

Comparing Mirtazapine to Megestrol Acetate for Appetite Improvement and Quality of
Life in Advanced Stage Cancer Patients: A Prospective, Randomized, Open-Label,
Comparative Study

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COMPARING MIRTAZAPINE TO MEGESTROL ACETATE FOR APPETITE IMPROVEMENT
AND QUALITY OF LIFE IN ADVANCED STAGE CANCER PATIENTS: A PROSPECTIVE,
RANDOMIZED, OPEN-LABEL, COMPARITIVE STUDY
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ABSTRACT

Malnutrition remains a common complication among patients with advanced stage cancer. Cancer-associated anorexia can lead to weight loss and malnutrition if not properly identified and addressed. Many treatments for anorexia have been explored and include both pharmacological and nutraceutical interventions. Common classes of pharmacological drugs used for the treatment of cancer-associated anorexia include progestational agents, corticosteroids, and cannabinoids. The anti-depressant mirtazapine has been gaining interest in the oncology population for the treatment of anorexia. Few clinical trials have been conducted to determine how mirtazapine compares to other treatments for anorexia. This project is a research proposal for a study to compare the effects of two different pharmacological drugs for the treatment of cancer-associated anorexia. The hypothesis is that mirtazapine will be as effective as megestrol acetate in treating patients with cancer-associated anorexia and be more effective at improving quality of life (QOL) measures than megestrol acetate. Studying other medications, such as mirtazapine that have potential to improve appetite and intake in cancer patients, can make it possible for a greater number of patients to receive treatment for cancer-associated anorexia and potentially decrease the risk of malnutrition in this vulnerable group. Findings may show mirtazapine will be at least as effective as megestrol acetate for improving appetite and QOL in patients with advanced stage cancer. In those who score higher on the Center for Epidemiological Studies-Depression (CES-D) questionnaire, higher scores for appetite and QOL with mirtazapine would be expected given that it may improve underlying depression better than megestrol acetate.

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Chapter 1: Introduction

In the United States, there was an estimated 800,000 new cases of cancer diagnoses and 270,000 deaths from cancer in the year 2013 (Azrad, Turgeon & Demark-Wahnefried, 2013). Malnutrition is a serious and very common complication among cancer patients. Incidence of malnutrition is estimated to be approximately 40-80% among cancer patients (Vergara, Monotoya, Luna, Amparo & Cristal-Luna, 2013). Malnutrition is associated with poorer outcomes of treatment, increased side effects of treatment, poorer healing, and a higher rate of infections.

Cancer-associated anorexia is a common cause of malnutrition. Research on pharmacological and nutraceutical agents to improve appetite in those who suffer from cancer-associated anorexia is underway. It is important for patients with advanced stage cancer to have options for treatment of cancer-associated anorexia as certain medications may not be tolerated or not be appropriate due to contraindications. Currently, options are limited for treating cancer-associated anorexia as few medications have been approved for this condition. Megace, marinol, and corticosteroids have been used and well-studied for anorexia in cancer patients (Loprinzi, Kugler, Sloan, Mailliard, Krook, Wilwerding, Rowland, Camoriano Jr., Novotny, Christensen, 1999 and Jatoj, Windschitl, Loprinzi, Sloan, Dakhil, Mailliard, Pundaleeka, Kardinal, Fitch, Krook, Novotny, Christensen, 2002). The anti-depressant mirtazapine is currently not approved for use as an appetite stimulant in cancer patients, but two of its main side effects reported are increased appetite and weight gain. It is because of

these reported side effects that physicians have started using this drug in the oncology population to help improve appetite.

One way in which mirtazapine may stimulate appetite is its ability to block serotonin receptors. Serotonin is believed to play a role in the pathophysiology of cachexia and in the development of cancer-induced anorexia (Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A, 2013). High serotonin levels have been shown to lead to early satiety (Fox CB, Treadway AK, Blaszczyk AT, Sleeper RB, 2009). Mirtazapine is a serotonin receptor antagonist, which may explain the effects it has on appetite stimulation. Given the fact that many cancer patients have underlying depression, patients may experience mood and appetite improvement with the use of this drug.

Megestrol acetate is one of the most well studied drugs for the treatment of cancer-associated anorexia yet to our knowledge there are no studies that have compared mirtazapine to megestrol acetate for the treatment of cancer-associated anorexia. Finding an effective alternative to megestrol acetate for the treatment of cancer-associated anorexia is important because many cancer patients have a history of or are at risk for developing blood clots which would not make them appropriate for megestrol acetate as this is a rare, but serious side effect of the medication. For this reason, our study aims to compare the effects of mirtazapine to megestrol acetate on appetite and quality of life (QOL) in patients with advanced stage cancer to determine the difference between the two.

Studying other medications, such as mirtazapine, that may have potential to improve appetite and intake in cancer patients, can make it possible for a greater number of patients to receive treatment for cancer-associated anorexia and potentially decrease the risk of malnutrition in this vulnerable group.

Hypothesis

Mirtazapine will be as effective as megestrol acetate in treating patients with cancer-associated anorexia and be more effective at improving QOL measures than megestrol acetate.

Subproblems

Additional questions include: What side effects are reported or observed with megestrol acetate and mirtazapine? What additional benefits are reported or observed with mirtazapine?

Limitations and Delimitations

Limitations of our study include self-reporting on questionnaires, potentially needing to rely on collecting data via phone interviews, and potential high attrition due to unforeseen problems or death. Delimitations include patients from only one location, Cancer Treatment Centers of American Mid-Western Regional Medical Center, due to the nature of the study design. We chose to only include patients who have advanced disease and who are at least 18 years of age yet not older than 65 years of age as our hospital does not treat patients under the age of 18.

Assumptions

We assume patients will answer all questions in an honest manner.

Definition of Terms

Agranulocytosis	A condition where there is a lack of white blood cells produced by bone marrow
Akathisia	A movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion, as well as by actions such as rocking while standing or sitting, lifting the feet as if marching on the spot, and crossing and uncrossing the legs while sitting
Angiogenesis	The formation of new blood vessels from existing blood vessels
Anorexia	Loss or desire or willingness to eat
Apoptosis	Programmed cell death
Ascites	The build-up of fluid in the space between the lining of the abdomen and abdominal organs
Bullous dermatitis	An inflammatory condition of the eardrum, characterized by painful fluid-filled vesicles on the tympanic membrane and the sudden onset of severe pain in the ear
Cachexia	Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutrition support and leads to progressive functional impairment.
Cancer anorexia-cachexia syndrome	A complex multifactorial condition, with loss of lean body mass, chronic inflammation, severe metabolic derangements, reduced food intake, reduced physical activity, and poor quality of life being key symptoms (Mantovani, Madeddu, Maccio, 2013).
Carcinomatosis	A condition where multiple carcinomas develop simultaneously usually after dissemination from a primary source
Cytokines	Protein molecules released by lymphocytes and/or monocyte macrophages. Numerous cytokines, including tumor necrosis factor-alpha (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-gamma (IFN- γ), may play a role in the development of cancer cachexia (Suzuki, Asakwa, Amitani, Nakamura, Inui, 2013).
Decubiti	A pressure-induced ulceration of the skin that occurs when people are confined to bed for long periods of time
Dysgeusia	The dysfunction of the sense of taste
Dysphagia	Difficulty swallowing with the sensation that food is stuck in the throat, or from the neck down to just above the abdomen behind

	the breastbone (sternum).
Emetogenic	Having the capacity to induce vomiting or emesis
Erythemas multiforme	An acute, self-limited, and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction associated with certain infections, medications, and other various triggers
Ghrelin	A peptide hormone secreted by the stomach and pancreas in response to fasting (Gullet, Mazurak, Hebbar, Ziegler, 2011).
Leptin	A peptide hormone that is produced by fat cells and plays a role in body weight regulation by acting on the hypothalamus to suppress appetite and burn fat stored in adipose tissue
Malnutrition	A decline in lean body mass with the potential for functional impairment
Mucositis	Painful inflammation and ulceration of the mucous membranes lining the digestive tract.
Myopathy	A muscular disease in which muscle fibers do not function properly
Neutraceutical	A foodstuff (as a fortified food or dietary supplement) that provides health benefits in addition to its basic nutritional value
Neutropenia	An abnormally low count of neutrophils, a type of white blood cell that helps fight off infections
Odynophagia	Pain produced by swallowing
Open-label	A type of clinical trial in which both the researchers and participants know which treatment is being administered
Phase II Trial	Testing of drug on patients to assess efficacy and safety
Orexigenic	A drug, hormone, or compound that increases appetite
Palliative	The relief of pain in the terminally ill
Stevens-Johnson syndrome	A rare, serious disorder of the skin and mucous membranes
Torsades de Pointes	An uncommon variant of ventricular tachycardia that can be the result of lengthening the QT interval
Toxic epidermal necrolysis	A potentially life-threatening dermatologic disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes
Xerostomia	Xerostomia, or dry mouth, is the condition of not having enough saliva, or spit, to keep the mouth wet

Chapter 2: The Literature Review

Introduction

In the United States, there was an estimated 800,000 new cases of cancer diagnoses and 270,000 deaths from cancer in the year 2013 (Azrad et al., 2013). Estimated incidence of malnutrition among cancer patients is approximately 40-80% (Vergara et al., 2013). Malnutrition can result in numerous negative clinical implications including increased chemotherapy-induced toxicity, impaired wound healing, poor response to treatment, and treatment delays (Gupta, Lammersfeld, Vashi, Dahlk, & Lis, 2008). As a result, impaired nutritional status can lead to poorer outcomes of treatment and quality of life (QOL) (Lis, Gupta, Lammersfeld, Markman, & Vashi, 2012).

Malnutrition is often characterized by significant unintentional weight loss, which is defined as $\geq 5\%$ in one month, $\geq 7.5\%$ in three months, and/or $\geq 10\%$ in six months (Stajkovic, Aitken, & Holroyd-Leduc, 2011). Multiple interventions aimed at preventing weight loss include increasing food intake, reducing anorexia, controlling the inflammatory process, neutralizing metabolic disturbances, and decreasing catabolism while increasing anabolism must be considered when treating cancer anorexia-cachexia syndrome (CACS). Recognizing and treating factors that contribute to anorexia is important in preventing unintentional weight loss and the subsequent complications. A combination of pharmacological agents, nutraceuticals, and nutritional support are usually considered for the treatment of CACS (Mantovani, Maccio, Madeddu, Serpe, Massa, Dessi, Panzone, & Contu, 2010).

Anorexia can accelerate the decline in nutritional status among cancer patients if not detected and treated early. A better understanding of the mechanisms and underlying causes of anorexia in cancer patients will allow care providers to prescribe the most effective medication and intervention to treat this problem. Many medications such as progestational drugs, cannabinoids, and corticosteroids have been studied to determine the efficacy in treating this debilitating condition (Suzuki, Asakawa, Amitani, Nakamura, & Inui, 2013). The purpose of this literature review is to critically analyze the research on medications currently being used for the treatment of CACS to help determine which are most efficacious. To begin with, background on malnutrition in cancer patients will be discussed.

