THE COMPARISON OF THE EFFECT OF DIETARY CHANGES OR DIRLOTAPIDE TREATMENT ON CANINE OBESITY IN A SMALL ANIMAL VETERINARY PRACTICE

A Report of a Senior Study

by

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ABSTRACT

One of the greatest clinical challenges in contemporary veterinary medicine is canine obesity, which in the U.S. is increasing similar to trends observed in humans. Obesity impedes the overall wellness of canine patients; it is associated with shorter lifespan in domesticated dogs. The purposes of this study were to evaluate the incidence of obesity in one particular East Tennessee small animal veterinary practice and to examine the efficacy of two readily available treatment tools for this disease: pharmaceutical therapy with dirlotapide or dietary intervention through either caloric restriction or a high fiber diet. The incidence of obesity was examined by recording the body condition score (BCS) on a 1-9 scale for every dog that entered My Pets Animal Hospital for 2 consecutive months during the summer of 2009. Data for 594 dogs was collected in this manner and 4 treatment groups were also evaluated to examine the efficacy of treatment protocols. This study presents two major findings: (1) that 67 % of dogs at this particular veterinary clinic were overweight/obese (based on a BCS score of 6 or greater) and (2) that both dietary changes and pharmaceutical treatment were equally effective at promoting weight reduction in obese canines, as there was no significant difference in the percent weight loss per 30 days ($p = 0.969$). There was a significant difference between the control group and the other 3 treatment groups ($p = 0.0119$), illustrating that therapy is necessary to induce weight loss. Some breeds including Beagles and Labrador retrievers, were more prone to obesity than others. The knowledge obtained from this study and the flexibility it provides for treatment options will hopefully reduce the prevalence of canine obesity.

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CHAPTER I

Introduction

Background of canine obesity incidence

One of the greatest clinical challenges in contemporary veterinary medicine is canine obesity, which is increasing with a similar trend observed in humans (Veiga et al., 2008). Canine obesity, defined as a body weight 15 percent above ideal, results from prolonged imbalance of energy intake and energy expenditure and the underlying cause of this widespread condition appears to be overfeeding (Laflamme, 2001). As animal models have provided fundamental contributions to the understanding of the basic parameters that regulate metabolism and energy balance, a thorough examination and understanding of dog obesity is crucial to reduce the incidence of obesity in both humans and domesticated animals (Speakman et al., 2008).

The incidence of obesity in domestic dogs in the US is now 20-40%, with overweight pets (defined as being 10-20 % above ideal weight for the breed (Czirjak & Chereji, 2008)) accounting for at least half of the general population (Gossellin et al., 2007a). Similar incidence has been reported in Western Europe (Jeusette et al., 2004) and Australia, indicating the epidemic is widespread and not limited to the US alone (German, 2006). There are numerous

variables that increase the likelihood of obesity in dogs including older age, neutering, and breed (see Table 1). Higher obesity occurrence is commonly seen in Labrador retrievers, Cairn terriers, Cocker spaniels, Dachshunds, Shetland sheepdogs, Basset hounds, Cavalier king Charles spaniels, Golden retrievers, and Beagles (Edney & Smith, 1986). Managing the disease through dietary restriction and increased activity level is often unrealistic with present sedentary lifestyles exhibited by many people in western culture and, consequently, their pets. With a reduced activity level and unhealthy eating habits so prevalent among the human population, a successful weight loss program largely depends upon owner compliance (Remillard, 2001). The lack of a healthy, properly implemented feeding and exercise regimen has led to obesity now being the most common nutritional disease in dogs, and although decreasing weight through dietary caloric energy restriction is successful in experimental studies, there as of yet has been scant success in programs for obese client-owned dogs (German et al. 2007). Over the past 40 years, canine obesity has gradually risen in the west, from 9% of the dog population (Krook et al., 1960) to 28% a decade later (Mason 1970). In 1974 the reported percentage was 34% (Edney, 1974), and the occurrence is presently from 20-40% in various Western nations (Czirjak & Chereji, 2008). Table 1 illustrates various risk factors contributing to the prevalence of obesity in canine companions.

Table 1. Risk Factors associated with canine obesity.

Risk Factors	Remarks	Source
Predisposed breeds	Data varies some according to the region and the year studies were made. Common breeds include Labrador Retrievers, Teckel, Shetland sheepdogs, Cocker Spaniels, Beagles, Basset Hounds, Cavalier King Charles Spaniels, Cairn terriers, Dachshunds, and Golden retrievers.	Czirjak & Chereji 2008 Gossellin et al. 2007
Genetic factors	Probability of the implication some genetic factors may be involved- individual predisposition	Czirjak & Chereji 2008
Age	Incidence of obesity is increasing after 2 years of age and will be highest at 6-8 years	Czirjak & Chereji 2008
Sex	Females are more predisposed than males.	Gossellin et al. 2007
Neuter Status	Decreased metabolic rate from neutering increases risk of obesity for inactive animals	Gossellin et al. 2007
Endocrine diseases	Diabetes mellitus	Gossellin et al. 2007
Medication	Can cause hyperphagy and weight increasing, especially antiepileptics and glucocorticoids, corticosteroids and progesterones	Czirjak & Chereji 2008; Jeusette et al. 2004
Sedentary lifestyle	Lack of exercise- maintaining a high activity level is important- daily walks or at least an hour of active movement essential	Czirjak & Chereji 2008
Unbalanced intake of food	Obesity is the result of prolonged higher energy intake than expenditure	Gossellin et al. 2007
Begging & owner attitude	Appeared and supported habit from the part of the owner- human food often unhealthy for canine consumptions & contributes to weight gain	Czirjak & Chereji 2008
Type of Food	Dogs that consume semi-moist as opposed to dry formulas more prone to be overweight- Ad libitum feeding of a high-fat diet, for example, is a well-known factor of obesity development	Lund et al. 2006

Implications of obesity: medical complications

Obesity is associated with shorter lifespan in domesticated dogs. Obese dogs are often found to experience expiratory airway dysfunction, and overfeeding in these animals led to a decreased lifespan and heightened risk of death due to secondary diseases (Bach et al., 2007). In addition, lean-fed dogs live 15 percent (1.8 years) longer than their ad libitum-fed counterparts (Kealy et al., 2002). Also, overfed dogs required treatment for secondary medical conditions 2.1

years earlier than lean-fed animals, implying that medical complications have a much more rapid onset in overfed dogs. Many studies have shown that life span may be substantially extended and quality of life significantly improved if owners carefully manage the animal's caloric intake and avoid overfeeding (eg., Kealy et al., 2002). Because obesity is known to predispose or exacerbate a range of serious medical conditions, the gravity of the present situation cannot be overstated.

Besides decreasing the lifespan of dogs, obesity contributes to many other diseases that detract from the quality of life of both the pet and owner (see Table 2). Osteoarticular diseases are especially prevalent among obese canines. Perhaps one of the most universal on the list of canine health problems is osteoarthritis (degenerative joint disease,) one of many locomotor and musculoskeletal complications. This frequently observed condition is characterized by cartilage erosion in joints resulting in the loss of protection against bone grinding. After the cartilage is reduced, the articulating bones come into direct contact and the persistent friction results in great inflammation and pain (Burkkholder, 2001). Obesity further complicates this development by greatly increasing the load on joints rendered already unstable. Veterinary treatment for this joint disease is typically initiated several years earlier in overfed dogs in comparison to their lean counterparts (Kealy et al., 2002). Indeed, there is general consensus that keeping an animal in optimal to slightly lean body condition has been shown to decrease the risk of development of osteoarthritis (OA) and to aid in its management (Laflamme, 2006). Hip dysplasia, another joint condition amplified by obesity, is a genetically inherited and potentially crippling malformation defined by the femoral head of the thigh bone not properly fitting in the hip socket (Kealy et al., 2002). Though incurable, the condition can be treated effectively by controlling the animal’s weight early in life to decrease limb pressure (Kealy et al., 2002).

As seen in human medicine, canine obesity is strongly associated with diabetes mellitus, an endocrine disease characterized by insufficient production of or response to insulin, the hormone essential to blood glucose regulation (Graham et al., 2002). Additionally, the association of obesity and low insulin sensitivity with lipoprotein abnormalities has been suggested as risk factors for coronary heart disease (Bailhache et al., 2003). Increased-energy diets not only correlate to substantial increases in body weight but also to a reduction in insulin-mediated glucose uptake (Bailhache et al., 2003). The low insulin sensitivity associated with obesity is also related to a plasma triglyceride increase through an increase in very-low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) (Bailhache et al., 2003).

Hyperlipidemia, or increased serum lipid levels, has been demonstrated as a health concern in dogs, and this common condition can be either primary or secondary to other diseases. Secondary hyperlipidemia typically is the result of endocrine disorders (e.g., pancreatitis, cholestasis, protein-losing nephropathy), and because of obesity and high fat diets. Total cholesterol and circulating triglycerides have also been found to be significantly higher in obese dogs with respect to normal weight dogs, linking obesity in dogs with higher serum lipid levels (Pena et al., 2008). In addition, chronic obesity in dogs also elevates plasma leptin and insulin concentration, and causes a significant decrease in plasma total ghrelin concentrations. While long-term effects of hyperlipidemia in dogs are unknown, hypercholesterolemia has been associated with ocular lesions and induction of acute pancreatitis (Jeusette et al., 2005).

Other potentially serious conditions exacerbated by obesity include respiratory distress, hypertension, cardiac disease, dystocia, decreased heat tolerance and increased chance of heat stroke, dermatologic problems and neoplasia, along with increased surgical risk and infertility (Kuruvilla & Frankel, 2003). Adipose tissue is not simply an energy storage organ, but also

produces a variety of proteins that influence not only metabolic rate but also endocrinologic and immunologic functions (Brunson et al., 2007). An excess of this tissue type results in a surplus of metabolically active secretory proteins including adipocytokines such as leptin, tumor necrosis factor-a, adipsin, resistin, interleukin-6, plasminogen activator inhibitor-1, and adiponectin (Acrp30), which further increase the likelihood of secondary complications (Brunson et al., 2007)

Table 2. Pathology and medical complications associated with canine obesity.

