acceptable because the MPC and 9-pt hedonic scale measured slightly different aspects of food preferences: the hedonic scale assessed general *liking* of food items (constant over time), whereas the MPC determined the *willingness* to eat certain types of foods and thus assessed more the *wanting* of foods at a point in time [4, 5]. As the MPC and 9-pt hedonic scale results were moderately correlated, it is feasible that the MPC measures not only the *wanting* of foods, but also the *liking* of these items.

Both Cronbach's alpha values and test-retest correlations confirm the reliability of the MPC to measure momentary macronutrient and taste preferences. Test-retest correlations were strong for the MPC scores and these correlations remained strong when controlling for age and gender. Test-retest correlation coefficients in this study were similar to those of the original European checklist [14]. A limitation of the MPC is the similar macronutrient composition for certain HP items (*i.e.* pork chop) and savory HF items (*i.e.* hamburger) as both are meat products. There are few foods that are savory, high in protein, and low in fat and well accepted by North Americans, making it difficult to identify HP items for the MPC that are uniquely different from HF items Still, as all items on the MPC have at least 50% of their calories contributing to their designated macronutrient category, we feel the MPC provides a valid assessment of macronutrient preference.

A secondary objective was to further confirm the MPC's validity and use in elderly and compromised populations, by comparing its results to other published works regarding factors that influence macronutrient preferences (Part 2). As expected, when participants were *hungry* they picked significantly more items on the MPC compared to participants who reported feeling *full*. De Castro *et al* [19] also reported hunger to influence palatability and hedonic ratings of food items. Finlayson *et al* (2007) noted that both the liking and wanting of HF foods was high when subjects were hungry, but when subjects were full only the liking of HF foods remained high and these foods were no longer

wanted. It follows that savory foods are less appealing in the satiated state, whereas sweet foods might still be appetizing even when full due to the rewarding aspects of these foods, *e.g.* the consumption of desserts after a large meal [20]. This may explain why mainly savory foods were chosen less frequently when subjects were *full* compared to other food categories.

Fewer *older* subjects reported feeling *hungry* at the time of data collection, compared to *young* and *middle aged* subjects. With age, gastric motility is slowed, stomach size and sensory abilities (*i.e.* taste and smell) are diminished, and physical activity is less frequent; all of which contribute to decreased appetite [12, 21]. For *older* subjects, the number of food items selected on the MPC was independent of hunger level, suggesting that *older* subjects found food items equally appetizing when they were *hungry* as when they were *full*. This may be in part due to the set meals and meal times followed by the majority of the *older* subjects in this study as most resided in elderly living facilities. The lack of community dwelling older subjects is a limitation of this study, however the observation that food choice in the elderly population tends to be little influenced by appetite is consistent with the literature; elderly tend to have fewer cravings for high energy foods and show general decrease in appetite and motivation to eat compared to younger adults [22]. Thus it is possible that the elderly are less sensitive to the MPC and similar questionnaires as the elderly do not experience hunger the same way as younger adults. In future food preference studies of elderly populations, this limitation should be considered as well as medications that may interfere with appetite and/or taste and smell abilities [21]. Still *older* subjects in this study displayed a preference for LE savory foods compared to the two other age groups. This preference may be of concern because the diets of elderly people are often low in calories and other nutrients leading to frailty and weight loss [23].

Compared to women, men were less influenced by hunger levels in their selection of HP and HF foods, suggesting that men found HP and HF foods appetizing even in a satiated state. Men generally consume more energy dense foods and thus more calories than women [9], which may in part explain the preference for these foods even when feeling *full*. It is not surprising then, that overall men preferred HP foods more so than women. These results agree with those of Logue and Smith [8] and Wyant and Meiselman [9], who reported greater preference for meats by men compared to women. Pelchat [22] noted that women had more frequent cravings for sweets and chocolates, as reflected in our observed trend for women to choose more sweet foods compared to men.