Background

Cancer patients receiving chemotherapy and radiation are at high risk for malnutrition and cachexia as these treatments can result in a number of nutrition related side effects including nausea, vomiting, taste changes, dysgeusia, mucositis, dysphagia, odynophagia, xerostomia, delayed gastric emptying, constipation and diarrhea (Topkan, Yavuz, & Ozyilkan, 2007). Anorexia can be a secondary consequence of these symptoms.

Subjective global assessment (SGA) is an effective and validated clinical nutritional assessment tool used for detecting malnutrition in cancer patients (Gupta et al., 2008). The SGA assessment score is based on weight changes, nutrition impact symptoms, dietary intake, functional capacity, and a physical examination component

that assesses for ascites/edema and muscle wasting (Gupta et al., 2008). After a skilled dietitian has assessed the patient using the SGA tool, patients are given a rating of well-nourished, moderately malnourished, or severely malnourished. A score of 0-4 indicates a rating of well-nourished (SGA-A), 5-9 indicates moderately malnourished (SGA-B), and a score ≥ 10 indicates a patient is severely malnourished (SGA-C).

Pathogenesis of Anorexia

Patients with advanced stage cancer have been found to produce large amounts of inflammatory cytokines and experience changes in hormone signaling. Cancer-associated anorexia has been implicated as a result of increased cytokine production and alterations in certain hormones and neuropeptides that influence appetite (Gordon et al., 2005). Emotional disturbance and decreased hunger cues caused by alterations in metabolism are additional causes of anorexia. Reducing these side effects may slow the cachectic process by preventing rapid weight loss that is associated with prolonged periods of inadequate intake as a result of these uncontrolled symptoms.

Cachexia is a multi-organ syndrome characterized by weight loss of at least 5%, muscle and adipose tissue wasting, and inflammation – often associated with anorexia (Argilés, Olivan, Busquets, & López-Soriano, 2010). Greater than 50% of cancer patients complain of anorexia (Gordon, Green, & Goggin, 2005). The two main pathways that control appetite regulation in the hypothalamus are driven by neuropeptide Y (NPY) and pro-opiomelanocortin/cocaine and amphetamine regulated transcript (POMC/CART). NPY stimulates food intake whereas POMC/CART inhibits food intake.

The appetite stimulating hormone, ghrelin, and appetite suppressing hormone, leptin, regulate these pathways. Inflammatory cytokines such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor α (TNF- α), have been implicated in the alteration of these systems (Gordon et al., 2005).

Neutraceutical Interventions for Cancer Anorexia-Cachexia Syndrome

Natural compounds are a growing interest in research for the treatment of cancer anorexia-cachexia syndrome (CACS) due to their low toxicity, anti-inflammatory effects, and catabolic pathway inhibitory properties. Fish oil, curcumin, and green tea are natural, safe compounds which have been found to possess inhibitory effects on the proteasome pathways, tumor growth, and inflammation (Chen & Dou, 2010 and Gullett et al., 2011). Their potential ability to correct metabolic disturbances, enhance anabolism, inhibit catabolism, and suppress inflammation make these natural compounds an attractive adjunct to other treatment modalities for the treatment of cancer-associated anorexia and the prevention of cancer cachexia.

Eicosapentaenoic Acid and Docosahexaenoic Acid

High levels of pro-inflammatory cytokines have been implicated in mediating cachexia, resulting in weight loss, hypermetabolism and loss of lean body mass in cancer patients (Van Der Meij, Langius, Smit, Spreeuwenberg, Von Blomberg, Heijboer, Paul, & Van Leeuwen, 2010). Two noticeable recurring neutraceuticals being used in many studies examining treatment approaches to CACS are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Murphy, Mourtzakis, Chu, Baracos, Reiman, &

Mazurak, 2011). EPA and DHA are long-chain poly-unsaturated essential fatty acids (LCPUFA) that serves many important roles in the body including maintaining cell structure and function. However, the more intriguing role, especially for scientists trying to unravel the mystery behind cancer cachexia, is the role LCPUFA's play in reducing inflammation, aiding in weight and muscle mass maintenance, and supporting and modulating immune function. These supportive roles make fish oil an ideal candidate to be used along with additional treatment modalities for cancer cachexia such as appetite stimulants, dietary and nutritional approaches, anti-inflammatory treatment, and treatment for secondary gastrointestinal symptoms (Suzuki et al., 2013).

Multiple studies have directed efforts toward ways to suppress the inflammatory response by reducing mediators of inflammation or discovering ways to inhibit signaling pathways that are responsible for accelerating skeletal muscle wasting. Van Der Meij et al. (2010) concluded that a protein- and energy-dense oral nutritional supplement containing (n-3) fatty acids beneficially affects nutritional status during multimodality treatment in patients with NSCLC. Murphy et al. found patients who supplemented with fish oil had significantly less weight loss than those in the standard of care group and patients with the greatest increase in plasma EPA concentration after fish oil supplementation experienced greatest muscle gain. The authors concluded that 2.2 g of fish oil per day provided a benefit over standard of care and resulted in weight and muscle mass maintenance during chemotherapy.

Recent research is finding a multi-modal approach for the treatment of cancer cachexia to be most effective (Mantovani et al, 2010, Rogers et al, 2011), possibly

because this approach has the potential to target more pathways and suppress a wider variety cytokines. Mantovani et al. (2010) compared medroxyprogesterone and megestrol acetate oral supplementation with eicosapentaenoic acid, L-carnitine, and thalidomide in 332 patients and found the combination therapy was more effective than any of the single drug arms for increasing lean body mass and improving appetite.

Curcumin

Curcumin is a commonly used nutraceutical in Asian medicine. Its many uses include respiratory conditions, liver disorders, anorexia, rheumatism, common colds and sinusitis (Alamdari, O'Neal, & Hasselgren, 2009). Curcumin is a substance in the spice tumeric that has been studied for its anti-inflammatory, antioxidant and anti-cancer properties. The inhibitory effects of curcumin on inflammation and carcinogenesis are in part due to suppression of the NF- κ B signaling pathway (Chen & Dou, 2012).

Studies using curcumin for cancer-related muscle-sparing effects have been conflicting (Alamdari et al., 2009). Most of these studies have been on rodents using various dosing regimens and routes of administration which may have resulted in inconsistent findings (Alamdari et al., 2009). Despite curcumin's poor bioavailability, results of preliminary studies show this natural compound may have huge potential as an adjuvant to cancer treatment. Due to its ability to suppress inflammation, curcumin may be a promising natural compound to use along with appetite enhancing pharmaceuticals to treat cancer-associated anorexia.

Green Tea

Epidemiological and clinical studies have reported green tea is associated with reduced risk of many cancers due to its numerous cancer-preventive effects (Chen & Dou, 2010). Polyphenols found in tea have been found to contain powerful antioxidant and anti-inflammatory properties and are reported to possess chemoprotective potential by proteasome inhibition and modulating intracellular signaling pathways responsible for inducing carcinogenesis (Chen, Milacic, Chen, Wan, Lam, Huo, Landis-Piwowar, Cui, Wali, Chan, & Dou, 2008). The most potent polyphenol suggested to have powerful cancer preventative properties is epigallocatechin-3-gallate, which has been shown to target molecules involved in apoptosis, angiogenesis, and metastasis (Chen & Dou, 2010).

In addition to green tea's ability to inhibit tumor growth, mice studies have shown that green tea extract decreased muscle wasting by suppressing NF- κ B activity (Evans, Call, Bassaganva-Riera, Robertsom, & Grange, 2010). Due to the numerous findings demonstrating green tea's ability to inhibit proteasome activity, it is plausible to presume it could have an important role in the prevention of muscle wasting in cancer patients.

More human studies are needed to better comprehend green tea's therapeutic potential for the prevention and treatment of cachexia. Based on recent findings, using green tea as part of a multimodal approach along with other proteasome inhibitors for

the prevention and treatment of cancer cachexia should be a consideration for future studies.

Pharmacological Interventions for Cancer Anorexia-Cachexia Syndrome

Interventions aimed at reducing the severity of nutrition related symptoms and preventing unintentional weight loss is paramount to improving nutritional status in cancer patients. The use of appetite stimulants is one approach to prevent unintentional weight loss. Numerous pharmacological agents have been studied for their potential to improve appetite (Mantovani, Madeddu, & Maccio, 2013). Three commonly used classes of drugs used for cancer-associated anorexia are corticosteroids, progestational drugs, and cannabinoids (Suzuki et al., 2013).

Corticosteroids

Corticosteroids were the first drugs used for cancer-associated anorexia, but several studies revealed only a temporary improvement in appetite with no beneficial effect on body weight (Tomiska, Tomiskova, Salajka, Adam, & Vorlicek, 2003). The mechanism of action of corticosteroids in CACS is not fully understood, although inhibition of prostaglandin activity and IL-1 and TNF- α suppression are likely targets (Mantovani et al., 2013). Due to side effects associated with long-term use of steroids such as weakness, delirium, osteoporosis and immunosuppression, short-term (no more than 1-2months) or alternating use of these agents is recommended in the management of CACS (Mantovani et al., 2013).

Progestational Agents

Progesterones were the first agents used for the treatment of CACS and are currently the only agents approved in Europe for its treatment (Mantovani et al., 2013).

Megestrol acetate, a progestational agent, is thought to improve appetite by stimulating neuropeptide-Y (NPY) and inhibiting the production of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) (Suzuki et al., 2013).

Numerous studies have been published on the use of megestrol acetate for appetite stimulation and weight gain in patients with acquired immunodeficiency syndrome (AIDS), advanced cancer patients who suffer from cancer-associated anorexia, and in geriatric patients with unintended weight loss (Yeh, Wu, Lee, Olson, Stevens, Dixon, Porcelli, & Schuster, 2000; Jatoi et al., 2002, and Tomiska et al., 2003). However, weight gain associated with its use has been mainly attributed to an increased fat mass, not to muscle mass.

Although some studies have found megestrol acetate to be effective at improving quality of life in cancer patients (Tomiska et al., 2003), a recent meta-analysis concluded megestrol acetate did not improve survival or quality of life in patients with CACS (Les'niak, Bala, Jaeschke, & Krzakowski, 2008). More randomized controlled trials are needed to confirm the impact megestrol acetate has on quality of life.

Cannabinoids

The mechanisms by which the cannabinoids dronabinol and Marinol® work, is uncertain. However, two receptors have been identified, CB1 and CB2, which mediate the effects of cannabinoids (Suzuki et al., 2013). Synthetic tetrahydrocannabinol (THC) is the active ingredient in dronabinol. The agonistic action of THC on CB1 and CB2 receptors may be responsible for the effects of dronabinol (Grotenhermen & Müller-Vahl, 2012). Antagonistic actions of other receptor systems, such as the serotonergic 5-hydroxytryptamine (HT)₃ receptor, may be responsible for the anti-nausea effects of dronabinol (Grotenhermen & Müller-Vahl, 2012).