Disease states and dysfunctions	Remarks	Source
Osteoarticular diseases	Osteoarticular distortion (irreversible), torn cruciate ligaments and fractures of the humeral condyle, hip dysplasia, intervertebral disk disease	Czirjak & Chereji 2008; Lund et al. 2006
Intolerance to effort and heat		Gossellin et al. 2007
Reproductive problems	The correlation between obesity and reproductive problems is not clear, although it is accepted that excess fat may lead to dystocia.	Czirjak & Chereji 2008
Cancers	Increasing of incidence of mammary tumors and a bladder carcinoma.	Czirjak & Chereji 2008; Lund et al. 2006
Malassezia dermatitis	Abnormal skin conditions & dermatopathy	Czirjak & Chereji 2008; Lund et al. 2006
Cardiorespiratory problems	Hypertension, tracheal collapse, thrombosis of the portal vein, hypoxia of the myocardium and valvular endocarditis.	Czirjak & Chereji 2008
Diabetes mellitus	The dogs which suffer diabetes present hyperphagia; glucose intolerance, excessive urination & dehydration, etc.	Gossellin et al. 2007; Lund et al. 2006
Reduced immunity	Heightened chances of contracting secondary diseases	Gossellin et al. 2007; Lund et al. 2006
Hyperlipidemia and dyslipidemia	HDL cholesterol decreases, VLDL cholesterol, fatty infiltration of the liver increases. Hypertriglyceridemia often results in decreases in serum cholesterol, chloride, amylase, and lipase concentration	Czirjak & Chereji 2008
Increases incidence of pancreatitis	Increases the risk of acute hemorrhagic pancreatitis.	Czirjak & Chereji 2008
Incontinence and urinary calculi	Formation of more urinary calcium oxalate calculi compare to the dogs with normal weight; increased incidence of urinary tract infections	Czirjak & Chereji 2008; Lund et al. 2006
Surgical complications Increasing morbidity and mortality during and after anesthesia.	Due to the excess of subcutaneous or abdominal fat. Many anesthetic drugs are lipid soluble- obese dogs eliminate them slower increasing chance of toxicity reactions	Czirjak & Chereji 2008
Modifications in thyroid function	The concentration of thyroid hormones is increased at the obese dogs and the restriction of the energy modifies the normal working of the thyroid.	Czirjak & Chereji 2008; Daminet et al., 2003.
Abnormal serum protein balance	Increase in blood leptin positively associated with obesity along with development of leptin resistance modulating food intake & energy consumption- positively correlated to fat storage. Leptin is released from adipose tissue into the peripheral circulation and binds to receptors in hypothalamus by crossing the blood-brain barrier	Nishii et al. 2006
Increased adipokine secretion	Metabolically active substances secreted by increased volume of adipose tissue have a wide range of secondary effects on the body	Brunson et al. 2007

Treatment options for obesity and weight management in dogs

The first step in implementing a weight loss program is to restore the balance between energy intake and expenditure by reducing calorie intake and increasing activity level (Gossellin et al., 2007a). If the total daily energy content of ingested food is less than the metabolic maintenance energy requirement (MER), then energy stored in the body in the form of glycogen, fat or other tissues will be utilized to compensate for the reduction in calorie intake. This reduced caloric intake and/or increased activity level should be a gradual process; however, visible results are an important component in owner compliance, which is often a barrier to successful feeding and exercise regimens. To minimize lean muscle tissue loss and to avoid regaining body weight at the end of the official treatment program, lifestyle changes in food consumption and exercise should be indefinite (Laflamme & Kuhlman, 1995).

It is not uncommon for attempts at weight loss through calorie restriction to fail for lack of owner follow through (Remillard, 2001). Assessing owner attitude towards the disease and proper education of all involved in the treatment process are integral components to increase likelihood of a successful program. Some owners may be reluctant to admit the obese state of their dog, while others are simply unable to resist their pet begging for food, especially high fat treats and human dietary components, which may be multiplied by several family members showing affection to the animal by extra feeding. Cooperation is essential in a calorie restriction program, which will work only with consistency (Remillard, 2001).

Although overfeeding is potentially the greatest contributor to the incidence of obesity and its wide range of accompanying health complications, quantifying that factor proves difficult due to variable differences in weight, morphologic characteristics, activity, sex, age, body composition, and environment (climatic and psychological) that must be taken into

consideration when trying to calculate ideal energy requirements for particular individuals (Pouteau et al., 2002). The energy requirements to support basal metabolic rate range from 410 to 652 kJ ME/kg0.75/d.3 depending on differing experimental conditions and those variables previously mentioned (Pouteau et al., 2002). To date, the metabolically valuable energy concentration in available dog foods is frequently unknown, but the amount of kilocalories consumed should be compared to true rate of energy expenditure of individuals to create and implement a plan for successful clinical understanding, prevention, and treatment of canine obesity.

Healthy targets for weight loss of obese dogs (body weight 15% above ideal) are generally set at a rate of 1–2% per week to achieve a 15–20% overall reduction in body weight over a 12- to 18-week period (Markwell et al., 1994; Burkholder & Bauer, 1998; Butterwick, 2001). Owner compliance often has a strong psychological element, and because of this, results should be readily apparent to avoid abandonment of the program if deemed unsuccessful by the owner. Owners may experience guilt, perceiving that their dog is not eating enough or 'doesn't like the food,' which encourages both the feeding of treats and scraps to oblige begging by the dog to supplement the perceived bland, "inferior" diet (Bierer & Bui, 2004). Manufactured low-calorie dietary formulas often have a high fiber content to provide bulk, and may also decrease fat digestibility by modifying pancreatic lipase secretion and reducing binding of bile acids, as well as promoting faster passage through the intestines due to its higher water-holding capacity (Gentry, 1993). However, the satiety promoted by a high fiber diet alone is questionable and many owners dislike the typical increase in stool volume, which also reduces compliance (Jewell, & Toll, 1996; Butterwick & Hawthorne, 1998; Jewell et al., 2000). Another approach to dietary modification is a high-protein low-carbohydrate consumption, which has been observed

in human weight loss programs such as the 'Atkins diet.' Proponents claim the reduced energy of this diet promotes increased catabolism of adipose tissue (although weight loss may be better explained by the reduction in ingested calories overall, rather than their source.) In dogs, these diets show success in reducing body weight while preserving lean tissue (Bierer & Bui, 2004).

Besides caloric restriction, another approach used for effective weight reduction is to decrease appetite, with the hopes of increasing owner compliance with diminished begging behavior from the dog. Appetite is regulated by hormonal factors, but these interwoven mechanisms can be very complex, involving various chemical messengers present both in local tissues and widespread circulation, interacting with a series of feedback loops, designed to anticipate future difficulty in energy acquirement. Molecules specifically involved in regulating satiety include ghrelin, leptin, insulin, glucagon, cholecystokinin (CCK), peptide YY, glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP), and oxyntomodulin as well as other circulating endocrine substances with less direct effects including growth hormone, thyroxine, cortisol, sex hormones and associated stimulating hormones (Martin et al., 2006). Many times, changes in systemic hormonal balance increase appetite, such as neutering a pet (therefore eliminating sex hormones produced by the removed testes and ovaries) or imbalances due to disease conditions like hypothyroidism or diabetes mellitus (Jeusette et al., 2004). The central nervous system contains four primary areas controlling appetite including the hypothalamus (especially the arcuate nucleus), the paraventricular nucleus, the perifornical area and lateral hypothalamus (PFLH) and finally the brainstem's dorsal vagal complex (Druce et al., 2004; Leibowitz & Wortley, 2004). Beta-endorphinergic and alpha-noradrenergic systems in the paraventricular nucleus stimulate eating behavior (Leibowitz & Hor, 1983). Orexins, chemicals secreted by the perifornical area and lateral hypothalamus, initiate food seeking behavior

following hypoglycemia or lipidemia while melanin-concentrating works to reduce activity and energy expenditure. Among various other factors secreted by the arcuate nucleus of the hypothalamus, galanin-like peptide (GALP) is known to reduce food intake and increase thermogenesis (Leibowitz & Wortley, 2004). These are just a few examples of chemicals secreted by these four central nervous structures to stimulate or suppress eating. Other structures are involved in chemical messaging, such as the duodenum, which releases CCK in response to intraluminal nutrients, which follows vagal pathways to the CNS to promote satiety (Woods, 2004). The stomach secretes ghrelin with certain nutrient levels, which stimulates hunger and acts locally to promote gastric emptying and downregulate gastric acid secretion (Druce et al., 2004). Two other compounds released from the distal small intestine, oxyntomodulin and GLP-1, as well as other anorectic peptides including peptide YY and CCK induces feelings of satiety from the CNS and inhibit gastric acid secretion, suppress ghrelin, and promote insulin secretion (Stanley et al., 2004). Plasma levels of CCK, GLP-1, peptide YY and PP increase rapidly after food ingestion, and while levels of CCK and GLP-1 return to baseline in a 1–2 hour period, peptide YY and PP levels remain elevated for over 6 hours, suggesting a role in regulating the time interval between meals (Stanley et al., 2004).

Pharmaceutical agents implemented in obesity treatment

Much research has gone into developing pharmaceuticals to aid in weight loss in humans, but until the release of the microsomal triglycide transport protein (MTP) inhibitor dirlotapide by Pfizer in 2007, licensed medication available for dogs was scarce (Wren et al., 2007a). Table 3 below presents a summary of pharmaceuticals that have been examined for their ability to cause canine weight loss.

Table 3. Pharmaceutical agents historically used to reduce weight in dogs.

Pharmaceutical agent	Mechanism of action in weight reduction	Side effects	Evaluation	Source
Dinitrophenol (DNP)	Introduced in 1930s to induce weight loss in humans by increasing MER, acting on mitochondria to uncouple oxidative phosphorylation and render ATP production less efficient, resulting in increased use of fat reserves as energy sources	Much of the energy is converted into heat production, rapid onset of cataracts	Resulting hyperthermia often fatal, serious adverse affects discourage use	Horner 1941, Harper et al. 2001
Ephedra (derived from Chinese medicinal herb *Ephedra sinica*)	Alkalloids ephedrine and pseudoephedrine have sympathomimetic action stimulating norepinephrine release from sympathetic nerves which binds beta-adrenergic receptors in skeletal muscle and adipose tissue to increase lipolysis and catabolism through increased thermogenesis	Increased blood pressure, tachycardia, elevated body temperature, anorexia, reduced gastrointestinal motility, anxiousness, nervousness, insomnia, death	Because of dangerous side effects in people, this drug is now banned in the US thought it is still used by some body-builders and athletes	Shekelle et al. 2003
Amphetamines	Release stores of norepinephrine & dopamine from nerve endings and stimulate seratonin release in CNS in high doses, stimulates catacholeamine release and anorectic appetite suppressant	Highly addictive, tachycardia, increased blood pressure, palpitations, insomnia in people	Prone to abuse and greatly restricted by legislation in people	Samanin & Garattini 1993
Phenylpropanol-amine	wide use by humans as an appetite suppressant by direct stimulation of alpha-1-adrenoceptors	hemorrhagic strokes and psychological side effects- banned in US	Though utilized as a sympathetic agonist in treating canine urinary incontinence, it has no effect to reduce body weight in dogs	Samanin & Garattini 1993 Kushner & Manzano 2002 Lewis et al. 1987
Sibutramine	Approved in 1998 for obesity treatment in people by acting as neurotransmitter reuptake inhibitor, increasing activation of alpha & beta-adrenoceptors and seratonin receptors, increases extracellular dopamine concentrations, enhances satiety, hypophagia and small contribution from increased energy expenditure	Dry-mouth, decreased intestinal motility, insomnia, increase blood pressure, tachycardia, psychological changes	Undesirable side-effects, unsuitable for canine use	Luque & Rey 2002