The MPC is a potentially useful clinical tool as it can help tailor dietary advice. Tailored dietary advice is important for those with compromised nutritional status (*e.g.* cancer and AIDS patients) who require individualized counseling and who may experience a change in preference due to disease-related treatments. Radiation and chemotherapy can destroy taste buds and olfactory receptors [24] as well as cause learned taste aversions due to post-treatment digestive malaise [25]. Ravasco [26] noted dietary advice to increase food intake in colorectal cancer patients who received radiation therapy. The MPC may be a quick and easy method of obtaining macronutrient and taste preferences from frail populations who may be unable to rate numerous food items on a hedonic scale and in research where a shift in macronutrient preference is expected due to a treatment or test-meal [14].

Conclusion

The MPC is a valid and reliable tool for measuring momentary macronutrient and taste preferences. The MPC showed good internal consistency, test-retest reliability, and concurrent and content validity. Therefore, the MPC may be used as a simple and efficient method of assessing momentary macronutrient and taste preferences in future research and clinical settings.

Table II.1 Demographics of the study population

		Part 1 n=160	Part 2 n=239
Gender [n (%)]			
	Male	80 (50)	100 (42)
	Female	80 (50)	139 (58)
Age [n (%)]			
Young	18-29 yrs	85 (53)	85 (35)
Middle	30-39 yrs	29 (18)	29 (12)
	40-49 yrs	21 (13)	21 (9)
	50-59 yrs	16 (10)	16 (7)
Older	60-79 yrs	9 (6)	19 (8)
	≥ 80 yrs	-	69 (29)
Recruitment Location [n (%)]			
	University of Alberta campus	100 (63)	100 (42)
	Oil company's office	49 (31)	49 (20)
	Shopping mall	11 (6)	11 (5)
	Elderly living facilities	-	79 (33)
Time of questionnaire completion [n (%)]			
	Morning (before lunch)	104 (65)	142 (59)
	Afternoon (after lunch)	42 (26)	83 (35)
	Evening (before supper)	14 (9)	14 (6)
Allergies			
	Milk Products	8 (5)	10 (4)
	Other	25 (15)	33 (12)
Dietary restrictions			
	Vegetarian*	12 (7)	12 (5)
	Low Energy	5 (3)	8 (3)
	Religious	3 (2)	8 (3)
	Diabetes	2 (1)	10 (4)
	High protein/High calorie	1 (1)	1 (<1)
	Low sodium	-	2 (1)
	Modified Consistency	-	2 (1)

*Excluded from analyses

Table II.2 Nutritional information for the 32-food items of the Macronutrient Preference Checklist and substitutions from the original European checklist

	Energy Kcal (MJ)	% Carb	% Fat	% Pro	Original Checklist Items
High Carbohydrate (HC)					
Sweet					
2 pieces of raisin bread with butter or margarine	206 (0.86)	61	29	10	*A currant bun*
4 small cookies	213 (0.89)	50	45	5	4 *ginger* biscuits
A small piece of pie	208 (0.87)	55	42	3	*A small slice of jam-filled sponge*
A dish of canned fruit in syrup	186 (0.78)	97	1	2	A dish of *tinned* fruit salad
Savory					
A baked potato	188 (0.79)	91	1	8	A baked potato *with a small knob of butter*
2 dinner rolls	192 (0.80)	71	16	13	*A crusty white or brown bread roll*
A medium sized dish of baked beans	201 (0.84)	67	13	20	
A medium sized bowl of fried rice	191 (0.80)	63	30	7	
High Fat (HF)					
Sweet					
A milk chocolate bar	225 (0.93)	41	54	5	*A large Cadburys Flake*
A small piece of cheesecake	193 (0.81)	30	63	7	
¾ cup ice cream	225 (0.93)	40	52	8	*2 lemon pancakes*
2 small brownies	224 (0.93)	39	56	5	*A cream filled chocolate éclair*
Savory					
2 fried eggs	183 (0.77)	5	68	27	*A small dish of fried mushrooms*
A hamburger	225 (0.93)	0	55	45	*A medium sausage roll*
A small bag of potato chips	214 (0.90)	37	58	5	*1 ½ packets of potato crisps (any flavour)*
2 slices of cheddar cheese	200 (0.84)	1	74	25	A *2oz wedge* of cheddar cheese
High Protein (HP)					
A roasted chicken breast	187 (0.78)	0	25	75	
A grilled cod fillet	199 (0.83)	0	12	88	
A grilled pork chop	195 (0.82)	0	46	54	*A grilled lean lamb cutlet*
2 slices of roast beef lunchmeat	201 (0.84)	13	21	66	
2/3 cup of canned tuna					Half a cup of *tinned salmon*
A slice of baked ham	186 (0.78)	3	36	61	A *grilled lean piece of gammon*
2 slices of turkey breast meat	187 (0.78)	0	15	85	*A dish of shelled prawns*
A steak	225 (0.93)	0	38	62	A *grilled ¼ lb rump* steak