Dronabinol is currently approved by the FDA for acquired immunodeficiency syndrome (AIDS)-related anorexia associated with weight loss and chemotherapy induced nausea and vomiting (Grotenhermen & Müller-Vahl, 2012). Multiple clinical trials have evaluated dronabinol as an appetite stimulant for patients with cancer-associated anorexia (Jatoi et al., 2002 and Brisbois, De Kock, Watanabe, Mirhosseini, Lanoureaux, Chasen, MacDonald, Baracos, & Wismer, 2010).

Anti-depressants

One of the less studied agents for treatment of cancer-associated anorexia, but one that is receiving a lot of attention for its potential use for this condition, is mirtazapine. Mirtazapine is a serotonin (5-HT₃) antagonist and a tetracyclic antidepressant used primarily for the treatment of depression and other mood disorders (Kumar, Kazi, Smith, Crocker, Yu, Reich, Reddy, Hastings, Exterman, Balducci, Dalton, & Bepler, 2010).

Because of its ability to act on numerous neurotransmitter systems and serotonin and histamine receptors, mirtazapine may help to reduce nausea and improve sleep and appetite in cancer patients (Theobald, Kirsh, Holtsclaw, Donaghy, Passik, 2002). The ability to potentially improve multiple symptoms including appetite, quality of life, pain and insomnia, and prevent weight loss makes mirtazapine a desirable medication for cancer patients (Theobald et al., 2002 and Kumar et al., 2010).

Over the recent years, much interest has been shown in mirtazapine's ability to cause weight gain. The potential to induce substantial weight gain early in therapy has made mirtazapine more appealing than other antidepressants for CACS. In practice, mirtazapine has become a popular intervention for geriatric patients with unintended weight loss (Fox, Treadway, Blaszczyk, & Sleeper, 2009).

Mirtazapine has a favorable safety profile and is generally well tolerated, which make it an appealing choice for CACS (Fox et al., 2009). Side effects that have been reported with mirtazapine are dizziness, blurred vision, sedation, somnolence, malaise/lassitude, increased appetite and subsequent weight gain, dry mouth, and constipation (Kumar et al., 2010).

Critical Analysis of the Research

Many pharmaceuticals and nutraceuticals have been studied for the clinical management of cancer-associated anorexia. Clinical trials have been conducted to study the safety and efficacy of certain drugs for the treatment cancer-associated anorexia. Below is a summary of the most relevant and referenced studies on

pharmaceuticals that are commonly used for the treatment of cancer-associated anorexia. Studies on megestrol acetate and its effects on appetite, weight, and QOL will be studied first, followed by studies on mirtazapine.

Megestrol Acetate versus Dronabinol for Cancer-Associated Anorexia

To determine whether dronabinol is comparable to other orexigenic agents for cancer-associated anorexia, Jatoi et al. (2002) conducted a study on dronabinol or megestrol alone or in combination to uncover which strategy was more efficacious for treatment of cancer-associated anorexia.

Four-hundred sixty-nine patients with advanced stage cancer were randomized, in a double-blinded manner, to receive either: 1) 800 mg/d liquid suspension of megestrol acetate plus placebo; 2) oral dronabinol 2.5 mg twice daily plus placebo; or 3) both agents. Patients were stratified prior to randomization by cancer type (lung cancer versus gastrointestinal cancer versus other malignancy), severity of weight loss in the preceding two months (less than 10 pounds versus ≥ 10 pounds), planned or ongoing chemotherapy at the time of recruitment (none versus cisplatin versus other), sex (male versus female), Eastern Cooperative Oncology Group performance status: 0 to 1 versus 2, physician estimate of patients survival (less than four months versus 4-6 months versus > 6 months), planned concomitant radiation (yes versus no), patients age (< 50 years versus ≥ 50 years), and medical center where patient was enrolled.

To be included in the study, patients had to report loss of appetite as a problem, a weight loss of ≥ 5 pounds during the preceding two months and/or a physician-

estimated caloric intake of less than 20 calories/kg of body weight per day. Exclusion for the study included: being fed by alternative nutrition including enteral or parenteral nutrition, the presence of edema or ascites, long-term treatment with adrenal corticosteroids, androgens, progestational agents, or other appetite stimulants within the previous month, brain metastases, insulin-requiring diabetes, pregnancy or lactation or unwillingness to use oral contraceptives, anticipated alcohol or barbiturate use during the study period, poorly controlled hypertension (HTN) or congestive heart failure (CHF), history of thromboembolic disease, and mechanical obstruction of the alimentary tract, malabsorption, or intractable vomiting.

Weight, appetite, reported perception of food intake, nausea intensity, perception of current weight, and QOL assessments were comparable at baseline among the three treatment groups. The median duration of time of the study did not vary significantly between groups. Those in the megestrol acetate group were on the study for a median duration of 80 days versus 57 days for the dronabinol group and 74 days for the combined group ($p = .21$). Reasons for withdrawal from the study included toxicity, patient refusal, and death.

Validated questionnaires for appetite and weight were conducted at baseline, weekly for four weeks, and monthly thereafter. The single-item Uniscale and the FAACT questionnaire were used to assess QOL. The results of the study revealed 75% of patients in the single agent megestrol acetate group reported an increase in appetite compared to 49% of patients receiving dronabinol alone ($p = 0.0001$). The combination

treatment did not result in statistically significant improvements in appetite and weight gain compared to megestrol acetate alone. The results of the FAACT questionnaire showed an improvement in QOL among megestrol acetate-treated and combination-treated patients. FAACT-AN scores were statistically significant between the megestrol acetate group and dronabinol group ($p = 0.002$), specifically the emotional and physical constructs, with megestrol acetate being superior to dronabinol within these constructs. However, the Uniscale detected no statistical differences in QOL assessment among the three groups. The megestrol acetate treated group showed more favorable weight gain than the dronabinol group, 14% versus 5%, compared to baseline ($p = 0.009$). Combination treatment showed no statistically significant improvements in appetite or weight gain compared with megestrol acetate alone. Reported toxicities among the groups were not significantly different with the exception of impotence among males receiving megestrol acetate ($p = 0.0032$). Nausea and vomiting, although not a primary end point in this study, were not found to be statistically different among treatment arms.

The authors concluded megestrol acetate alone provided superior benefit over dronabinol alone for improvement in cancer-associated anorexia in patients with advanced stage cancer. They found no additional benefit in taking dronabinol in combination with megestrol acetate.

This was a large, multi-institutional, randomized, double-blinded clinical trial that demonstrated that megestrol acetate was more effective than dronabinol for the

treatment of cancer-associated anorexia and QOL. This was the first study to compare dronabinol and megestrol acetate for the treatment of cancer-associated anorexia. However, of note is the 49% response rate to a relatively low dose of dronabinol. If patients had received a higher dose of dronabinol, it may have resulted in equal or superior outcomes compared to megestrol acetate.

Palliative Treatment of Cancer Anorexia with Megestrol Acetate

Progestational agents are among the most effective medications for the treatment of anorexia/cachexia syndrome. Randomized controlled trials have shown megestrol acetate to be effective for improving appetite and quality of life in individuals with cancer associated anorexia (Bruera, Ernst, Hagen, Spachynski, Belzile, Hanson, Summers, Brown, Dulude, & Gallant, 1998). Tomiska et al. (2003), aimed to evaluate the effect of megestrol acetate (MA) in oral suspension on appetite, quality of life and nutritional parameters in palliative treatment of cancer anorexia/cachexia syndrome.

A total of 22 patients with advanced stage cancer were randomized to either a fixed dose of 840 mg/day in group A or an individual dose of 480 mg/day in group B with the option to titrate to 720 mg and 840 mg/day if no effect was found with the initial dose of 480mg. One patient never started the medication and two patients died from rapid cancer progression. Of the 19 evaluable patients, 11 were in treatment group A and eight were in treatment group B.

Patients were eligible for the study if they had a non-hormonal dependent cancer, advanced stage of disease beyond the scope of anticancer treatment, anorexia

related weight loss of 5-15% of usual body weight, WHO performance status of no more than 2, life expectancy of at least three months and adequate laboratory hematological, renal and liver findings. Patients were excluded if they were receiving concurrent cytostatic or hormonal treatment, had preexisting edema, had a recent history of myocardial infarction or thromboembolic disease and uncontrolled hypertension or diabetes with hyperglycemia.

The majority of patients had lung or gastrointestinal cancer. The QLQ-C30 questionnaire for quality of life, visual analogue scale (VAS) for appetite, anthropometry, handgrip strength and laboratory values were measured prior to therapy and at two, four, and eight weeks thereafter. A registered nurse administered the questionnaire prior to the physician examination. The four parameters of QOL that could directly influence appetite and that were chosen to evaluate QOL were 1) overall health and quality of life, 2) fatigue, 3) physical functioning, and 4) appetite. Handgrip strength, as an indicator of functional status, was measured by a dynamometer and the mean values for each hand were calculated from the best three readings. Lab values included albumin, prealbumin, C reactive protein, liver enzymes, blood glucose, and serum cortisol.

As expected, attrition rate was high in this study and reasons for attrition included death (8 patients), edema (1 patient), and stopping medication due to ineffectiveness (1 patient). The median time of medication was 56 days. Results were

evaluated for those who continued on the medication for two weeks (19 patients), four weeks (16 patients), eight weeks (12 patients) and 12 weeks (seven patients).

Fluid retention is a side effect of MA therapy. In this study, three patients began the study with edema, which worsened throughout the study. No new cases of edema were reported while on study. One patient withdrew from the study due to edema after two weeks.

The majority of patients, 18 (95%), reported an improvement in appetite after two weeks ($p = 0.0001$) and 82% of patients reported an improvement in appetite after eight weeks of treatment ($p = 0.022$). Weight change was not significant after eight and 12 weeks of MA therapy, although the study did show a gradual increase in weight even after subtracting the four patients with clinical edema.

Maximal handgrip strength showed very low initial values. However, the authors found 45-70% of patients had an improvement in handgrip strength during treatment when the opposite was expected due to progression of disease.

QOL improved in 12 patients (63%) after two weeks and in 55% of patients after eight weeks. Fatigue improved in 47% of patients after two weeks and in 45% of patients after eight weeks while worsening in 36%. Physical function improved in 21% of patients after two weeks and 18% of patients after eight weeks. By intention to treat analysis, QOL improved in 32% out of all evaluable patients after eight weeks of megestrol acetate therapy.

The authors concluded that a maximal positive effect can be achieved by megestrol acetate after only eight weeks of therapy and may be an effective palliative treatment for patients with advanced cancer suffering from anorexia/cachexia syndrome. Oral suspension of megestrol acetate was well tolerated without any serious side effects and may contribute to the improvement of QOL in some patients.

The authors chose the liquid suspension because they thought it would be better tolerated for patients with advanced cancer in poor condition and also for its better bioavailability. The authors did not discuss which dose of MA showed greater effect.

The small sample size may have influenced the outcome of certain parameters including QOL in this study. The authors noted that many previous studies did not choose standard instruments to measure QOL and some were not sensitive for advanced stage cancer patients and that these may be the reasons for low overall scores for QOL after megestrol acetate therapy. In this study, the authors used a sensitive evaluation tool for those with advanced stage cancer and were careful in selecting which parameters to choose to measure QOL. A larger randomized controlled trial may be helpful in determining the true efficacy of megestrol acetate on overall QOL.