Hormone & peptide supplements	thyroid hormone, growth hormone, and human chorionic gonadotrophin, which act to regulate appetite and increase MER Anorectic peptides administered IV to laboratory species and human volunteers have been found successful in reduce food intake, including substances CCK, oxyntomodulin, GLP-1, PP, and peptide YY	Thyroid hormone promotes weight loss through lean tissue reduction instead of the targeted adipose tissue	due to the large peptide composition of these substances, oral administration renders them ineffective as enzymes such as pepsin in the stomach often break them down before reaching systemic circulation, limiting appeal as a treatment option	Gossellin et al. 2007a Woods 2004 Smith et al. 1981, Cohen et al. 2003, Druce et al. 2004, Stanley et al. 2004 Batterham et al. 2002
L-carnitine	Essential cofactor of several enzymes necessary for fatty acid transport into the mitochondria- vitamin-like nutrient crucial to fat and carbohydrate metabolism- Successfully treated hepatic lipidosis in cats, promoting weight loss by increasing fatty acid b-oxidation through its role in mitochondrial transportation standard supplement in restricted calorie diets for dogs	An undesirable effect on weight loss, lean body mass or adipose tissue with supplements above or below an optimal level	can facilitate weight loss and assist in maintaining lean body mass- Further study needed to determine if there is a linear dose response in dogs; in several other species, a curvilinear response recognized	Center et al. 2000; Center 2001
Amylase blockers, laxatives	reduce digestibility or absorption of nutrients and increase intestinal transit time	Malnutrition and nutrient deficiency	Not encouraged in people or animals	Gossellin et al. 2007a
Sucrose polyester	a non-absorbable fat substitute used in food preparation which adds no calories and accelerates gastric emptying and slows transit time through the small intestine, also acting to reduce gall bladder contraction and release of CCK	diarrhea, flatulence, increased fecal weight, and intestinal discomfort/pain, as well as vitamin A, D, K, and E deficiency	Side effects may be problematic and discourage use	Thomson et al. 1998
Orlistat	anti-obesity drug used in humans which acts locally in the gastrointestinal tract to inhibit lipase, preventing the digestion of long chain triglycerides and therefore reducing dietary fat absorption by about 30% at therapeutic doses	Steotorrhea development, and other intestinal symptoms such as flatulence, discomfort and leakage	This drug has been evaluated in dogs in toxicity studies but any therapeutic effect is not yet seen	Batterham et al. 2002; Stanley et al. 2004 Ballinger & Peikin 2002
Dirlotapide & mitratapide	microsomal triglyceride transfer protein (MTP) inhibitors that act primarily within the endoplasmic reticulum of enterocyte intestinal cells, preventing the formation and release of chylomicrons into the lymphatic circulation and reduces food intake in dogs	mild emesis episodes and loose stools, fecal fat content may increase	Side effects are seen to improve with continued exposure to the drug	Kirk et al. 2007, Chandler et al. 2003, Wren et al. 2007a

The most promising medications available today for weight reduction in dogs are dirlotapide and mitratapide, microsomal triglyceride transfer protein (MTP) inhibitors that act primarily within the endoplasmic reticulum of enterocyte intestinal cells, preventing the formation and release of chylomicrons into lymphatic circulation. Dirlotapide (1-methyl-N-[(1S)-2-[methyl(phenylmethyl)amino]-2-oxo-1-phenylethyl]-5-[[[4α-(trifluoromethyl)[1,1α-biphenyl]-2- yl]carbonyl]amino]-1H-idole-2-carboxamide) administration reduces food intake in dogs, which may be related to peptide YY and GLP-1 release (Hickman, 2005). MTP, originally isolated from bovine liver microsomes, is important in the transferring of triglycerides, cholesterol esters, and phosphatidylcholine between membranes, catalyzing the assembly of triglyceride-rich apolipoprotein-B containing lipoproteins to form chylomicrons in the intestinal mucosa for release into the lymphatic system for general circulation. Recent research has explored MTP inhibitors, which have the ability to lower plasma cholesterol and triglyceride concentrations and cause a reduction in the absorption of dietary fat from the small intestine (Chandler et al., 2003). Enterocytes retain fatty acids, monoglycerides and cholesterol from micelles of digested dietary fat with MTP inhibition and fail to release chylomicrons into circulation as a result. These cells are sloughed, with the contained fat, increasing fecal weight and fat content (Berriot-Varoqueaux et al., 2000). Because MTP inhibition of dirlotapide occurs within the enterocyte, lipase activity in the small intestine is not affected. Dietary lipids are therefore effectively sequestered in the intestinal cells. Fecal fat content may increase (up to 30% mean increase following dirlotapide administration, but main side-effects consist of mild emesis episodes and loose stools, and incidence has been seen to decrease with continued exposure to the drug (Kirk et al., 2007). In addition to reducing intestinal fat absorption, dirlotapide also acts indirectly to reduce food intake, and it is this secondary effect that is primarily responsible for

weight loss following oral administration to overweight dogs (Wren et al., 2007a). It is suggested that fat sequestered in the enterocyte causes gastrointestinal peptides associated with satiety to be released into circulation (Hickman, 2005). The fat content of the diet has a significant impact upon required dirlotapide dose needed to achieve an ideal weight loss response, with low (5%) fat diets requiring higher dosages than diets containing 10% fat or greater (Gossellin et al., 2007c). Efficacy depends on oral administration producing local gastrointestinal activity (Hickman, 2005). However, dosing recommendations can be complex as the dose–response relationship changes over time, requiring dosage to be increased to maintain a consistent rate of weight loss (Gossellin et al., 2007c). Although the reasons for this are unclear, it may be a consequence of decreased maintenance energy requirements, following reductions in body weight and dietary energy intake, which is common in weight-loss programs (Laflamme et al., 1997).

Using dirlotapide to enhance weight loss programs has several benefits, especially in improving owner compliance by providing visible results along with implementing a reduced calorie diet and increased activity level (Wren et al., 2007a). Following withdrawal of the drug, healthy feeding practices can then be maintained. Owner education is extremely important, because some owners in recent studies regarded appetite loss as a sign of illness and were reluctant to continue treatment (Wren et al., 2007d). Visible improvements in weight and body condition score along with encouragement from the veterinarian on the health benefits of weight loss were found to facilitate more enthusiastic compliance. After arriving at a weight stabilization phase of treatment, the dirlotapide dose is gradually reduced until it can finally be eliminated and the dog can continue a healthy eating and exercise plan as a lifestyle (Wren et al., 2007a).

Purpose

The purpose of this study is to examine the efficacy of two readily available treatment tools in the management of the growing canine obesity disease: pharmaceutical therapy with dirlotapide or dietary intervention through caloric restriction or a high fiber diet. This study will identify the incidence of canine obesity in one particular East Tennessee small animal veterinary practice, and compare the outcome of treatment protocols to see if reduced or altered food intake alone effectively treats obesity, or if medicating obese patients with dirlotapide promotes significant weight loss.

CHAPTER II

MATERIALS & METHODS

Excepting three dirlotapide case studies from Bluegrass Animal Hospital in Knoxville, Tennessee, all test subjects were canine patients of My Pets Animal Hospital, located in Alcoa, Tennessee. All dogs were privately owned and varied in breed, age, and gender (see Table 4). This study was designed to assess both obesity incidence in the general clinic population and the efficacy of different treatment protocols to promote weight loss.

Incidence of obesity

The general clinic population's overall weight status was examined by recording the body condition score (BCS) for every dog that entered My Pets Animal Hospital for 2 consecutive months during the summer of 2009. BCS data was collected for 594 dogs and their breed noted to determine if body condition was dependent on breed. Scores were assigned on a scale of 1 to 9 according to Laflamme (1997, see Appendix A), with any score greater than 5 considered overweight and any score greater than 7 considered obese. Lastly, a survey was conducted of randomly selected dogs that came in to the clinic for annual wellness exams when their owners had the time or inclination to report on their feeding and exercise practices of their dogs. This included information on the specific type, brand, and amount of food given (see Appendix B). Other variables were also assessed on this survey that could play a potential role in weight gain, including inactivity, neutering, and membership in multiple pet households. Owner attitude was also examined in regards to their pet's body condition. Their assessment of their dog's weight status was compared to the body condition score (BCS) assigned by the veterinarian (see Appendix A).

Table 4. Demographic data of canine test subjects.

Breed	Male Count	Female Count	Mean Age (years)
Airdale	1	0	6
American staffordshire terrier	1	0	5
Australian Shepherd	2	4	7.2
Basenji	1	0	5.5
Basset hound	5	2	2.9
Beagle	10	15	6.1
Bichon frise	4	5	5.3
Bird dog	2	1	1.2
Bloodhound	1	0	5
Blue Heeler	0	1	6
Border collie	4	2	8.2
Boston terrier	6	5	7.5
Boxer	9	8	4.8
Brussels griffon	1	0	7
Bull mastiff	0	1	8
Bulldog	0	1	9
Cairn Terrier	1	0	6
Cavalier King Charles Spaniel	2	1	5.6
Chesapeake Bay retriever	1	0	5
Chihuahua	14	18	6.3
Chow mix	1	3	6.1
Cockapoo terrier	1	0	2
Cocker spaniel	4	5	4.8
Collie	1	0	5
Corgi mix	2	1	4.1
Dachshund	8	10	6.1
Dakota Sheepdog	1	0	7
Dandy Dinmont Terrier	1	0	11
Doberman	2	1	5..9
English bulldog	2	0	6.8
Eskimo mix	1	0	5
Fox terrier	1	0	7
German Shepherd	8	6	6.8
German Shorthair pointer	1	0	4
Golden retriever	9	11	7.2
Great Dane	2	0	3.9
Great Pyrynese	1	2	4.8
Greyhound	0	2	10.1
Hound mix	3	0	5.7
Husky	5	3	6.8
Irish Water Spaniel	1	0	2
Jack russell	5	9	8.6
Labrador retriever	20	33	7.1
Labradoodle	0	1	1
Lhaso apso	2	6	5.8
Main coon	1	0	5
Malamute	1	0	3
Maltese	3	6	4.8
Maltese/yorkie	0	1	1
Malti-poo	1	2	3.2
Mini poodle	2	2	3.7
Mini schnauzer	10	13	7.9
Minpin	2	4	6.7
Mix	21	22	6.5
Morkie	1	0	2
Norweigian Elkhound	1	0	6
Novia Scotia Duck Tolling Retriever	1	0	5
Papillion	0	2	2.2
Peekapoo	0	4	4.5
Pekinese	3	5	8.9
Pit bull	4	6	2.7
Plott hound	1	0	5
Pomeranian	4	5	7.6
Poodle	5	8	7.2
Pug	2	4	8.1
Puggle	0	1	2
Rat terrier	3	2	6.8
Rottweiler	2	1	4.3
Schnauzer	12	8	7.8
Scottie	2	1	4.6
Shar-pei	3	0	6.9
Sheltie	2	4	6.8
Shepherd mix	3	4	7.2
Shih poo	0	1	1
Shih tzhu	16	20	8.3
Spitz	3	0	6.7
Springer Spaniel	2	0	3.4
Terrier mix	3	7	5.7
Toy poodle	1	1	7.9
Walker hound	2	0	5.2
Weimeraner	1	2	4.8
Welsh terrier	1	0	6
West highland white terrier	2	6	7.3
Wheaton	1	0	3
Whippet	1	0	2
Yorkshire terrier	7	11	6.8
Yorkie-poo	2	5	4.6

Comparison of Treatments

Four groups of dogs were examined to compare the efficacy of available treatment options for overweight/obese pets. One group was treated with the pharmaceutical agent dirlotapide, one was treated with a restricted-calorie diet, one was assigned a specially formulated high fiber diet, and the fourth group acted as the control, receiving no treatment.

Table 5. Demographic data on treatment groups.