Table II.2 continued

	Energy Kcal (MJ)	**% Carb**	**% Fat**	**% Pro**	**Original Checklist Items**
Low Energy (LE)					
Sweet					
A medium size peach	40 (0.17)	92	2	7	
A dish of strawberries	46 (0.19)	81	11	8	
A carton of fat-free flavoured yogurt	81 (0.34)	75	0	25	A carton of *natural* yoghurt
A small slice of honeydew melon	44 (0.18)	92	3	5	
Savory					
2 average size tomatoes	52 (0.22)	70	14	16	
A mixed green salad	18 (0.08)	48	13	39	
2 pickles	20 (0.08)	83	0	17	2 pickled *onions*
2 sticks of celery	10 (0.04)	73	8	19	

Abbreviations: Kcal, kilocalories; MJ, megajoule; carb, carbohydrates; pro, protein

Table II.3 Effect of appetite, age, and gender on Macronutrient Preference Checklist scores based on SLIM appetite categories

	Hungry		Neutral		Full		
	Mean	SD	Mean	SD	Mean	SD	p-value
Appetite							
HP	2.9[a]	0.2	2.6[a]	0.4	1.7[b]	0.3	0.0227
HF savory	1.6[a]	0.1	1.4[ab]	0.2	1.1[b]	0.2	0.0205
Total savory	4.5[a]	0.3	3.8[ab]	0.5	3.4[b]	0.4	0.0423
Age*Appetite	*N (%)*		*N (%)*		*N (%)*		
Young	*44 (52)*		*19 (22)*		*22 (26)*		
Middle	*43 (65)*		*8 (12)*		*15 (23)*		
Old	*20 (23)*		*43 (49)*		*25 (28)*		
HP							
Young	3.4[a]	0.4	2.9[a]	0.5	0.9[b]	0.5	<0.0001
Middle	3.1[a]	0.4	2.8[ab]	0.9	0.9[b]	0.6	0.001
Old	2.0	0.5	2.2	0.5	2.9	0.6	0.3476
HC savory							
Young	1.5[a]	0.2	1.3[a]	0.3	0.4[b]	0.3	0.0017
Middle	1.5[a]	0.2	0.7[ab]	0.5	0.6[b]	0.3	0.0297
Old	0.9[a]	0.3	1.0[a]	0.3	1.8[b]	0.3	0.0431
Total savory							
Young	4.9	0.5	4.5[ab]	0.7	2.7	0.7	0.0097
Middle	4.8	0.5	3.2	1.3	2.3	0.8	0.0095
Old	3.9	0.7	3.8	0.6	5.2	0.8	0.1632
Total							
Young	13.8	1.2	12.4	1.8	8.4	1.7	0.0096
Middle	12.8	1.2	9.8	3.2	7.0[b]	2.1	0.0154
Old	10.6	1.8	10.2	1.5	14.0	1.9	0.1318
Appetite*gender	*N (%)*		*N (%)*		*N (%)*		
Men	*58 (58)*		*18 (18)*		*24 (24)*		
Women	*49 (35)*		*52 (38)*		*38 (27)*		
HP							
Men	3.2	0.3	2.5	0.7	2.8	0.5	0.1869
Women	2.5[a]	0.3	2.8[a]	0.4	0.7[b]	0.4	0.0005
HF							
Men	3.0	0.3	1.8	0.7	2.8	0.5	0.0894
Women	2.9	0.3	3.2	0.4	2.0	0.4	0.0467

Abbreviations: N, number of subjects; %, percentage of subjects; SLIM, satiety labeled intensity magnitude scale; SD, standard deviation; HP, high protein; HF, high fat; HC, high carbohydrate

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