Megestrol Acetate Versus Corticosteroids for Cancer-Associated Anorexia

Corticosteroids and progestational agents have both been reported to alleviate cancer-associated anorexia. Megestrol acetate is typically preferred over the use of

corticosteroids due to the toxicity profile associated with use of corticosteroids (Loprinzi et al., 1999). Peptic ulcer disease, cataracts, opportunistic infections, glucose intolerance, and myopathy have all been associated with the use of corticosteroids (Loprinzi et al., 1999). In a study by Loprinzi et al. (1999), researchers compared a progestational agent, a corticosteroid, and an anabolic corticosteroid for the treatment of cancer anorexia/cachexia.

To be eligible in the study, patients had to report an unintentional weight loss of ≥ 5 pounds in the previous two months or have an estimated daily calorie intake of less than 20 calories/kg. Patients did not qualify for the study if they had ascites, receiving alternative means of nutrition, such as enteral or parenteral nutrition, had brain metastases, thromboembolic disease within the previous six months, or uncontrolled hypertension (HTN) or congestive heart failure (CHF). Mechanical obstruction of the alimentary tract, persistent vomiting, malabsorption, and treatment with adrenal corticosteroids, estrogens, or progestational agents were additional exclusion criteria.

Prior to randomization, patients were stratified by primary disease site, weight loss, sex, performance status, treatment plan, and physician estimate of survival. Four-hundred fifty-five patients with advanced stage cancer suffering from cancer anorexia/cachexia were randomized into one of three treatment arms: 1) dexamethasone 0.75 mg four times daily; 2) megestrol acetate 800 mg orally once per day; or 3) fluoxymesterone 10 mg orally twice per day. Weight changes and drug toxicity were evaluated on a monthly basis. Validated questionnaires to evaluate food

intake, appetite, nausea, vomiting, drug toxicities, and QOL were administered at baseline and at monthly intervals for approximately two months.

Sixty-six percent of the patients completed a baseline questionnaire. Authors speculated severe cancer anorexia/cachexia, illness, or comorbid problems related to advanced cancer were potential reasons for the 34% drop-out rate.

Results of the combined questionnaire data revealed megestrol acetate had superiority over fluoxymesterone ($p = 0.0004$) at one month in all parameters. Improvements in appetite compared to baseline were significantly greater in the megestrol acetate treatment group compared to the fluoxymesterone group ($p = 0.001$). A greater percentage of subjects in the megestrol acetate group reported that their food intake was better compared to baseline than in the fluoxymesterone group, 71 versus 56%, respectively ($p = .03$). A higher percentage of subjects in the megestrol acetate group (10%) gained $\geq 10\%$ of their body weight from baseline compared to the fluoxymesterone group (4%) ($p = .08$). Megestrol acetate and dexamethasone were found to have similar improvements in appetite and similar changes in non-fluid weight status.

Subjects were asked nine questions measuring improvements in appetite, intake, taste, early satiety, and QOL. More than one-third of patients (35%) receiving megestrol acetate improved on eight or more of the nine variables compared with only 23% of patients receiving dexamethasone ($P = 0.03$) and only 16% of patients receiving fluoxymesterone ($P = 0.0001$).

Due to a large number of patients (34%) not completing the follow-up questionnaires, an intent-to-treat analysis was performed. A total of 311 patients completed a baseline questionnaire and at least one follow-up questionnaire. The intent-to-treat analysis revealed approximately 30-40% of all patients reporting an improvement in appetite after 1 month of treatment. Dexamethasone was found to have higher toxicities associated with its use and a higher dropout rate than megestrol acetate due to these toxicities ($p = 0.03$). However, subjects on megestrol acetate had a higher rate of deep venous thrombosis than dexamethasone (5% vs 1%; $p = 0.06$). The authors concluded that fluoxymesterone was the inferior choice for treating cancer anorexia/cachexia. However, despite megestrol acetate and dexamethasone having similar appetite enhancing efficacy, these drugs were associated with various toxicities.

Strengths of the study include the large sample size and study design. This randomized-controlled clinical trial assessed both the benefits and risks of using corticosteroids and progestational agents for the use of cancer-associated anorexia. A major limitation to this study was the primary outcome. Weight gain was a primary endpoint in the study, yet nowhere in the study did it reveal how weight was measured or what tool analyzed body composition.

Weight gain in patients taking progestational agents and corticosteroids tends to be associated with an increase in fluid and fat mass. Therefore, future studies would be strengthened using devices that measure lean tissue and total fat mass. Future studies should also consider the use of liquid formulation of megestrol acetate as this is more

bioavailable. Using the liquid formulation may have resulted in more a dramatic outcome in this study.

Megestrol Acetate Effects on Quality of Life and Weight Gain in Geriatric Cachexia

Wasting and cachexia can negatively impact physiological, psychological, and immunological processes. Severe weight loss can lead to increased infection, decubiti, and death (Yeh, Wu, Lee, Olson, Stevens, Dixon, Porcelli, & Schuster, 2000). Since MA has been approved for the treatment of anorexia and cachexia in patients with AIDS, Yeh and colleagues wanted to investigate megestrol acetate for the treatment of cachexia or unexplained weight loss in a non-cancer, geriatric nursing home population.

The authors conducted a 12-week randomized, double-blind, placebo controlled trial with a 13-week follow-up period. The primary outcome of their study was weight gain and improvement in appetite and the secondary outcome measures were sense of well-being, enjoyment of life, change in depression scale, energy intake counts, body composition, and adverse events.

Patients were eligible for the study if they were a resident at Northport Veterans Administration Medical Center (VMAC) nursing home, ≥ 55 years old, experienced a weight loss of $\geq 5\%$ of their usual body weight over the previous three months, or were 20% below their ideal body weight, had a life expectancy of ≥ 24 weeks, and a Karnofsky performance status of $\geq 40\%$. Patients were excluded from the study if they had poorly controlled hypertension or CHF, ascites or mechanical obstruction of the alimentary tract, untreated systemic infections or other serious simultaneous illnesses, were

receiving steroids, androgens, or other progestational agents, or had a weight loss due to hyperthyroidism or depression.

Appetite was measured using an appetite scale ranging from 1 (very poor) to 5 (excellent), depression was evaluated using a scale of 0 to 15 with a higher score indicating a higher degree of depression, enjoyment was measured using a 4-category checklist consisting of four responses, ranging from 1 (not at all) to 4 (very much), improvement in sense of well-being was evaluated using a nine-item linear analog scale with higher scores indicating improved sense of well-being, body composition was measured by a bioelectrical impedance analysis (BIA) machine. Food intake was assessed from three consecutive daily energy intake counts prior to enrollment and at week 12. Adverse events were measured weekly and weight and body composition were determined at four-week intervals. Weight continued to be measured every four weeks for a total of 13 weeks after completion of the study.

A total of 69 patients were randomized to either a placebo (n = 33) or a dose of 800 mg/day of megestrol acetate (n = 36) for 12 weeks. Fifty-one of the 69 enrolled patients completed the study after 12 weeks. Reasons for dropping out of the study included withdrawing from the study due to intolerance or ineffectiveness or violating entry criteria. Groups were similar with regards to concurrent medical conditions. Twenty-three patients from the megestrol acetate group and 21 patients in the placebo group completed the additional 13 week off medication evaluation.

Weight change from baseline to week 12 was not significant with a mean weight gain of 1.05 ± 1.0 kg and 0.91 ± 0.68 kg in the megestrol acetate and placebo group, respectively. By week 20, the megestrol acetate group gained 2.45 ± 1.1 kg and the placebo group lost 0.41 ± 0.82 kg, statistically significant difference ($p = 0.037$). At week 25, 61.9% of megestrol acetate-treated patient had gained ≥ 1.82 kg compared to 21.7% of placebo patients ($p = 0.013$). Changes in body composition as determined by body impedance analysis (BIA) after 12 weeks between the two groups was not statistically significant; however, the authors noted that those in the megestrol acetate-treated group who gained weight, did gain more fat and lean body mass. A statistically significant improvement in appetite from baseline to 12 weeks was noted in the megestrol acetate treated group ($p = 0.004$). No significant changes in depressive symptoms were found between the two groups. Statistical significance was achieved for improvement in enjoyment score in the megestrol acetate-treated patients ($p = 0.0245$) and a lower enjoyment score from baseline to 12 weeks in the placebo group was reported. A statistically significant difference in mean improvement score for sense of well-being between the two groups was noted ($p = 0.045$) with a mean improvement score in the megestrol acetate-treated group being 7.76 ± 1.16 and 4.65 ± 0.73 in the placebo group. No statistically significant differences in the nutrition status parameters, including albumin, prealbumin, and energy intake, were noticed at week 12.

The authors concluded that short-term treatment with 800 mg/day of megestrol acetate enhanced appetite, may promote weight gain, and improved quality of life in

cachectic and anorexia geriatric nursing home patients. The authors suggested that future studies look into possible mechanisms of action on appetite and weight gain.

One limitation noted in this study was the data collection process. Many of the data points were collected only for the initial 12-week treatment period and not the follow-up 12-week period. Considering the delayed response to treatment with regards to weight gain, the additional data may have provided useful information in accounting for the delayed response. Albumin, prealbumin, and energy intake measures may have been found to be significant after 6 months. Another limitation was the small sample size. A larger sample size would have been required to more accurately represent the general nursing home population. Lastly, although both males and females were eligible for the study, there were no female subjects enrolled onto the study. This limits understanding of how females may have responded to the effects of megestrol acetate.

The strengths of this study included the randomized, double-blinded, placebo controlled design which helped to establish causality. This was the first study to examine the effects of megestrol acetate in the geriatric population for appetite and weight gain. Another strength of the study included monitoring weight gain/maintenance after the 12-week study period. Had the study and data collection terminated after the initial 12-week treatment period, the statistically significant difference in mean weight gain between the megestrol acetate and placebo group would not have been detected.

Mirtazapine in Advanced Cancer Patients

Theobald et al. (2002) designed a pilot open-label crossover study to determine the efficacy of mirtazapine on pain and other distressing symptoms in cancer patients using daily dose of 15 mg or 30 mg.

Patients were eligible for the study if they were experiencing visceral, somatic, or neuropathic pain and were on opioid medication, and who had a life expectancy of at least 3 months. Patients were excluded from the study if were on antidepressant medication or if they were receiving corticosteroids, benzodiazepines, neuroleptics, or serotonin 5HT₃ receptor antagonists. Twenty out of thirty-six patients (seven females and 13 males, average age of 60.2 years), completed the study.

After patients were assessed at baseline, they completed a one week observation period. Patients were then randomized to a dose of 15 mg or 30 mg of mirtazapine prior to bedtime. Patients switched to the alternate dose after three weeks. The study completed after three weeks of being on the alternate treatment.