Treatment	Number of Dogs	Mean Age	Representative breeds
Dirlotapide	15	7.2	Labrador, Poodle, Beagle, Weimeraner, Pomeranian, Walker hound, Cocker spaniel, Siberian husky, Australian shepherd, Dachshund
Restricted Calorie	33	5.2	Beagle, Labrador, Golden retriever, Basset Hound, Chihuahua, Pug, Shih tzu, Schnauzer, Yorkshire terrier, Cocker spaniel, American Eskimo, Boxer, West highland terrier, Pit bull, Boston Terrier, Miniature pinscher, American Eskimo, Dachshund
High fiber diet	36	6.8	Labrador, Schnauzer, Chihuahua, Golden retriever, German shepherd, Beagle, Shih tzu, Shetland sheepdog, Boxer, Chesapeake bay retriever, Basenji, Lhaso apso
Control	50	6.9	Labrador, Schnauzer, Golden retriever, German shepherd, Beagle, Jack Russell, Chihuahua, Shih tzu, poodle, rat terrier, Bichon frise, Shetland sheepdog, Boxer, Pit Bull, Border collie, Boston terrier, Dachshund, Pomeranian, Cocker spaniel, Australian shepherd

Dirlotapide

Fifteen dogs were prescribed the pharmaceutical agent dirlotapide, whose active ingredient was administered in a gel dosage added to each dog's food once daily (see Appendix C for drug data by Pfizer). The dog's regular food type and amount given remained unchanged. Dosage was calculated according to recommendations from Pfizer, the manufacturer. During the first month of therapy, the dosing regimen consisted of 2 fixed rates. The initial dose was 0.01

ml/kg body weight and administered once daily for 14 days. The dose was then doubled to 0.02 ml/kg of body weight for the following 14 days. After the initial 28 days of treatment, the patient was weighed, and the dose adjusted each month thereafter to maintain adequate weight loss with a maximum dose of 0.2 ml/kg body weight. If the dog was not losing weight, then the dose **was** increased by 1.5 times the previous dose. If a dog lost more than 1% body weight per week the first month, the dose was decreased by 0.5 times the previous month. If a dog lost between 0-1% of his body weight the dose remained unchanged. The dogs on dirlotapide came in for monthly weigh-ins and dosage adjustments, and data from these case studies was incorporated in assessment.

Restricted Calorie diet

This group was selected from the population whose owners completed the survey outlined in the above incidence section. From that data each dog's current weight was factored into an equation provided by *Hill's Science Diet Key to Clinical Nutrition* (Hill's Inc. 2007) to calculate the individual's resting energy requirement (RER) and maintenance daily energy requirement (DER, see Table 6). These values detailed the specific daily caloric intake the animal should theoretically be receiving. The optimal daily caloric intake was compared with the daily energy amount the animal was actually receiving and the difference was computed (calculated from the amount of food and kilocalories/oz contained by the specific diet according to the owner survey). These equations are shown in Table 6 below.

Table 6. Energy requirement calculations.

Name	Equation
Resting energy requirement (RER) (kcal/day)	$70 \times wt_{kg}^{0.75}$
Maintenance Daily energy requirement (DER)	1.6 x RER
Average neutered adult	
Intact adult	1.8 x RER
Obese-prone	1.4 x RER
Weight loss	1.0 x RER

After difference in caloric intake with optimal intake was calculated it was then determined if the dog should begin a restricted-calorie feeding regimen. This was indicated if the dog was receiving more calories than required based on the results of the calculations and on the individual's body condition. The food type (formulation each individual dog was receiving) was not altered, only the amount the patient consumed daily. Recommendations were made according to this information, and after approximately 2 months of treatment a new weight was obtained for the 33 dogs in this group.

High Fiber Diet

Thirty-six dogs with an overweight/obese body condition were placed on a special high fiber diet (Hill's Prescription Diet R/D) targeted to reduce weight in canines (formulation in Table 7 below). This group was fed only this specific formula for approximately 2 months and a final weight was then obtained and compared to the initial weight.

Table 7. Hill's Prescription diet R/D dry dog food formulation.

Nutrient	Dry matter percentage
Protein	34.3
Fat	8.2
Carbohydrate (NFE)	38.7
Crude Fiber	13.5
Total Dietary Fiber	26.5
Soluble Fiber	1.6
Insoluble Fiber	24.8
Calcium	0.7
Phosphorus	0.66
Sodium	0.24
Potassium	0.86
Magnesium	0.101
Carnitine	301 ppm

Control

Dogs from the previous three treatment groups were compared with a control group of overweight and obese patients who were neither on pharmaceutical or dietary intervention, and therefore received no treatment.

Statistical Analysis

Initial and final weights were obtained for the dogs in all treatment groups after an approximate two-month period. The control group was compared to the three treatment groups of caloric restriction, dirlotapide, or therapeutic high-fiber diet to reveal if any of these therapies resulted in significant weight reduction. The data was standardized to percent weight loss per 30 days for each individual. Statistical analysis was conducted with the standardized data to visualize which therapeutic treatments were most effective in promoting weight loss. A one-way

ANOVA was used to compare groups, and Fisher's PLSD was conducted for post-hoc evaluation. The results were examined to determine if dirlotapide treatment enhances significant weight reduction compared to diet management alone.

CHAPTER III

RESULTS

Incidence of Obesity

The majority of the canine patients at My Pets Animal Hospital were determined to be overweight or obese based on the BCS of the 594 dogs, thus showing incidence of this condition at an elevated level compared to the smaller average group and a minimal underweight group (Figure 1). Owner perception of their dogs' weight often did not agree with the BCS assigned by the veterinarian. Of those surveyed, 57.9 % perceived their dogs to be "average" when they were in fact overweight or obese. Of the total 594 dogs assessed for body condition score over a consecutive 2 month period in June and July of 2009, it was found that breed and body condition were linked. The 15 most prevalent breeds (those represented by ten or more individuals over the 2 month period) had significantly different body condition scores (p-value of 0.0004; see Table 8).

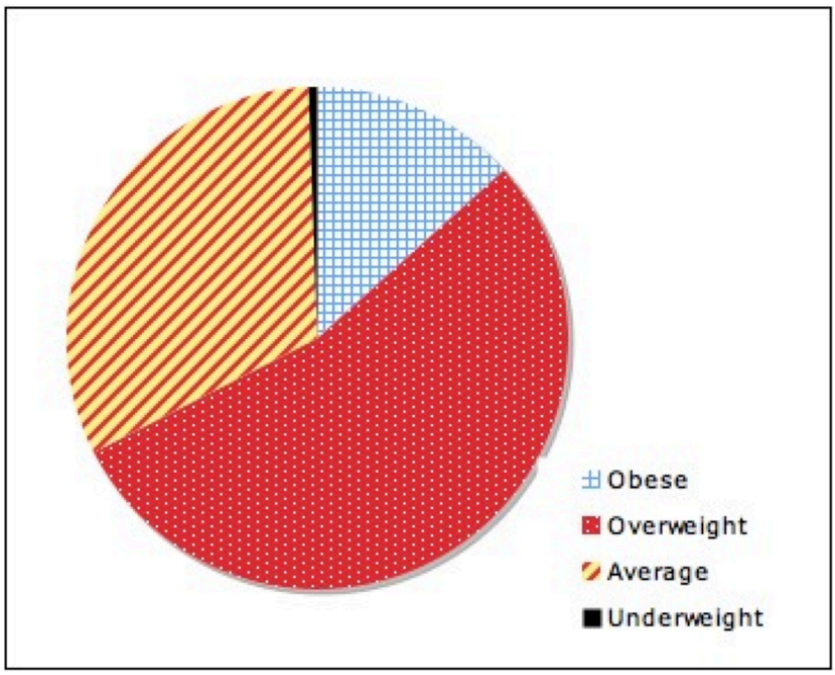


Figure 1. Incidence of obesity in 594 canine patients of My Pets Animal Hospital for the consecutive summer months of June and July 2009.

Table 8. Average BCS for most prevalent breeds brought to My Pets Animal Hospital over 2 month period (only those represented by 10 or more individuals are included)

Breed	Count	Mean BCS	Standard Error
Golden Retriever	20	6.875	0.217
Beagle	25	6.660	0.263
Labrador	53	6.604	0.173
Pit Bull	10	6.600	0.221
Schnauzer	20	6.450	0.223
Terrier Mix	10	6.400	0.427
Jack Russel1	13	6.385	0.266
Shih tzu	36	6.278	0.185
Poodle	13	6.077	0.265
Chihuahua	32	6.063	0.220
Boxer	17	6.059	0.201
Dachshund	18	6.056	0.206
German Shepherd	14	6.000	0.331
Mini Schnauzer	23	5.826	0.174
Boston Terrier	11	5.545	0.247
Yorkshire Terrier	18	5.333	0.198

Four groups were administered different treatments to evaluate their efficacy in weight loss. However, upon conduction ANOVA and Fisher's PLSD statistical analysis for the test subject's initial BCS, it was determined that there was a significant difference at the beginning of the trial period ($p = 0.0119$). There were a variety of breeds and genders represented in each treatment group, and age did not differ significantly ($p > 0.05$). Most patients in the three treatment groups (dirlotapide, calorie-restriction, and high-fiber therapeutic diet) lost weight, but some patients did gain weight. Initial and final weight data were standardized to percent weight lost over a 30 day period, and upon comparing these values, it was found that each of the three treatments promoted effective weight loss, while the control actually gained weight over the course of the study (see Figure 2 below).

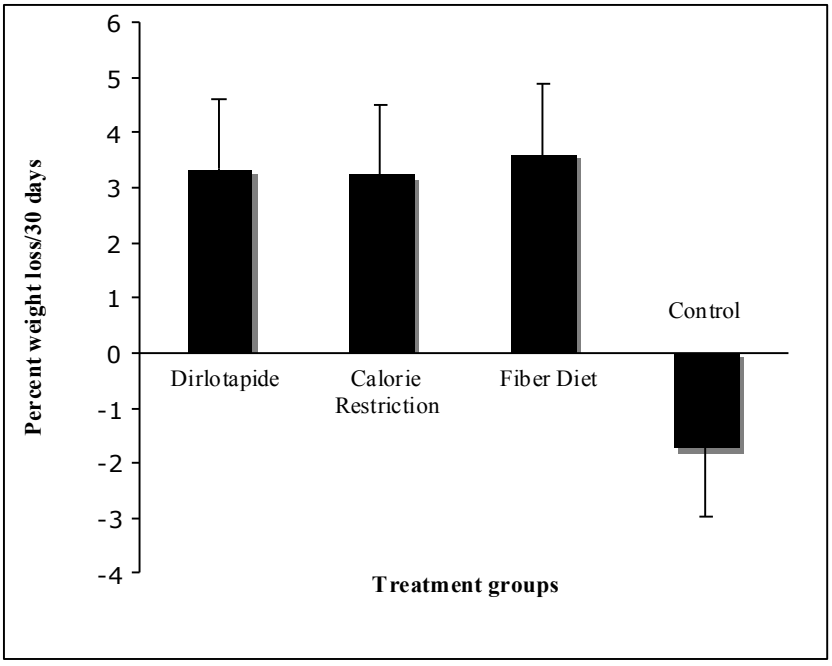


Figure 2. Mean percent weight loss (+ 1 SE) per 30 days for 4 treatment groups.

Pharmaceutical intervention through dirlotapide, restricted-calorie intake and a high-fiber diet did not differ significantly in percent weight loss ($p = 0.969$), but the control group did differ significantly from the three treatment groups ($p = 0.0119$). Each of the treatments was essentially equally effective in promoting weight loss. The mean values of percent weight loss per 30 days were 3.33, 3.22, and 3.59, respectively. Conversely, the control group yielded a percent weight loss of -1.73 per 30 days, showing that the current trend is weight gain in dogs that are left untreated (Figure 2). There were 2 breeds, Beagles and Labrador retrievers that were represented in each of the four treatment groups. For these breeds, the treatment results were compared to see if there was a particular treatment was more effective at enhancing percent weight loss per 30 days. Whereas the same trend was noted in both breeds (Figure 3), the treatment did not show any significant difference in promoting weight loss for beagles ($p = 0.970$) or Labrador retrievers ($p = 0.660$).