Major endpoints of the study included depression, pain intensity, appetite, insomnia, weight, and overall quality of life. No significant differences were noted in the drop-out group from the completers based on age, gender, race, marital status, or tumor type. A 20-item self-report Zung Self-Rating Depression Scale (ZSDS) was used to measure depressive symptoms. The 27-item self-administered Functional Assessment of Cancer Therapy—General (FACT-G) questionnaire was used to assess quality of life. The Memorial Pain Assessment Card (MPAC) was used to measure pain intensity, pain

relief and mood. Numeric rating scales (NRS) consisted of four questions to assess nausea, anxiety, insomnia, and appetite.

Average weight was significantly higher at both week 4 ($p = <0.05$) and week 7 ($p = <0.05$), independent of dosage. The average weight gain after four weeks was 2.6 pounds and 2.0 pounds after 7 weeks. A trend toward improvement in nausea (mean = 2.4 to mean = 0.9) ($p = 0.10$), anxiety (mean = 2.7 to mean = 2.1) ($p = 0.07$), insomnia (mean = 3.4 to mean = 2.3) ($p = .25$), and appetite (mean = 3.9 to mean = 3.2) ($p = 0.10$) was observed from baseline to week seven. Overall ZSDS scores were significantly improved ($p = <0.05$) at the end of the study (Week 7) and were not dependent on mirtazapine dosage.

The authors concluded this open-label pilot study suggests that mirtazapine may be effective for improving multiple symptoms, depression and quality of life in patients with advanced cancer. The authors encouraged the development of controlled trials using mirtazapine.

One weakness of the study was the small sample size. A larger study will be necessary to yield more significant results. If a larger study is conducted, a control should be included to be able to determine the true effect of the drug. A strength of this study was the multiple endpoints that were assessed. It is believed that mirtazapine has the potential to impact multiple symptoms. Assessing a variety of symptoms is important to help researchers better understand mirtazapine's full potential and to help guide future research.

Mirtazapine for Cancer-Related Anorexia

Mirtazapine has been shown to induce weight gain and may have the potential to improve anorexia in cancer patients. Riechelmann et al. (2010) conducted an eight-week open-label phase II trial of mirtazapine to investigate its effects on weight, appetite, and health-related quality of life (HQOL) in non-depressed patients with cancer-related cachexia and anorexia (CRCA).

Out of 58 eligible patients, 21 consented to participate. Three patients scored high on the depression scales and were referred to psychiatry and one patient began a highly emetogenic chemotherapy prior to the study. A total of 17 patients completed baseline questionnaires. The primary endpoint of the study was a 1 kg weight gain at the end of week four. Secondary endpoints were appetite and HQOL improvement.

A starting dose of 15 mg was given to patients for three days and if tolerated, was increased to 30 mg for the remainder of the study. Weight, appetite, and side effects were recorded at the end of 2, 4, and 8 weeks. Appetite was measured using the Edmonton Symptom Assessment Scale (ESAS) and HQOL was measured using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) measure. An improvement in appetite was defined as a decrease of ≥ 2 points on the ESAS appetite scale from baseline and an improvement in HQOL was defined as an increase of at least 10% (16 points) from baseline on the FAACT questionnaire. Health-related quality of life was measured at baseline and at 4 and 8 weeks. Information on patients age,

gender, site of disease, performance status, Eastern Cooperative Oncology Group (ECOG) score, and concurrent medications were recorded.

Four out of 17 patients (24%) gained at least 1 kg after four weeks, one maintained weight, and two patients lost weight. Twenty-four percent of patients reported an improvement in appetite after four and eight weeks and 6% of patients had an improvement in HQOL. The authors conclude that mirtazapine appears to be a promising therapeutic agent for the management of CRCA, but does recommend future randomized clinical trials with mirtazapine versus placebo, steroids, or megestrol.

Weakness noted in the study included the small sample size and the associated increased risk for false positive results, limited to a single institution, and the possibility of sample bias due to the strict inclusion criteria. High attrition is frequently seen with this population and this study was no exception. Reasons for the high attrition in this study included poor clinical condition, death, and study contamination.

This phase II trial illustrated the potential for mirtazapine to be an effective medication for the treatment of CRCA. Cancer cachexia is a very complex disorder and its mechanisms are multifactorial. More randomized clinical trials are needed to best determine which medications and neutraceuticals can effectively target multiple underlying mechanisms responsible for cancer-associated anorexia.

Mirtazapine for the Treatment of Anorexia Nervosa

Antidepressants are a well-studied group of psychotropic drugs used for the treatment of anorexia nervosa (AN). Studies using antidepressants specifically for the goal of weight restoration has been limited and the results have been controversial (Hrdlicka, Beranova, Zamecnikova, Urbanek, 2008). Mirtazapine is an antidepressant in which weight gain and increased appetite are commonly reported. In a retrospective study by Hrdlicka et al. (2008), the authors aim was to determine if AN patients who had been treated with mirtazapine for depression and anxiety showed an improvement in weight and BMI compared to drug-free controls.

A systematic chart review of patients with anorexia nervosa (AN) receiving routine clinical care in the Department of Child Psychiatry was conducted. In this case-control study, the authors used the ICD-10 criteria for the diagnosis of AN. Nine female adolescent patients (cases) were found to have AN and were treated with mirtazapine for depression or anxiety during their hospitalization and nine controls were found who were not receiving pharmacotherapy. Subjects in the case and control groups were matched based on age and BMI.

Weight and BMI were evaluated at baseline and after 1, 2, 3 and 4 weeks of treatment using Repeated Measures Analysis of Variance (ANOVA). Cases and controls received nutritional rehabilitation and psychotherapy equally. The mean dose of mirtazapine was 21.7 ± 1.8 mg at the end of week 4.

The authors found no significant differences between cases and controls with regard to weight. However, there was a non-significant trend in weight gain and BMI in those treated with mirtazapine at the end of weeks 1, 2 and 3, compared to controls.

The authors concluded that mirtazapine could be useful in the treatment of AN in adolescence and warrants further investigation.

This was the first study to describe the effect of mirtazapine on body weight and BMI in AN patients being treated with mirtazapine (monotherapy) for depression or anxiety. The limitations of this study included the small sample size and retrospective study design. Larger, prospective studies are advised for future research.

Effect of Mirtazapine on Body Composition and Metabolism

Weight gain is a common side effect of psychotropic medications and the most reported side effect with mirtazapine (Laimer, Kramer-Reinstadler, Rauchenzauner, Lechner-Schoner, Strauss, Engl, Deisenhammer, Hinterhuber, Patsch, & Ebenbichler, 2006). Weight gain from antidepressants is thought to be in part due to disturbances in neurobiological regulations and a reduction in basal metabolic rate. Laimer et al. (2006) conducted a prospective controlled study to investigate the effects of mirtazapine on body weight, body fat mass, glucose metabolism, lipoprotein profile, and leptin.

Seven women who met the ICD-10 diagnostic criteria for a depressive episode were assigned to a 30 or 45 mg dose of mirtazapine for 6 weeks and seven mentally and physically healthy females served as a control group. Subjects were matched on age and body weight. Body composition was measured by impedance analysis with a multifrequency bioelectric impedance 2000-M analyzer and fat-free mass and fat mass was determined by Nutri 4 software.

After 6 weeks, the study group gained a mean of 3.0 kg of total body weight and a mean of 1.2 kg in fat mass. In the control group, weight and fat mass remained stable. Between-group analysis of change scores revealed significant differences for body weight ($p = 0.010$), body mass index ($p = 0.013$), fat mass ($p = 0.035$), and leptin ($p = 0.013$).

The authors concluded that the antidepressant mirtazapine is associated with significant weight gain and an increase in body fat. An increase in serum leptin was associated with both weight gain and increase in body fat. Glucose metabolism was not influenced by mirtazapine therapy nor did it alter the lipid profile.

This study, although small, reveals impactful, significant effects of mirtazapine and weight on fat mass gain. Larger, prospective studies are warranted to substantiate these findings. A weakness of the study included not using a more accurate method for assessing body composition such as dual-energy X-ray absorptiometry (DXA) or computed tomography (CT). CT can distinguish visceral from subcutaneous fat with a higher level of precision than BIA and is considered the gold standard for assessment of visceral adiposity.

Comparing and Contrasting the Literature

Multiple studies have demonstrated the efficacy of megestrol acetate for appetite and weight gain in cancer patients. Study durations varied from 4-12 weeks and the most common dose was 800 mg/day of the liquid oral suspension. The impact of megestrol acetate on weight gain was variable. One study revealed an average

weight gain of only 1.05 kg after 12 weeks of megestrol acetate treatment, whereas another showed a 3.1 kg weight gain after the same duration using the same dose (Yeh et al., 2000). Of note, subjects who only gained 1.05 kg in the first 12 weeks did go on to gain a total of 2.95 kg after a total of 25 weeks of therapy. This is consistent with other review findings reporting a mean range of weight gain of 1.06-5.4 kg in patients with cancer using megestrol acetate over varying study durations (Fox, Treadway, Blaszczyk, & Sleeper, 2009).

Significant results were noted in appetite improvement in most studies. Tools for measuring appetite included the FAACT-AN, ESAS, NRS, and VAS. One study (Jatoi et al., 2002) found that seventy-five percent of patients reported an increase in appetite at some point during an 80 day treatment with megestrol acetate, while in another study (Tomiska et al., 2003), 95% of patients reported improvement in appetite after just two weeks of megestrol acetate therapy.

Tools measuring QOL varied. The FAACT-AN questionnaire, FACT-G, QLQ-C30 questionnaire, and various analog scales and checklists were used to measure a variety of QOL components. One study revealed after intent-to-treat analysis, 32% of patients reported an improvement in QOL (Tomiska et al., 2003). Another study (Yeh et al., 2000) did not find a statistically significant improvement in depressive symptoms in those who received megestrol acetate, but did notice a significant improvement in enjoyment and sense of well-being scores. Variation in QOL scores may be a result of using multiple QOL tools that measure a variety of parameters. Study sizes also varied

that may have impacted the scores. Using a standardized QOL tool which is sensitive to the advanced stage cancer population will be important for future studies measuring QOL parameters.

Few human trials have been conducted using mirtazapine for the treatment of cancer-associated anorexia in advanced cancer patients. A dose of 15-30 mg per day was the most commonly used. Weight gain ranged from a gain of 1 kg after four weeks in 24% of patients in one study (Riechelmann et al., 2010) to an average weight gain of 2.6 pounds after four weeks and 3 kg after six weeks in two additional studies (Theobald et al., 2002). One review noted mirtazapine led to a mean 2.4 kg weight gain after only one week of treatment (Fox et al., 2009). Mirtazapine may have the potential to produce rapid, significant weight gain which is an appealing side effect for those suffering with cancer anorexia/cachexia syndrome.

A trend toward appetite improvement after four weeks was noted in one pilot trial studying the effects of mirtazapine in advanced cancer patients. In another study (Riechelmann et al., 2010) with advanced cancer patients, twenty-four percent of patients reported an improvement in appetite after four and eight weeks of taking mirtazapine.

Mirtazapine has the potential to improve multiple symptoms including appetite, nausea, quality of life, mood and sleep disturbances that could lead to or exacerbate malnutrition. A small phase II trial study (Riechelmann et al., 2010) on patients with advanced cancer revealed six percent of the subjects reported an improvement in

health-related QOL. Another study (Theobald et al., 2002) found significant improvements in depression and FACT-G QOL scores after seven weeks of mirtazapine therapy.

High attrition rates were common in both the megestrol acetate and mirtazapine studies with advanced cancer patients. Common reasons for non-completion included illness, intolerable side effects, stopping due to ineffectiveness, and death. This needs to be taken into account when designing studies using this population. One should consider broadening inclusion criteria to capture the number of patients necessary to interpret the findings and produce reliable results. In addition, oral suspension of megestrol acetate should be offered over the pill form to increase patient compliance and reduce pill burden in those with advanced disease.

Results have been promising with both megestrol acetate and mirtazapine for the treatment of cancer-associated anorexia. Due to small sample sizes, larger randomized trials are needed to substantiate the findings of previous studies and help set guidelines for the use of these drugs. A logical next approach would be to study megestrol acetate and mirtazapine in a randomized trial to determine which drug is more efficacious at improving appetite and quality of life in those with advanced cancer.

Conclusions

Malnutrition is a common complication among patients with advanced stage cancer. Cancer-associated anorexia is often reported in malnourished patients. Despite

the promising studies demonstrating the efficacy of megestrol acetate and dronabinol for the treatment of cancer-associated anorexia, the side effects associated with these medications limit the use of these agents to specific patient types. Megestrol acetate would not be appropriate for someone with a history of thromboembolism, adrenal insufficiency, edema, uncontrolled hypertension or congestive heart failure (CHF). The elderly and someone complaining of dizziness and confusion may not be appropriate for dronabinol. Future clinical trials should study the effects of mirtazapine on appetite and QOL in patients with advanced stage cancer as this medication may be better tolerated than dronabinol and more appropriate than megestrol acetate in certain patients.

Mirtazapine has been shown to lead to weight gain and increased food intake, and is associated with improved scores on depression rating scales in approximately 15% of adult non-cancer patients (Riechelmann et al., 2010). Mirtazapine is a safe and well tolerated medication with only around 5% of patients needing to stop taking it due to intolerable side effects. The low cost and its potential to improve a variety of side effects associated with advanced cancer makes mirtazapine an appealing choice for treatment of cancer-associated anorexia. Randomized controlled trials that study mirtazapine alone, against, or in combination with other medications to improve anorexia are important to help establish guidelines for the treatment of cancer-associated anorexia. Identifying interventions that improve the nutritional status of cancer patients may help improve cancer treatment outcomes.

Chapter 3: Methodology

Options are limited when it comes to treating cancer-associated anorexia as few medications are FDA approved for this condition. More research is needed in the area of treatments for cancer-associated anorexia, since this is an approach to potentially improve cancer treatment and quality of life. A literature review was conducted and to our knowledge, there are no trials that have compared mirtazapine to megestrol acetate for the treatment of cancer-associated anorexia. The primary aim of our study is to compare the effectiveness of mirtazapine to megestrol acetate on appetite and QOL in patients with advanced stage cancer. Additional aims are to determine whether mirtazapine in comparison to megestrol acetate can improve distress/anxiety, nausea, fatigue and depression in advanced stage cancer patients with anorexia/cachexia. This randomized open-label intervention study will examine the effect of mirtazapine and megestrol acetate in up to 200 cancer patients over an eight week period. Appetite, body weight, and quality of life are measured outcomes. This study was approved by the Institutional Review Board (IRB) at Cancer Treatment Centers of America (CTCA) and Mount Mary University (MMU).

Study Design

The study was a randomized, open-label, comparative study to determine if mirtazapine is as effective as megestrol acetate in treating patients with cancer-associated anorexia and more effective at improving QOL measures than megestrol acetate.

Eligibility

The study was limited to patients 18-65 years of age with any advanced stage solid malignancy, excluding pancreatic cancer, currently in active treatment at CTCA MRMC cancer. Patients will be recruited from the inpatient center and outpatient clinic. A target of 200 subjects was recruited for this study due to an estimated attrition rate of 30%. However, on data from the first 140 enrolled subjects (70 in each arm) that fully completed the study were included. Patients are eligible if they have complaints of anorexia and have at least a 5% weight loss over the previous three months or 10% weight loss over the previous six months. Exclusion criteria includes having a history of thromboembolism, uncontrolled hypertension or diabetes, have CHF, have edema or ascites, pancreatic cancer, liver enzyme levels \geq three times the normal range, with normal ranges defined as: ALP: 45-117; AST: 15-37; ALT: 12-78, a bilirubin level above 2.5, have renal failure as defined by having a creatinine level greater than 2.5, are currently taking another medication which may increase appetite such as steroids or certain psychotics, currently receiving enteral or parenteral nutrition, have a bowel obstruction or carcinomatosis, using monoamine oxidase (MAO) inhibitors or have used an MAO inhibitor within the past 14 days, and pregnant women or women trying to become pregnant.

Enrollment and Intervention

Patients eligible for the study will be evaluated by the registered dietitian who will perform the Center for Epidemiological Studies-Depression questionnaire (CES-D)

evaluation prior to enrollment. This is a screening tool for depression that includes 20-items that asks patients to rate how often over the past week they experienced symptoms associated with depression. If the subject scores >20 on the CES-D they will still be eligible for the study, however will also be referred to a psychiatrist for further evaluation. Prior to randomization, the patient will be evaluated by a medical oncologist and referred to a dietitian for eligibility and consent. After the informed consent is signed, patients will be randomly placed into one of two treatment arms: 1) megestrol acetate liquid suspension 800mg/20ml orally daily; or 2) mirtazapine 15mg tablet orally once daily. Prescriptions will be written by the evaluating medical oncologist. Patients will be instructed to take megestrol acetate at the same time every morning with food or mirtazapine prior to bedtime for a total of eight weeks. Randomization will be achieved by means of a random number table. Patients will be instructed to take the medicine daily for a total of eight weeks and compliance will be measured by review of the medication diary in which patients keep daily entries of when they took their medication.

Informed consent will be obtained at the first visit, along with demographic information such as age, ethnicity, weight, height, and sex will be collected. Medical information regarding past medical history, stage and type of cancer and treatment received for cancer will also be gathered through medical records. Data will be collected at baseline, week four, and week eight.

Patient Withdrawal Criteria

Patients may be terminated from the study for the following events and reasons: the patient chooses to withdraw for any reason, the investigator chooses to terminate the patient from the study, patient non-compliance, patient discovered after enrollment not to have met the protocol entrance criteria, patient lost to follow-up, the sponsor-investigator terminates the study, if the patient experiences any toxicity or intolerable side effects, or if the patient develops any of the criteria listed in the exclusion criteria.

If a patient does not return for a scheduled visit every effort will be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. Patients will only be considered lost to follow-up if study personnel are unable to communicate with the patient. Three phone call attempts will be made and if unable to connect, then a certified letter will be issued informing the patient of their termination from the study. Reasons for withdrawal will be specified in the patient's study file, and will include date of discontinuation of investigational product and date of study withdrawal.

Data Collection

Appetite, nausea, depression, and anxiety were completed using the Edmonton Symptom Assessment Scale (ESAS) (Chang, Hwang, Feuerman, 2000) at baseline and every three weeks (± 1 week) thereafter. ESAS will be administered by RD either by phone or during outpatient follow up visit. To assess QOL and fatigue, patients will complete the Functional Assessment of Anorexia/Cachexia Therapy (FAACT)

questionnaire (Ribaud, Cella, Hahn, Lloyd, Tchekmedyan, Von Roenn, Leslie, 2000) at baseline and every three weeks (± 1 week) thereafter. FAACT will be administered by RD either by phone or during outpatient follow up visit. Nutritional status will be assessed using the Subjective Global Assessment (SGA) (Laky, Janda, Cleghorn & Obermair, 2008) which measures a person's nutrition risk and is another tool to measure symptoms such as appetite, nausea, intake, and functional status. SGA data will be collected at baseline, at midpoint (4 weeks ± 1 weeks) and at eight weeks. Weight will be measured every four weeks (± 1 week) by a patient care technician (PCT) on a standardized outpatient scale. Body composition and hand grip strength will be measured by a RD using BIA and dynamometer at baseline, at midpoint (4 weeks ± 1 weeks) and at 8 weeks (± 1 week). Hand grip strength will be carried out by using the dynamometer and having patients perform three consecutive measures with one minute rests between attempts using the dominant hand and averaging the three attempts.

Medical information regarding past medical history, stage and type of cancer and treatment received for cancer will also be gathered through medical records

Diagnostic Tests

The following diagnostic laboratory tests will be performed: blood urea nitrogen (BUN), creatinine, glucose, and a liver panel: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, total protein, total bilirubin, pre-albumin.

The investigator, or a qualified designee who is part of the study team, will promptly review each lab report as it becomes available. If the investigator deems a value outside the reference range to be “clinically significant,” then she/he will record it as an adverse event (AE) and be immediately reported to the IRB. Lab reports will become a part of the source documentation.

Sample Size Estimation

Based on appetite loss as the primary outcome of interest (as assessed using ESAS), an equivalence test of means using two one-sided tests on data from a parallel-group design with sample sizes of 70 in the Mirtazapine group and 70 in the Megestrol Acetate group achieves 81% power at a 5% significance level when the true difference between the means is 0.00, standard deviation is 3.00, and the equivalence limits are -1.50 and 1.50. This means that a change of up to 1.5 points in the anorexia subscale in either direction is not considered as clinically significant.

All data will be analyzed using IBM SPSS version 20.0 (IBM, Armonk, NY, USA). All analysis between the two interventions will be two-tailed for a comparison of means for continuous variables. A difference will be considered to be statistically significant if the p value is less than or equal to 0.05.

Drug Information

Adverse Events and Common Reactions Associated with Mirtazapine

Adverse reactions associated with mirtazapine include: agranulocytosis, neutropenia, hypotension, orthostatic, suicidality, depression, exacerbation, hypomania/mania, seizures, akathisia, Torsades de pointes, hyponatremia, Stevens-Johnson syndrome, bullous dermatitis, erythemas multiforme, toxic epidermal necrolysis, withdrawal symptoms if abruptly discontinues medication. Common reactions include: somnolence, xerostomeia, increased appetite, hypercholesterolemia, constipation, weight gain, asthenia, dizziness, hypertriglyceridemia, influenza-like symptoms, abnormal dreams, abnormal thinking, tremor, confusion, peripheral edema, elevated ALT, AST, myalgia, back pain, urinary frequency, and photosensitivity.

Contraindications with Use of Mirtazapine

Contraindications with use of mirtazapine include: hypersensitivity to mirtazapine or any component of the formulation; use of MAO inhibitors intended to treat psychiatric disorders (concurrently or within 14 days of discontinuing either mirtazapine or the MAO inhibitor); initiation of mirtazapine in a patient receiving linezolid or intravenous methylene blue.