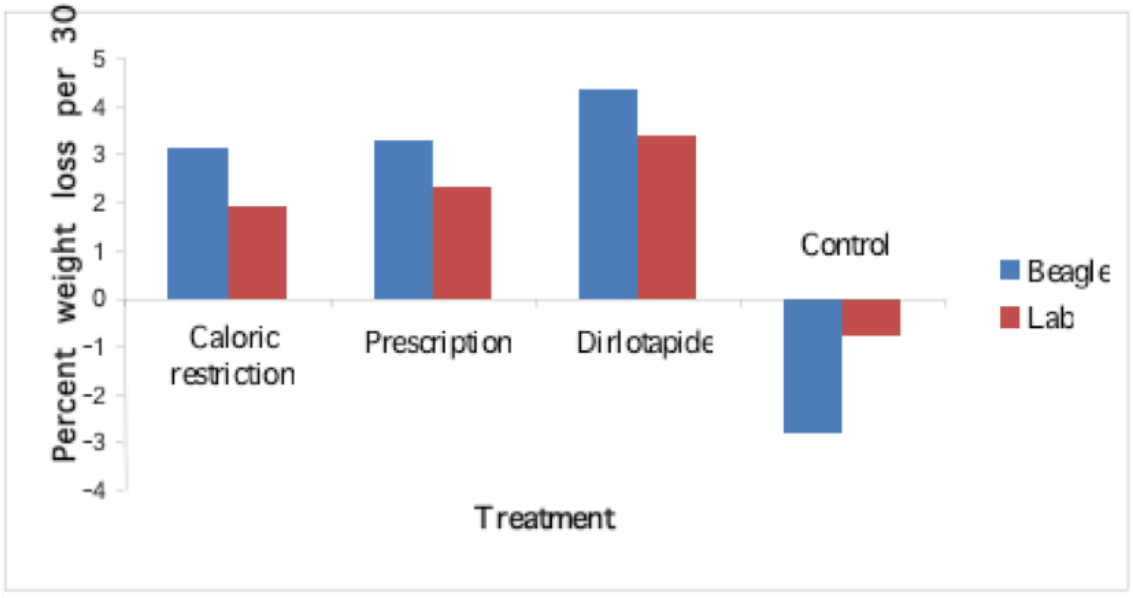


Figure 3. Comparison of treatment efficacy in percent weight loss per 30 days for beagles and Labrador retrievers.

CHAPTER IV

DISCUSSION

The present study has two major findings: (1) that 67 % of dogs treated at an east Tennessee small animal veterinary clinic were overweight or obese (based on a BCS score of 6 or greater) and (2) that both dietary change and pharmaceutical treatment were equally effective at promoting weight reduction in obese canines. This knowledge and the flexibility it provides in treatment options is beneficial, thereby hopefully reducing the prevalence of this unhealthy overweight/obese condition.

Incidence of Obesity

This study confirmed that the majority of canine patients at a small-animal veterinary clinic are overweight or obese, supporting the results of other similar studies conducted in animal hospitals in western society (e.g., Czirjak & Chereji, 2008, Gossellin et al., 2007a, Jeusette et al., 2004). Less than 1 % of dogs were underweight, some were at a healthy average (32 %), but most (67%) were overweight based on body condition scores. Most owners, when asked, declared that their dogs were at an average weight, while the data clearly indicate otherwise. With the trend in increasing weight and subsequent threats to patient health and well being, implementation of a successful treatment plan is vital.

The dog owner plays a central role in carrying out recommended treatments; therefore owner attitude is an integral component to the overall health and body condition of their dogs (Michel et al., 2008). It is important to continue to acquire a better understanding of attitudes regarding nutrition for dogs because attitude inevitably influences subsequent action (Michel et al., 2008). Education of companion animal owners is crucial in promoting a nutritional, balanced diet and healthy lifestyle for their pet. Studies have indicated that although the majority of dogs in the United States and Australia consume commercial pet food for at least half their intake, noncommercial foods, such as table scraps, home-prepared diets, or bones and raw food, are integrated into the main diet of many pets (Michel et al., 2008). Excessive supplementation of noncommercial foods, especially table scraps from meals created for human consumption likely contributes to the trend in weight gain seen in many dogs.

It is also interesting to note that there is a trend linking some breeds to a higher BCS score, suggesting that these breeds may be genetically predisposed to gain weight more readily. In this study, Labrador retrievers, beagles, and golden retrievers were breeds with the highest BCS, an observation that has been previously made (Edney & Smith, 1986). A tendency to readily gain weight may have a genetic basis. Thus, future studies should examine in more detail the relationship between breed and BCS.

Treatment of Obesity

All of the treatment options evaluated in this study, including pharmaceutical therapy with dirlotapide and dietary intervention with a restricted calorie or a high-fiber diet, proved equally effective to treat canine obesity. At the onset of the study, dogs in

different treatment groups had significantly different initial body condition scores (though all were overweight/obese), but this does not necessarily detract from the value of the results generated. The fact that these treatments are each equally effective is useful, as recommendations can be tailored to client's individual preferences or financial constraints and still have valid medical efficacy. The control group of dogs, which were not receiving therapy or dietary adjustments of any kind, actually gained weight over the 2-month period, suggesting that, if left uncontrolled and unattended, the trend in average daily feeding would lead to increased body weight. Restricted-calorie feeding is optimal for owners who may not have the resources to purchase a specially formulated high-fiber diet from their veterinarians, or an expensive medication such as dirlotapide, which varies in cost depending on the size of the dog and the amount dispensed. Because simply restricting calories does not involve a specially formulated diet or expensive medication, but rather decreases the daily amount of food given, this treatment option may be desirable for those clients under financial constraints wishing to save money. It has been consistently shown that restricted feeding not only increases canine lifespan but also delays the onset of clinical signs of chronic disease (Kealy et al., 2002). Other studies have found that greater food restriction appears necessary to successfully induce weight loss in female dogs as opposed to their male counterparts (Roudebush et al., 2008).

However, some dogs may not optimally adjust to ingesting a smaller amount of food, and may persistently frustrate the owner begging for more, initiating complications in the owner-pet relationship (Roudebush et al., 2008). In these cases, the high-fiber prescription diet, such as the Hill's Prescription diet R/D for weight loss used in this study, could be applied in a weight-loss program. The dog can ingest the same amount as

it has formerly received, but the high fiber content results in less of the bulk being absorbed and excess calories stored as adipose tissue, instead increasing fecal matter. High-fiber and protein diets which are lower in fat content have been shown to effectively promote weight loss while maintaining lean tissue mass (Roudebush et al., 2008). The high fiber also promotes a feeling of satiation more rapidly than other diets, and should aid in reducing canine begging behavior.

Some dogs, however, are selective in their food preference, so this adjustment to a different diet may prove more difficult if the pet resists the new formula. In that event, pharmaceutical therapy through dirlotapide is recommended, as the gel suspension is delivered along with their preferred, typical food type, and reduces appetite and fat absorption into systemic circulation, sloughing the enterocytes that contain the fat-mimicking compound (Wren et al., 2007a).

Two breeds, beagles and Labradors, were represented in each of the four treatment groups, and therefore treatment outcomes could be compared to see if there was a particular treatment more effective specific to breed. Though the actual percentages of monthly weight loss differed (most likely due to different initial body condition scores), the same trend was noted for both breeds. The three treatments were equally effective in promoting a healthy percent weight loss over a 30-day period.

This study investigated effective treatments for weight loss, but further inquiry into successful methods for weight maintenance after weight loss would also be beneficial. Other studies have found that dogs whose food intake was restricted during a 26-week weight maintenance period after weight loss were able to maintain their lower weight, whereas dogs fed ad libitum gained weight, suggesting that lifestyle changes are

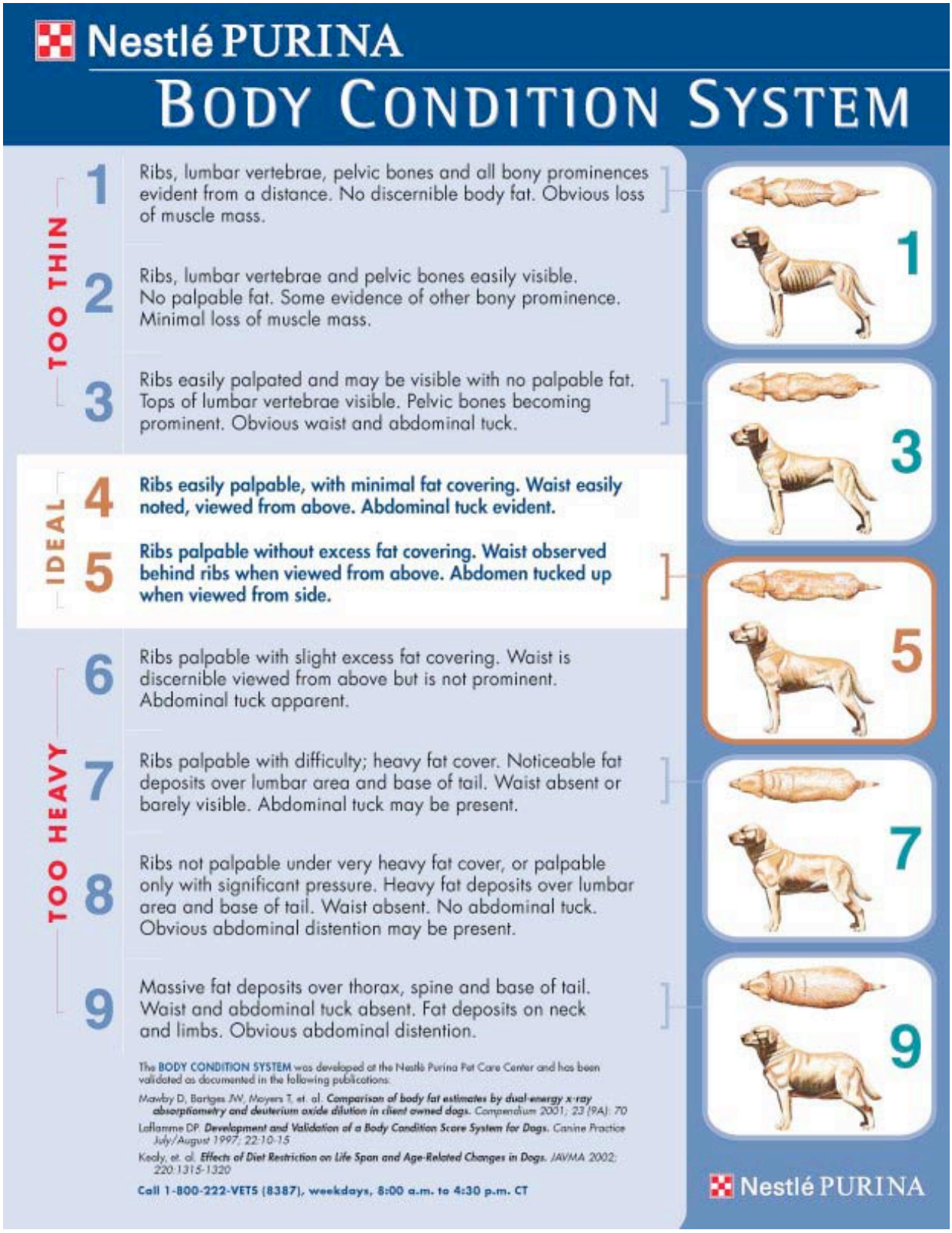
important for canine obesity programs (Yaissle et al., 2004). In addition to permanent calorie restriction, another lifestyle change that was not addressed in this present study is increased output of energy. Exercise has many benefits in facilitating weight loss, and in helping maintain a healthier weight in addition to monitoring ingestion. Further investigation into the nutritional factors and energy expenditure promoting overall canine wellness is recommended.