Adverse Events and Common Reactions Associated with Megestrol Acetate

Adverse reactions associated with megestrol acetate include: adrenal suppression, diabetes mellitus, thrombosis/thromboembolism, thrombophlebitis, and cardiomyopathy. Common reactions with the use of megestrol acetate include: sexual dysfunction, rash, flatulence, HTN, insomnia, nausea/vomiting, decreased libido, dyspepsia, hyperglycemia, and alopecia.

Contraindications with Use of Megestrol Acetate

Contraindication with the use of megestrol acetate include: hypersensitivity to megestrol or any component of the formulation and known or suspected pregnancy (suspension).

Concomitant Medications/Treatment

The patient will be queried regarding concomitant use of medications at all study visits. All concomitant medication use (both prescription and over-the-counter, including herbal medications and nutritional supplements) will be reported during the study, and recorded in the patient's study file.

Chapter 4: Discussion

More research is needed on potential treatments for cancer-induced anorexia. Studying high risk populations such as patients with advanced stage cancer has its challenges including high drop-out rates. Future studies are needed to best determine the safest, most effective approach for treating cancer-induced anorexia.

Potential Difficulties

Potential difficulties with this study include the large sample size needed to show statistical significance. Capturing a large sample size in a high risk, health compromised group is challenging due to a potentially low number meeting all the inclusion and exclusion criteria or a high drop-out rate expected in such a population. If accrual rates prove to be very low, modifications to the exclusion and inclusion criteria may be necessary or a smaller pilot study may have to be considered. High attrition is another potential challenge. Drop-out rates in similar studies in the advanced cancer population have been approximately 35% (Loprinzi CL, et al., 1999). Close follow-up of study participants will be required throughout this study and a potential problem may be lack of people and resources throughout the process in helping collect the data, administer questionnaires, and monitor adverse events.

Expected Results

This is not a superiority study, but instead a comparative study hypothesizing that mirtazapine will be at least as effective as megestrol acetate for improving appetite and QOL in patients with advanced stage cancer. In those who score higher on the CES-D questionnaire, higher scores for appetite and QOL with mirtazapine would be

expected given that it may improve underlying depression better than megestrol acetate.

Clinical Implications/Application

This study will be the first that we know of that compares a progesterone drug, megestrol acetate, against an anti-depressant, mirtazapine, for the treatment of cancer-associated anorexia. If the findings of this study reveal that mirtazapine is as effective as megestrol acetate for the improvement of cancer-associated anorexia and QOL, patients will have more treatment options to help manage side effects, improve QOL, and prevent malnutrition during their treatment. Many physicians are reluctant to use megestrol acetate in cancer patients because of the risk for blood clots or thromboembolism. Mirtazapine may be a safe and effective treatment that more physicians feel comfortable giving their patients.

Future studies

The pathophysiology of anorexia and cachexia is complex and involves alterations in a variety of compounds and pathways. Future studies should consider using a combination of therapies using both nutraceuticals and pharmaceuticals as a treatment for anorexia and maintaining lean body mass in advanced cancer patients. Due to lack of appropriate software for CT to measure lean body mass, our study will use BIA to measure weight and body composition, however more accurate and sophisticated tools to measure lean body mass should be used in future studies.

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Appendix A

RESEARCH PARTICIPANT INFORMED CONSENT and PRIVACY AUTHORIZATION FORM

Midwestern Regional Medical Center

Study Title: *Comparing Mirtazapine to Megestrol Acetate for Appetite Improvement and Quality of Life in Advanced Stage Cancer Patients: A Prospective, Randomized, Open-Label, Comparative Study*

Principal Investigator: Kristina Stodola, RD, LDN

Midwestern Regional Medical Center

2520 Elisha Avenue

Zion, IL 60099

Introduction

Midwestern Regional Medical Center requires your written informed consent in order for you to take part in this clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who voluntarily choose to take part. This Informed Consent document describes the clinical research study that you are being asked to participate in and what the study will involve. Please take your time to make your decision about taking part in this clinical trial. Discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more information.

You are being asked to take part in this study because you have advanced stage cancer and suffer from loss of appetite. In addition, you have lost at least 5% of your body weight over the past three months or 10% over the past six months. Your participation in this study is entirely voluntary.

Why is this study being done?

The research is being done:

to determine whether mirtazapine (“Study Drug” or “MZ”) is at least as effective as megestrol acetate (“Study Drug” or “MG”) for improving appetite, body weight and composition and more effective at improving quality of life in advanced stage cancer patients with anorexia/cachexia.

It is also hoped that through this research we may be able to determine whether mirtazapine in comparison to megestrol acetate can improve depression and anxiety, nausea, fatigue, and functional status.

How many people will take part in the study?

It is expected that 200 of participants will be enrolled in this research study over a period of 3-4 years at Midwestern Regional Medical Center

What will happen if I take part in this research study?

PROCEDURES

If you choose to participate, a complete nutrition assessment and physical examination will be done to be sure you are able to enter the study. Many of the tests are the same as those you have had in the past to diagnose and treat your cancer. Some of these same tests will also be performed during your treatment in order to follow your progress.

Your participation in this study is divided into different visits:

- Screening Visit
- Treatment Visits
- End of Treatment Visit

Different tests are run during each of these different visits as described below.

Screening Visit

This Screening Visit is necessary to determine if you are eligible to participate in the study. The Screening Visit will take place before you receive any study related treatment.

The following will be performed during the Screening Visit:

- A full nutrition assessment which will include a weight and diet history and review of your nutrition related labs will be conducted by the registered dietitian during the screening visit.
- A RD will administer the Center for Epidemiological Depression Scale. The CED-S is a short self-report scale designed to measure depressive symptoms in the general population.

All of these tests may be completed over several clinic visits. If a recent test result is already available in your medical records, we may not need to do that test again.

Treatment Visits

Treatment visits are necessary to receive the investigational drug, Mirtazapine or Megestrol Acetate. Randomization will be achieved by means of a random number table generated by statistical software

Once your eligibility is confirmed, you will be able to participate in the study.

The following will be performed on the day you begin treatment of study drug and during each follow up visit with your oncologist. The tests listed below will be completed over several hours during each Treatment Visit:

- You will be examined by your oncologist.

- Your treating oncologist or attending physician will prescribe you either mirtazapine or megestrol acetate.
- The doctor, nurse, or dietitian will ask you to tell them of any side effects that you may have felt since your last visit and to give them a list of all medications that you are currently taking.
- The dietitian will provide a complete nutritional assessment
- The dietitian will review your compliance medication journal
- The dietitian will administer two questionnaires that assess appetite, quality of life, fatigue, nausea, depression, anxiety. You will either complete these questionnaires every four weeks in person or over the phone depending on how often you will follow up with your oncologist.
- During your initial visit, midpoint, and at the end of the study, you will perform a body composition analysis and your hand grip strength will be measured. Tests will be conducted by a dietitian and physical therapist.

End of Treatment Visit

- The doctor, nurse, or dietitian will ask you to tell them of any side effects that you may have felt since your last visit and to give them a list of all medications that you are currently taking.
- The dietitian will provide a complete nutritional assessment
- The dietitian will review your compliance medication journal
- The dietitian will administer two questionnaires that assess appetite, quality of life, fatigue, nausea, depression, anxiety.
- You will perform a body composition analysis and your hand grip strength will be measured. A dietitian will conduct the body composition analysis and a physical therapist will conduct the hand grip strength test.

How long will I be in the study?

Your participation in the study will be 8 weeks.

What side effects or risks might happen if I am in the study?

You may have side effects from the mirtazapine or megestrol acetate drug used in this study, and they will vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, your doctor(s) and the researchers do not know all the side effects that may happen as a result of study participation; there may be unknown side effects that could occur. Side effects can vary from mild to very serious. Your doctors may give you drugs to help lessen side effects. Many side effects go away shortly after you stop therapy, but, in some cases, side effects can be serious, long-lasting, cause you to be hospitalized, and/or may never go away.

Unknown risks

As is true for any experimental drug or treatment, there may be unknown and potentially serious, life-threatening, or fatal side effects that could occur with mirtazapine or megestrol acetate. If you are unable to tolerate this experimental treatment, the amount of drug given may be reduced or you may be discontinued from therapy but will still be asked to continue in the study. You should talk to your study doctor about any side effects that you have while taking part in the study.

The following are side effects have been seen with mirtazapine:

- Sleepiness
- Dry mouth
- Appetite increased
- High Cholesterol
- Constipation
- Weight gain
- Asthenia
- Dizziness
- High triglycerides
- Influenza-like symptoms
- Abnormal dreams
- Abnormal thinking
- Tremor
- Confusion
- Fluid retention in the extremities
- ALT,AST elevated
- Muscle pain
- Back pain
- Urinary frequency
- Photosensitivity

The following are side effects have been seen with megestrol acetate:

- Sexual dysfunction
- Rash
- Flatulence
- Hypertension
- Insomnia
- Nausea/Vomiting
- Libido decreased
- Indigestion
- Hyperglycemia
- Loss or thinning of hair

For more information about risks and side effects, ask your study doctor. You should talk to your study doctor about any side effects that you have while taking part in the study. If the investigational drug causes severe side effects or if your appetite worsens despite the study drug, the treatment with mirtazapine or megestrol acetate will be discontinued. In that case your study doctor will discuss other treatment options with you.

As with any drug, unknown risks and side effects are also possible. You could experience a side effect that is more severe than those mentioned above or a side effect that has not been anticipated with this investigational drug. There is a chance that you could be allergic to the study drug or to one of the chemicals used in its formulation. There is also a chance that other medications you may be taking could interact with this investigational drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study. Also, please tell the study doctor or nurse before starting any non-study medications while you are on the study, including any over the counter medicines such as cough and cold remedies.

You cannot take part in this study if you are pregnant or lactating (breast-feeding). Therefore, all women who are sexually active and can become pregnant must use birth control measures while in this study. Breast-feeding mothers must stop breast-feeding to take part in this study.

If you are a male, you must use birth control measures to prevent a female partner from becoming pregnant while you are in the study. The following birth control measures are acceptable: birth control pills, contraceptive shots or implants, condoms or a diaphragm. Women who could possibly become pregnant must have a pregnancy test before taking part in the study. For the pregnancy test, a blood sample will be taken within 7 days before you receive

your first dose of mirtazapine or megestrol acetate. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study.

If you become pregnant or impregnate a partner while on the study, you must notify the study doctor and your regular doctor immediately. If you (if you are female) or your female partner (if you are male) becomes pregnant within 30 days after receiving your last dose of mirtazapine or megestrol acetate you must inform the study doctor. Ask about counseling and more information about preventing pregnancy.

Bioelectrical Impedance Analysis: Bioelectrical impedance analysis is a method of assessing your body composition, the measurement of body fat in relation to lean body mass. The test takes only a few minutes and involves standing on the machine while holding two handles and having a painless electrical current flow through your body that measures lean tissue, fat mass, and fluid.

Dynamometer: A dynamometer is a tool that measures hand grip strength. Hand grip strength can help us determine your functional status. The test will take only a few minutes and you will be instructed to use your dominant hand while performing the test. An average of three attempts will be recorded. You will have a one minute rest between each attempt.