This study found that dietary changes were effective at achieving weight reduction, supporting previous findings (Yaissle et al., 2004), but pharmaceutical treatment with dirlotapide (including monthly weigh-ins and dosage adjustments) was shown to be equally successful. The key to successful canine weight loss is a consistent plan and subsequent follow-up for all protocols.

Acknowledgements

I would like to thank Dr. Sam Meisler, Dr. Tisha Webb, Dr. Paige Brock, Dr. Becca Archer, and the supporting technicians and staff from My Pet's Animal Hospital in Knoxville, Tennessee, as well as the clients and patients there who participated and made this study possible. I would also like to thank the Maryville College Biology Department, and especially Dr. Andrew Crain, for all of the support and instruction that enabled me to complete this study.

Appendix A. Canine Body Condition Scoring (BCS) on a 9 point scale (Laflamme 1997)



Appendix B. Research survey on owner feeding practice of their dogs.

Maryville College Department of Natural Sciences Senior Study
Human Participant Consent Form

This research in survey form will investigate the relationship between canine weight and daily feeding practices. Owners will fill out the brief survey below regarding their practice of feeding their dogs. Patient contact information will not be published as part of the study, only statistical data. One expected benefit of this research is a greater knowledge of the factors that contribute to canine obesity. Each dog will receive an assessment of body condition upon consent of the owner and calculation of resting metabolic requirements (amount of food they should ideally intake daily for their size, breed, etc.) There are no costs of participation. We are interested only in aggregate data. No report of the project will contain data that can be identified with any individual participant. For questions about the research, contact the principal investigator: Anna McRee
719-7113 (865)
annamcree@gmail.com

Taking part in this study is completely voluntary. If you do not take part, you will receive no penalty. If you have any questions call or write: **Dr. Andrew Crain**
Department of Natural Sciences
Maryville College
502 E. Lamar Alexander Pkwy.
Maryville, TN 37804
855-981-8268

I have read and understood the information above. I consent to take part in this study by volunteering information about my pet. The researchers have answered my questions to my satisfaction. I understand a copy of this form is available upon request.

_____ _____
Participant's Signature Date

_____ _____
Investigator's Signature Date

Survey- Owner fill out:

Current diet (specific brand & type of food):_____.

Amount (given daily- circle one):
½c.(4 oz) 1 c(8 oz) 1½ c. (12 oz) 2 c.(16 oz) 2½ c.(20 oz) 3 c.(24 oz) 3½ c.(28oz)
4 c.(32 oz) 4½ c.(36 oz) 5 c.(40 oz) 5½ c.(44 oz) 6 c.(48 oz) 6½ c.(52 oz) 7 c.

Supplements (treats, table scraps, etc. and how often given):_____

Daily Exercise: Y/ N if yes, activity and duration:_____.

Multipet household: Y/ N
Indoor/Outdoor: _____
Do you think your pet is overweight/average/underweight?_____.
Optional- Phone number (for follow up): ( ) -

Patient Information:

Name: _____Breed:_____Age:____Sex: F /FS /M /MN
Current Weight:
Slentrol (Dirlotapide)?
BCS (body condition score assigned by DVM):_____.
RER (resting energy requirement from formula):_____. kcal in 8 oz of food:
Current daily intake (calc. from info provided above):_____.

Assessment: Overfeeding?? Y /N
Additional notes:_____
_____
_____
_____
_____
_____
_____

Appendix C. Specifications of dirlotapide released by Pfizer, the manufacturer.

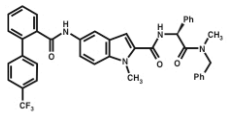
SLENTROL™
(dirlotapide)

Oral solution for use in dogs only.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: SLENTROL (dirlotapide) is a solution formulated at a concentration of 5 mg/mL of dirlotapide for oral administration to dogs. Dirlotapide is a selective microsomal triglyceride transfer protein inhibitor that blocks the assembly and release of lipoprotein particles into the bloodstream (via the lymphatic system) in dogs.[1] The empirical formula is $C_{40}H_{33}F_3N_4O_3$ and the molecular weight is 674.73. The chemical name is (*S*)-*N*-[2-[Benzyl(methyl)amino]-2-oxo-1-phenylethyl)-1-methyl-5-[4'-(trifluoromethyl)[1,1'-biphenyl]-2-carboxamido]-1*H*-indole-2-carboxamide.

The chemical structure of dirlotapide is:



INDICATIONS: SLENTROL (dirlotapide) Oral Solution is indicated for the management of obesity in dogs.

DOSAGE AND ADMINISTRATION: SLENTROL should be prescribed as part of an overall weight management program that incorporates a complete and balanced canine diet and physical activity. The dog will need to be weighed at the start of treatment and then at monthly intervals so that the dosing regimen can be adjusted according to the prescribing instructions below.

During the first month of therapy, the dosing regimen for SLENTROL consists of two fixed dose rates (number of mL administered per unit of body weight) in all dogs. In subsequent months of therapy, the recommended dosing regimen prescribed for SLENTROL varies for each individual dog and the dose volume must be specifically calculated each month, based on the amount of weight lost (expressed as a percent) during the previous month of therapy.

With regard to dosing it is important to note that:

- Initial body weight is used to calculate the dose that is first administered.
- Subsequent dose adjustments are made by adjusting the volume of solution administered.
- Dose adjustments are determined at monthly intervals.

The dose should not exceed a maximum daily dose of 0.2 mL/kg (0.09 mL/lb), based on the dog's current body weight, during any part of treatment.

Dose Preparation and Administration: To prepare for oral administration, remove the bottle cap and insert the supplied oral dosing syringe through the membrane into the bottle. Invert the bottle and withdraw the appropriate volume required using the graduation marks on the side of the oral dosing syringe.

SLENTROL can be administered directly into the dog's mouth or on a small amount of food. It can be given with a meal or at a different time of day.

Wipe the oral dosing syringe clean after each use with a clean dry cloth or disposable towel. Do not introduce water into the oral dosing syringe or the SLENTROL solution.

WEIGHT LOSS PHASE

Initial assessment and dosing in first month

Assess the dog prior to initiation of therapy with SLENTROL to determine the desired weight and to assess the animal's general health (See Precautions).

The initial dosage of SLENTROL is 0.01 mL/kg (0.0045 mL/lb) body weight, administered once daily, orally, for the first 14 days. After the first 14 days of treatment, the dose volume of SLENTROL should be doubled to 0.02 mL/kg (0.009 mL/lb) of body weight, administered once daily for the next 14 days (days 15 to 28 of treatment).

Subsequent Monthly Dose Adjustments for Weight Loss

Dogs should be weighed monthly and the dose volume adjusted every month, as necessary, to maintain a target percent weight loss of ≥ 0.7% per week.

If the dog has gained weight since the last visit, the dose volume should be increased. Go directly to the First (or Subsequent) Dose Adjustment Section below.

If the dog has lost weight, determine if an adjustment in dose is required using the following calculations:

(Number of weeks between visits)
X 0.7 % per week
= Target % weight loss

$$\left(\frac{\text{Weight at last visit} - \text{Weight at current visit}}{\text{Weight at last visit}}\right) \times 100 = \text{Actual \% loss}$$

Example – in 4 weeks (28 days) the Target weight loss would be 4 X 0.7% per week, or at least 2.8% of the total body weight

Compare the Target % weight loss (of ≥ 0.7% per week) with the Actual % weight loss for that dog.

To determine if a dose adjustment is necessary, compare the Actual % weight loss to the Target % weight loss and use the following guidelines. **Note: All dose adjustments are based solely on volume (mL).**

Monthly weight loss rate achieved

- If the Actual % weight loss is the same or greater than the Target % weight loss, the dose volume (number of mL administered each day) should remain the same for the next month of dosing until the next scheduled assessment.

Monthly weight loss not achieved

- If the Actual % weekly weight loss is less than the Target % weight loss of 0.7% weekly, the following dose adjustment instructions apply:
  - **First dose adjustment**
    - The dose volume (number of mL administered each day) should be increased by 100%, resulting in an increase of the dose volume to 2.0 times the dose administered during the previous month of dosing. Only perform a 100% dose increase once during treatment after day 14.
  - **Subsequent dose adjustments**
    - If additional dose increases are necessary in the following months, the dose volume (number of mL administered each day) should be increased by 50%, resulting in an increase of the dose volume to 1.5 times the dose administered the previous month of dosing. Based on the dog's current body weight a daily dose of 0.2 mL/kg (0.09 mL/lb) should not be exceeded.

If a dog's food consumption is greatly reduced for several consecutive days, the dose may be withdrawn until the appetite returns (usually 1-2 days) and then resume dosing at the same volume.

The monthly adjustments should continue in this way until the desired weight determined at the start of therapy is reached. When the desired weight is reached, begin the weight management phase.

WEIGHT MANAGEMENT PHASE

A 3-month weight management phase is recommended to successfully maintain the weight loss achieved with treatment. During the weight management phase, the veterinarian and the pet owner should establish the optimal level of food intake and physical activity needed. SLENTROL administration should be continued during the weight management phase until the dog owner can establish the food intake and physical activity needed to stabilize body weight at the dog's desired weight.

To dose for weight management, body weight should continue to be assessed at monthly intervals.

- **First dose adjustment**
  - If the dog lost ≥ 1% body weight per week in the last month of the weight loss phase, the dose volume (number of mL administered each day) should be decreased by 50% resulting in a decrease of the dose volume to 0.5 times the dose administered the previous month.
  - If the dog lost between 0 and 1% the dose should remain the same.
  - If the dog gained weight, the dose should be increased by 50% resulting in an increase of the dose volume to 1.5 times the dose administered the previous month.
- **Subsequent dose adjustments**

  In subsequent months the dose volume should be increased or decreased by 25% to maintain a constant weight.
  - If the dog is within -5% to +5% of the body weight at the end of the weight loss phase, the dose volume (number of mL administered each day) should remain unchanged.
  - If the dog lost >5% body weight, then the dose should be decreased by 25%.
  - If the dog gained >5% body weight, then the dose should be increased by 25%. Based on the dog's current body weight a daily dose of 0.2 mL/kg (0.09 mL/lb) should not be exceeded.

When SLENTROL is discontinued, the daily amount of food offered and physical activity should be continued as established during the weight management phase. Reverting to previous food intake or physical activity levels at this point can contribute to a re-gain of some or all of the weight loss that has been achieved.

The safety of SLENTROL use in dogs has not been evaluated beyond 1 year.

INFORMATION FOR OWNER OR PERSON TREATING ANIMAL: Successful implementation of any weight loss program for dogs requires active, on-going communication between the dog owner/caretaker and the veterinary professional treating the pet. It is important that the prescribing veterinarian maintains an active veterinarian-client-patient relationship with the dog and the dog owner/caretaker during all phases of therapy and proactively communicates about their role in making the program successful in the short as well as the long-term. When drug therapy such as SLENTROL is included in the program, this discussion may include, but may not be limited to:

- SLENTROL is not a cure for obesity. The decreased appetite experienced when dogs are treated with dirlotapide is only temporary and lasts no longer than 1-2 days beyond the cessation of therapy. Weight gain will occur if the amount of food offered is not limited at the time SLENTROL is discontinued.
- Successful, long-term weight management requires changes that extend beyond the period of drug therapy. To maintain the weight lost when treated with SLENTROL, the adjustments in dietary management as well as physical activity that were begun as part of the overall weight loss program must be continued by the owner after drug therapy is discontinued.
- SLENTROL decreases the food intake of the dog. A decrease in appetite and associated begging behavior can be expected with SLENTROL treatment. However, if total inappetence or anorexia is observed for more than one day, these signs should be reported to the prescribing veterinarian.
- Almost 1 in 4 of dogs placed on SLENTROL therapy experienced occasional episodes of vomiting and diarrhea. In most cases these episodes lasted for one or two days. The vomiting occurred most often during the first month of treatment or within a week of a dose increase. If vomiting does occur it is recommended to continue dosing at the same dose volume, however, the time of day or method of administration (with or without food) may be changed. If vomiting is severe or lasts longer than 2 days, consult your veterinarian and have your dog evaluated.

CONTRAINDICATIONS: SLENTROL should not be used in cats. SLENTROL increases the risk of producing hepatic lipidosis during weight loss in obese cats. SLENTROL is not recommended for use in dogs currently receiving long-term corticosteroid therapy. Do not use in dogs with liver disease.

WARNINGS: Not for use in humans. Keep this and all drugs out of reach of children.

Adverse reactions associated with humans ingesting dirlotapide include: abdominal distention, abdominal pain, diarrhea, flatulence, headache, increased serum transaminases, nausea, and vomiting.

SLENTROL may cause eye-irritation. If accidental eye exposure occurs, flush the eyes immediately with clean water.

PRECAUTIONS: Safety in breeding, pregnant, or lactating dogs has not been established. Caution should be taken when considering any weight loss program in growing dogs, including treatment with SLENTROL. SLENTROL has not been evaluated in dogs less than 1 year of age.

All dogs should undergo a thorough history and physical examination that includes laboratory tests to screen for underlying conditions. Pre-existing endocrine disease, including hyperadrenalcorticalism (Cushing's disease), should be managed prior to use of SLENTROL.

SLENTROL may produce a mild to moderate elevation in serum hepatic transaminase activity. If the elevation in alanine aminotransferase (ALT) activity is mild, continue SLENTROL and monitor as needed. If there is a marked elevation in ALT activity above the normal reference range or there is a simultaneous increase in aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), or total bilirubin, discontinue treatment with SLENTROL. Elevations in hepatic transaminase activity usually decrease when SLENTROL is discontinued.

The safety of SLENTROL use in dogs has not been evaluated beyond 1 year.

ADVERSE REACTIONS:

The adverse reactions associated with treatment with SLENTROL include vomiting, loose stools/diarrhea, lethargy, and anorexia. These adverse reactions were mainly observed during the first month of treatment or during the week after a dose increase. Vomiting was usually mild in severity, of short duration, and resolved with continued SLENTROL treatment. The SLENTROL-treated dogs generally had an increased frequency and duration of vomiting and diarrhea compared to the control dogs. The control dogs received corn oil.

Adverse Reactions During Weight Loss:

Treatment	Percentage of Patients with Reported Signs	
	Control n = 88	SLENTROL n = 170
Vomiting	21.6%	24.7%
Diarrhea	6.8%	12.4%
Lethargy	3.4%	9.4%
Anorexia	2.3%	7.6%
Constipation	1.1%	2.4%
Dehydration	0%	1.2%

In addition to the adverse reactions listed above, there were other abnormal findings. Many control and SLENTROL-treated dogs had dental disease, abnormal skin and ear findings, and lameness/arthritis. The incidence of these findings were similar in both control and SLENTROL treated groups and most dogs had similar lesions noted pre-treatment. Two dogs in the SLENTROL treatment group developed corneal ulcers. One SLENTROL-treated and one control dog developed signs consistent with pancreatitis. One treated dog developed inappropriate urination and defecation and another treated dog developed polyuria and polydipsia.

A 5 year old Beagle with no medical history of seizures in the SLENTROL treatment group had a seizure on Day 52 of the study. The dog continued to receive SLENTROL until additional seizures occurred 11 and

12 days later. The investigator referred the case to a neurologist and the seizures continued approximately twice weekly. The neurologist found no lesions that support the causality of the seizures.

A 5 year old Dachshund developed a hepatopathy after 82 days of treatment and was withdrawn from the study for vomiting, increased hepatic enzymes, and anorexia. Vomiting continued for a few days after stopping treatment and the dog was hospitalized due to the anorexia. ALT activity levels continued to rise after all clinical observations resolved.

During weight stabilization, vomiting (16.1%) and lethargy (4.8%) were the most frequent adverse reactions associated with treatment with SLENTROL. Other adverse reactions included diarrhea (1.6%), anorexia (1.6%), and ataxia (1.6%).

In the post-treatment period, a 6 year old spayed female Chihuahua, was found dead by the owner 7 days after stopping dirlotapide therapy. The cause of death was not conclusive but did not appear to be related to the dirlotapide therapy.

Some dogs treated with SLENTROL displayed a mild to moderate elevation in serum hepatic transaminase activity early in treatment that decreased over time while treatment continued. Hepatic transaminases generally returned to normal when treatment was discontinued (See Precautions for further information).

Serum Chemistry Results:

	Percentage of Dogs			
	Control n = 88		SLENTROL n = 170	
Serum Analyte	Pre[d]	Post[e]	Pre[d]	Post[e]
ALT[a] > 60 IU/L	3.4%	6.0%	4.7%	9.9%
AST[b] > 120 IU/L	0%	4.8%	3.5%	9.2%
ALP[c] > 125 IU/L	11.4%	16.9%	17.6%	9.9%
Cholesterol > 320 mg/dL	14.8%	9.6%	14.7%	4.6%

[a] ALT = serum alanine aminotransferase activity,
[b] AST = serum aspartate aminotransferase activity,
[c] ALP = serum alkaline phosphatase activity. Dogs with ALP activity >325 IU/L were excluded from the study.
[d] Pre = % of dogs with values above the laboratory reference range at pre-treatment.
[e] Post = % of dogs with values above the laboratory reference range after 4 months of treatment.

To report a suspected adverse reaction call Pfizer Animal Health at 1-800-366-5288.

For a copy of the Material Safety Data Sheet (MSDS) for SLENTROL oral solution call 1-800-733-5500.

CLINICAL PHARMACOLOGY:

SLENTROL (dirlotapide) is a selective microsomal triglyceride transfer protein inhibitor that blocks the assembly and release of lipoproteins into the bloodstream. The mechanism of action for producing weight loss is not completely understood, but it seems to result from reduced fat absorption and a satiety signal from lipid-filled enterocytes.

SLENTROL mainly acts locally in the gut to reduce appetite, increase fecal fat and produce weight loss in the management of obesity in dogs. Dirlotapide is available systemically, but absorption in dogs is highly variable. Absorbed SLENTROL is metabolized in the liver. Dirlotapide and its metabolites are secreted in the bile and may undergo enterohepatic circulation. The fecal and biliary routes are the predominant routes of elimination. Dirlotapide in circulation is highly protein bound.

Although systemic blood levels do not directly correlate with effectiveness (effectiveness has been linked to drug concentrations in the gut), they seem to correlate with the systemic toxicity observed for this drug. Non-linear pharmacokinetics with less-than-proportional exposure, drug accumulation (at higher doses), and large inter-individual variability has been observed in multiple studies and at various dose levels. The mean elimination half-life ranged between 5 and 18 hours, and it seemed to increase with dose and with repeated dosing.

EFFECTIVENESS:

The effectiveness of SLENTROL for the management of obesity was confirmed in two controlled, multi-site field studies using client-owned dogs. The control dogs received corn oil. More than 65 different pure breeds and mixed breed dogs were represented in the 276 dogs receiving SLENTROL during the clinical field studies. SLENTROL was evaluated in dogs receiving 135 other commonly used veterinary products such as vaccines, anthelmintics, antiparasitics, antimicrobials, collars, shampoos, dips, short-acting oral steroid preparations, and otic, ophthalmic, and topical steroid preparations. SLENTROL was not tested concomitantly with long-acting steroid products, anabolic steroids, or other products known to affect appetite.

In one field study evaluated for weight loss only, SLENTROL was effective in producing ≥0.7% weekly (≥0.1% daily) weight loss at an initial dosage 0.023 mg/lb (0.05 mg/kg), doubled at 14 days, and then adjusted monthly for 4 months. Two hundred and fifty eight (88 control and 170 SLENTROL) obese dogs, from 23 veterinary clinics, 21 in the US and 2 in Canada, with a body condition score (BCS) ≥8 on a 9-point scale[2], participated in the study. SLENTROL-treated dogs lost a statistically significant ($P \leq 0.0001$) 11.8% body weight and 39% lost ≥13% body weight, an amount that has been shown to provide a health benefit in obese dogs[3]. At the end of treatment the final mean dosage was 0.12 mg/lb with a range of 0.05 mg/lb to 0.24 mg/lb (0.26 mg/kg, range 0.11 to 0.56 mg/kg) based on current body weight.

In a separate study, conducted at 14 different US veterinary clinics, 63 dogs that completed 4 months of SLENTROL treatment for weight loss were evaluated for weight management during a 3 month retraining phase. The weight management period was designed to educate the owner on the optimal amount of food necessary and exercise required to maintain the dog's desired body weight. SLENTROL dosage was adjusted monthly (50% first adjustment and 25% subsequently) to maintain the desired body weight ± 5%.

Daily oral treatment with SLENTROL was safe and effectively stabilized body weight ± 5%, when adjusted monthly by 50% the first month and then by 25% monthly, as needed based on individual body weight changes. Vomiting and lethargy still occurred during the weight management phase.

At the completion of the weight management phase, SLENTROL was discontinued and body weight measured for an additional 2 months. Dogs regained approximately 3% of their body weight in 2 months, primarily during the first month after treatment was discontinued (n = 51).

Polyphagia was reported as an abnormal clinical finding in 8 of 106 dogs when SLENTROL was discontinued.

ANIMAL SAFETY:

Margin of Safety: In a controlled laboratory margin of safety study in neutered, obese Beagle dogs, SLENTROL (dirlotapide) was administered orally at 0, 0.5, 1.5 and 2.5 mg/kg once daily for 90 days. The control used was medium chain triglyceride oil.

Clinical Observations: Vomiting and loose stools were the most frequent clinical signs observed. Vomiting was dose-related and was observed in all treatment groups. Vomiting tended to occur within 3 hours of dosing and was more frequent during the first two to four weeks of treatment. Sporadic episodes of loose stools occurred throughout the 3-month dosing period in all dose groups. SLENTROL administration also resulted in a decrease in body weight, body condition score, and food intake in the treated dogs.

Clinical Chemistry: Dogs treated with SLENTROL revealed a dose-related decrease in serum cholesterol and high-density lipoprotein (HDL) concentration. Mean ALT activity and AST activity were increased at doses of 1.5 and 2.5 mg/kg/day. At 1 month, mean values of the mid and high dose-groups (versus control values) were ~2- to 4-fold and ~10- to 12-fold higher than controls for AST and ALT activity, respectively. The increases in ALT activity diminished during 3 months of continued treatment and were generally within normal limits for the 1.5 mg/kg/day group and ~5- to 6-fold higher than control values in the 2.5 mg/kg/day groups. The alkaline phosphatase levels mildly decreased in the treated dogs. Decreases in plasma concentrations of vitamins A and E were observed early in treatment for all SLENTROL-treated groups. Other effects included decreased blood urea nitrogen, total proteins, albumin, globulin, and calcium. All treatment-related clinical chemistry changes had reverted to normal at the end of the 1-month recovery phase.