Functional Assessment Anorexia/Cachexia Therapy (FAACT): The FAACT is a questionnaire that you will take every 4 weeks, either over the phone or in person. This questionnaire measures aspects of quality of life. This should take approximately 10 minutes to complete. All FAACT responses are strictly confidential and will be filed in a locked cabinet.

Edmonton Symptom Assessment System (ESAS): The ESAS is a questionnaire you will complete every 4 weeks, either over the phone or in person. This questionnaire will tell us if your appetite is improving and if other side effects are getting worse, better, or staying the same. All ESAS responses are completely confidential and will be filed in a locked cabinet.

Center for Epidemiological Depression Scale (CED-S): The CED-S is a short self-report scale designed to measure depressive symptoms in the general population.

Are there benefits to taking part in this research study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Your appetite may improve, get worse, or stay the same. The information obtained from this study may help doctors better understand cancers and this may eventually be helpful to future cancer patients.

What other choices do I have if I don't take part in this research study?

You do not have to be in this study to receive treatment for your condition. Your other choices may include dronabinol a corticosteroid if appropriate. You can also choose to receive no further therapy for your cancer. You should talk to the study doctor and your regular doctor about each of your choices before you decide if you will take part in this study.

Can I stop being in the study?

Study participation is voluntary. You can decide not to be in the study or you can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from either mirtazapine or megestrol acetate can be evaluated. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Leaving the study will not affect your medical care. You can still get your medical care from us.

Why might I be taken out of the study early?

The study doctor and/or study Sponsor may decide to take you off this study without your consent if:

- You fail to follow the study doctor's instructions.
- You experience a serious adverse event (harmful side effect) that may require evaluation.
- Your disease does not respond to this treatment.
- You experience side effects that are considered to outweigh benefits of your participation.
- You become pregnant.
- The research physician feels it is in the best interest of your health and welfare.

You may stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first.

In the event that you withdraw from the study, we will ask you to continue to be followed and clinical data will continue to be collected from your medical records.

What are the costs for taking part in this study?

You or your insurance company/third party pay or will be billed for all routine procedures and drugs associated with this study including the cost of treating injuries resulting from such routine procedures. Routine procedures and drugs are those that you would likely receive whether or not you are in this study. You will be responsible for any deductibles or co-payments that are associated with your insurance coverage. Examples of procedures and drugs that may be billed to your insurance company include mirtazapine, metestrol acetate, and lab tests.

Will I be paid for taking part in this study?

No, you will not be paid for participation in this study.

What happens if I am injured because I took part in this research study?

If you require immediate medical care to treat an illness or injury that is determined by the Investigator to be caused directly by the study drug, or by a test that has been run because it is required for the study, then Midwestern Regional Medical Center (MRMC) agrees to pay the cost to cover this immediate medical care. You understand that MRMC is not responsible for the costs of further treatment beyond immediate and necessary care, nor will they give you money

as compensation for such injury. The cost for long term care for illness or injury will remain the responsibility of you, the patient, your health insurance carriers, or Medicare. If you are injured, your study doctor will discuss the available treatment options with you.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study in a timely manner.

What are my rights regarding the information gained in this study?

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get your health information and why they may be able to get your health information. The study doctor must get your authorization (permission) to use or give out any health information that might identify you. Every effort will be made to maintain your confidentiality throughout this study to the extent permitted by the applicable laws and regulations. Your health information may be published in a manner in which your identity will remain anonymous.

What personal information will be obtained, used or disclosed?

If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. Your personal health information (PHI) from your original and current medical records and all data resulting from your participation in this research will be collected during the course of this study. This may include (but not be limited to): results of tests or examinations, medical procedures, tissue or blood sampling and medication records.

How will my health information be utilized in the study?

Your PHI will be used to analyze results of this research study. It may also be used in scientific presentations and publications, but in a way that will not identify you by name. Your PHI will be kept confidential, and unless required by law, will not be made publically available.

Who may use and disclose information about me?

The following parties are authorized to use and/or disclose your PHI in connection with this study:

- The Principal Investigator, Kristina Stodola, RD, LDN

- MRMC research personnel
- MRMC's Institutional Review Board body that ensures the protection of human subjects enrolled in research studies at MRMC

The parties listed in the preceding paragraph may share this information with:

- The Office for Human Research Protection in the U.S. Department of Health and Human Services (OHRP)
- The Food and Drug Administration (FDA)
- Sponsor representatives

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will this authorization expire?

Unless withdrawn, your authorization for the use and/or disclosure of your PHI has no expiration date, since information collected for research purposes continues to be analyzed for many years.

Do I have to sign this authorization form?

You do not have to sign this form. But if you do not, you will not be able to participate in this research study (or receive any research-related treatment). Signing this form is not a condition for receiving any medical care outside of the study.

If I sign this form, can I revoke it or withdraw from the research study later?

You are free to withdraw your authorization of use and disclosure of PHI (and to discontinue participation in this study) at any time. If you withdraw your permission, your PHI will no longer be used or disclosed in the study, except to the extent allowed by law (e.g., necessary to maintain the integrity of the research). If you wish to withdraw authorization for the research use and disclosure of PHI in this study, you must write to:

Kristina Stodola, RD, LDN
Midwestern Regional Medical Center
2520 Elisha Avenue
Zion, IL 60099

Will I have access to my medical records during the study?

To maintain the integrity of this research study, you may not have access to any health information collected and developed as part of this study until the study is completed. At that time, you would have access to such health information if it was used to make a medical decision about you (e.g., if included in your medical record).

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this study.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your health information. However, if you decide to be in this study and sign this consent form, you will not be allowed to look at or copy study related information about you until after the study is complete.

May I withdraw or revoke (cancel) permission to share information about me?

Yes, but this permission will not stop automatically. Your permission will remain in effect until you cancel it in writing.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

If you want to withdraw from the study, you should send your request in writing to:

Kristina Stodola, RD, LDN
Midwestern Regional Medical Center
2520 Elisha Avenue
Zion, IL 60099

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may be re-disclosed and no longer protected. There is a risk that your information will be released to others without your permission. Every effort will be made to maintain your confidentiality throughout the study.

What does “conflict of interest” mean?

A *conflict of interest* is when the investigator or another member of the research team could benefit financially, or some other way, from the results of the research study. (

You should be aware that the Principle Investigator for this study, as well as other investigators, and members of the research team are employed by the study sponsor and/or an affiliate of the study sponsor. Before entering this study or at any time, you may ask for a second opinion about your care from another doctor who is not a part of the study.

What do I do if I have questions about the study?

If you have any questions concerning your participation in this study, or if you experience a research-related injury or become ill as a result of being in this study, contact the study doctor:

Dr. Pankaj G. Vashi, MD

Lead National Medical Director

Midwestern Regional Medical Center

2520 Elisha Avenue

Zion, IL 60099

(847) 872-6415

OR

Dr. Laura Sunn, PhD

Consultation-Liason Psychiatry

Midwestern Regional Medical Center

2520 Elisha Avenue

Zion, IL 60099

(800) 458-1975

If you have questions about your rights as a research subject, you may contact:

Dr. Harland Verrill at hverrill@umflint.edu or 810-845-0838.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. You will be given a copy of this signed and dated informed consent to keep.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Consent

What does your signature on this consent form mean?

Your signature on this form means that:

- You understand the information given to you in this form
- You accept the provisions in the form
- You voluntarily agree to join the study
- You have had all your questions about the study answered
- You authorize the use of your health information to the parties listed in this form as described above.

I have read the information in this consent form. All of my questions about the study and my participation in it have been answered. I freely consent to participate in this research study.

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Patient

Signature of Patient Date

Printed Name of Person Conducting Informed Consent Discussion

Signature of Person Conducting Informed Consent Discussion Date

Appendix B



Midwestern Regional Medical Center
 Institutional Review Board Office
 2610 Sheridan Road
 Zion, IL 60099

Tel: (847) 746-4362

fax (847) 746-4117

web cancercenter.com

July 21, 2014

Kristina Stodola, RD, LDN
 Principal Investigator
 Dr. Laura Sunn, PhD
 Sub-Investigator
 Nutrition
 Midwestern Regional Medical Center
 2520 Elisha Avenue
 Zion, IL 60099

MRMC 14-06: Comparing Mirtazapine to Megestrol Acetate for Appetite Improvement and Quality of Life in Advanced Stage Lung and Colon Cancer Patients: A Prospective, Randomized, Open-Label, Comparative Study.

Dear Ms. Stodola:

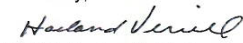
On behalf of the IRB committee, I am pleased to inform you, IRB expedited approval has been granted on July 21, 2014 for one year on Protocol Amendment version 1.2 dated 03Jul2014, revised Informed Consent dated 30Jun2014 and addition Sub-Investigator Raakhee N. Patel, PT. You may continue with patient enrollment.

As principal investigator, you are responsible for reporting any research related injuries or unanticipated problems which involve risk to human subjects to the chairperson of the Institutional Review Board for Research and Ethics of this Institution, and the Food and Drug Administration (FDA). No changes in the approved research activity may be instituted without review and approval of the Institutional Review Board for Research and Ethics of this Institution except where necessary to eliminate immediate hazard to human subjects. As principal investigator you are also responsible for notifying the IRB and the Food and Drug Administration whenever it is anticipated that an IND or IDE exemption will be required.

The frequency of review for this project is annual. In order to ensure timely review of the progress of the study, please submit your continuing review request to the Office of the IRB at least three weeks before your expiring annual review date and for inclusion on the agenda. If the continuing review report is not received as requested, the activity on this research project will be suspended until the report is received and the IRB reviews the report at a convened meeting.

If you have any questions or I can be of assistance in any way, please contact me at (810) 845-0838 or the IRB Office at (847) 746-4362. You may also respond in writing to the address above.

Sincerely,


 Harland L. Verrill, Ph.D.
 IRB Chairman

RESEARCH SUBJECT INFORMED CONSENT AND AUTHORIZATION FORM

Title: Comparing Mirtazapine to Megestrol Acetate for Appetite Improvement and Quality of Life in Advanced Stage Cancer Patients: A Prospective, Randomized, Open-Label, Comparative Study

Investigator: Kristina Stodola, RD, LDN

Sponsor: Midwestern Regional Medical Center, Inc.
2520 Elisha Avenue
Zion, IL 60099

Site: Midwestern Regional Medical Cent, Inc.

**Study-related
Phone number:** (847) 731-5859

MIDWESTERN REGIONAL
MEDICAL CENTER
CTCA® IRB *EXPEDITED*
Approved
Date July 21, 2014

Introduction

Midwestern Regional Medical Center requires your written informed consent in order for you to take part in this clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who voluntarily choose to take part. This Informed Consent document describes the clinical research study that you are being asked to participate in and what the study will involve. Please take your time to make your decision about taking part in this clinical trial. Discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more information.

You are being asked to take part in this study because you have advanced stage cancer and suffer from loss of appetite. In addition, you have lost at least 5% of your body weight over the past three months. Your participation in this study is entirely voluntary.

Why is this study being done?