Pathology: On gross necropsy, the mucosal surface of the small intestine appeared pale (presumably unabsorbed fat) primarily in the high dose groups. Enterocytes in the villus tips of the small intestine contained lipid vacuoles.

Individual Responses: In the high dose (2.5 mg/kg) group, two of six dogs (one male and one female) had AST elevations >100 U/L in combination with ALT elevations >500 U/L and a mild increase in bile acids. In the female, there were also mild increases in gamma-glutamyltransferase activity (GGT) and alkaline phosphatase (ALP) activity in the first month of treatment. These elevations decreased over time with continued treatment.

Acute Tolerance: In a separate 14-day acute tolerance study the safety of SLENTROL (dirlotapide) was evaluated following daily oral administration of 0, 2.5, 5.0 and 10 mg/kg body weight in normal weight Beagle dogs. The control used was medium chain triglyceride oil.

Clinical Observations: Vomiting was observed in all groups. Vomiting generally occurred within 4 hours of dosing and had the highest incidence during the first three days of treatment. The incidence of loose stools was lower than the incidence of vomiting, occurred intermittently throughout the study, and was also similar between the treated and control groups. SLENTROL administration produced reductions in food intake, organ weights, and body weight.

Clinical Chemistry & Histopathology: Changes in serum chemistry included a significant dose-related decrease in mean serum cholesterol and high-density lipoprotein, a non-dose-dependent mild to moderate elevation in serum hepatic transaminase enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, and mean decreases in serum total protein and albumin. Histopathology revealed accumulation of lipid vacuoles in the apical third of enterocytes in the small intestine in all treated dogs and minimal to mild periportal fatty change in the liver in five treated dogs.

Individual Responses: After 14 days of treatment, one high-dose female had an elevation in both ALT activity (257 U/L (~9-fold pre-treatment value) and AST activity (99 U/L (~4-fold pre-treatment value) and one mid-dose female had mild increases in ALT activity (102 U/L (~3-fold pre-treatment value), AST activity (71 U/L (~2-fold pre-treatment value) in combination with a moderate increase in bile acids (57.0 uM/L (~5-fold pre-treatment value). In the remaining dogs elevated hepatic transaminase enzymes were not accompanied by increases in other liver function indicators such as ALP, GGT, or total bilirubin.

1-Year use-dose study: In a separate long-term laboratory study, the efficacy and safety of SLENTROL (dirlotapide) was evaluated following daily oral administration of an initial dosage of 0.009 mL/lb medium chain triglyceride oil (control) or 0.1 mg/kg (dirlotapide) for 12 months in seventy-two obese Labrador Retrievers. The dosage was adjusted monthly to produce ≥1% weekly body weight loss for 6 months and then adjusted to maintain body weight constant (retraining or weight stabilization phase) for the next 6 months, up to a maximum dosage of 0.2 mL/kg (1 mg/kg) current body weight.

Clinical Observations: Diarrhea, vomiting, and excessive salivation were observed more frequently in SLENTROL-treated dogs than in control-treated dogs. Diarrhea was mild and observed intermittently throughout the study. Most episodes were of short duration and most dogs had only one or two episodes of diarrhea during the 12 months of treatment. Vomiting was also mild and the majority was observed during the first month of treatment. Excessive salivation was noted in approximately 4 of 48 SLENTROL-treated dogs, primarily during the first 28 days of treatment. Some treated dogs had ocular lesions at the end of the study including retinal degeneration and cataracts. Based on the available safety data, these lesions were considered incidental to the Labrador breed.

Clinical Chemistry: Serum cholesterol concentrations were significantly decreased during the first 6 months of treatment at the weight loss dosage and were at the low normal or below the laboratory reference range (135 to 270 mg/dL). Mean serum triglyceride concentration was not changed. A mild increase in mean ALT and AST activity was observed, which remained well within the published reference range for these analytes (ALT: 2 to 102 U/L, AST: 23 to 66 U/L). ALT activity tended to gradually increase as the SLENTROL dose increased during the first 6 months of weight loss and then decreased during the next 6 months despite continued SLENTROL treatment at the weight stabilization dosage. Other clinical pathology changes included low total proteins, low serum albumin and globulins, low blood urea nitrogen and low serum creatinine compared to control dogs. Mean and individual values were usually within the published normal range. Gamma glutamyl transferase, and total bilirubin were not changed during 12 months of SLENTROL treatment. Other abnormal clinical pathology values included sporadic findings that were similar in the control dogs, were not progressive with continued treatment, and returned to normal concentrations during a one-month post treatment period.

Individual Responses: A total of 10 of 48 dogs had sporadic mild to moderate ALT measurements that exceeded the upper limit of the reference range at some point during 12 months (maximum of 366 U/L) of SLENTROL treatment. The ALT elevations were not sustained despite continued treatment during the 6 months of weight stabilization. AST activity was marginally elevated in 1 of 48 dogs (maximum 84 U/L in a SLENTROL-treated dog and 116 U/L in a control dog) during 12 months of treatment. One dog, excluded from the totals, had a consistently elevated ALT and also had an elevated alkaline phosphatase prior to treatment. Except in this dog, no other changes in other liver function indicators accompanied these mild elevations in hepatic transaminases.

Fat Soluble Vitamins: During the first 6 months of treatment, plasma vitamin A and E concentrations of the SLENTROL-treated dogs were significantly below the vitamin A and E concentrations of the control dogs. Plasma vitamin A concentration was low after one month and the median values did not decline any further. Plasma vitamin E concentrations were lowest after 6 months of SLENTROL treatment but adipose tissue levels of vitamin E appeared to be increased compared to control dogs after 12 months of treatment. Plasma vitamin A and E concentrations appeared to increase during the weight stabilization phase (second 6 months of treatment) and returned to concentrations similar to the control dogs when SLENTROL treatment was discontinued. Prothrombin times were similar in the SLENTROL-treated and the control dogs and there were no clinical signs of abnormal hemostasis observed during the 12-month study.

STORAGE INFORMATION:

Store in original container at room temperature 15° to 30° C (59° to 86° F).

HOW SUPPLIED:

SLENTROL is available in 20, 50 and 150 mL bottles containing 5 mg/mL of dirlotapide in solution.

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U.S. Patent No. 6,720,351

NADA #141-260, Approved by FDA

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820 600 000
October 2006

Appendix D. Human Participants Research Proposal Form

MARYVILLE COLLEGE

Human Participants Research Proposal Form

Principal researcher(s): Anna E McRee

Faculty sponsor: Dr. Andrew Crain

Division: Natural Sciences

Mailing address of the principal researcher: Box 2701

Title of proposed research: Incidence of canine obesity and comparison of the effect of caloric restriction and dirlotapide treatment on disease management in an east Tennessee small animal veterinary practice

Proposed starting date: May 2009

Ending date: August 2009

Purpose and objectives of proposed research:

The purpose of this study is to examine the efficacy of two readily available treatments for the management of the growing canine obesity disease: pharmaceutical therapy with dirlotapide or dietary intervention through caloric restriction. This study will identify factors associated with canine obesity in one particular East Tennessee small animal veterinary practice, and compare the outcome of treatment protocols, to see if reduced food intake alone is enough to treat obesity, or if medicating obese patients with dirlotapide promotes significant weight loss. The reality of owner compliance shall also be assessed to see if follow up increases likelihood of successful diet management and return visits.

Participants:

I will have a total of around 200 dogs initially assessed when they come into the vet clinic for an annual wellness exam, and the survey will be offered to their owners at that time. The number of dirlotapide treatment cases may be limited to fewer than 10 logistically, and so other data may be requested from other local veterinary clinics.

Methods and procedures:

First, to visualize the average nutritional state of companion dogs in the Knoxville area, a brief survey will be conducted with those animals that come in for an annual wellness exam, to gather data from the owner on how much they are fed per day, along with the specific type and brand of food, and other variables that may potentially play a role in weight gain, such as inactivity, neutering, and membership in multiple pet households. Owner attitude will also be examined in regards to their pet's body condition, when they are asked their opinion on their pet's current state, and this will be compared to the body condition score (BCS) assigned by the veterinarian. Their current weight will be factored into an equation provided by *Hill's Science Diet Key to Clinical Nutrition* to calculate the individual's resting energy requirement (RER) and maintenance daily energy requirement (DER, see Table 5), which details the specific daily caloric intake the animal should theoretically be receiving. This shall be compared to the energy amount they are actually receiving (calculated from the amount of food and kilocalories/oz contained by the specific type they are fed according to the owner survey).

Table 5. Energy requirement calculations.

Name	Equation
Resting energy requirement (RER) (kcal/day)	$70 \times wt_{kg}^{0.75}$
Maintenance Daily energy requirement (DER) Average neutered adult	1.6 x RER
Intact adult	1.8 x RER
Obese-prone	1.4 x RER
Weight loss	1.0 x RER

It shall then be determined if the animal needs to enlist a restricted-calorie feeding regimen, if they have an overweight or obese BCS. With owner compliance, it shall be interesting to track if caloric restriction alone is enough to result in significant weight reduction over a 90 day period, compared to case studies on individuals who are currently on dirlotapide treatment. Those on dirlotapide come in for monthly weigh-ins and dosage adjustments, and data on these case studies shall be incorporated in assessment.

Principal Researcher _____ Signature **Faculty Supervisor** _____ Signature

Committee Approval _____ **Date**_____
Signature

Appendix E. Institutional Animal Care & Use Committee (IACUC)

Student Animal Research Form

MARYVILLE COLLEGE
Institutional Animal Care & Use Committee (IACUC)
Student Animal Research Form

Student Name: Anna McRee

Student Email Address: annamcree@gmail.com

Date: 4.09.09

Senior Study Advisor: Dr. Andrew Crain

Species to be used: *Canis lupus familiaris*

Age of animals: 6 wks-15 yrs

Number of animals in study: ~200

Duration of study: 3 months

Location of animals during the study (building and room): My Pets Animal Hospital
3075 Lois Lane
Alcoa, TN 37701

List personnel to call if problems with animals develop:

Name	Daytime Phone	Nighttime Phone	Emergency No.
Sam Meisler, DVM at My Pets Animal Hospital (MPAH)	(865) 984-5620	693-4440	(865) 719-7113
Paige Brock, DVM at MPAH	(865) 984-5620	693-4440	(865) 719-7113
Becca Archer, DVM at MPAH	(865) 984-5620	693-4440	(865) 719-7113

Husbandry Requirements: Is anything other than routine care and equipment required?
YES___ No _*_ If "YES", please list below.

What will happen to the animals at the end of the study? If euthanasia is required, state the methods. They are in private homes during and after the study.

(Do not write below line: For MC IACUC Use)

Maryville College IACUC Approval Number: _____
Date Approved: _____
Signed:

_____

Is it likely that pain/discomfort will be experienced by animals in this protocol?
YES___ NO_*__If "YES", describe:

Pain or Distress Category: B (See listing of Pain or Distress Categories below)

For categories C, D, or E, USDA regulations require that the investigator consider alternative procedures. Please provide a narrative (for instance the end of Chapter 1) describing the methods and sources used to determine that alternatives are not available. If a computer assisted literature search was conducted, provide the names of the database(s) and date(s) of the search.

Pain or Distress Categories

A. ACUTE STUDIES
Studies performed under anesthesia from which the animals are not permitted to regain consciousness, or performed on excised animal tissues collected under anesthesia or following euthanasia.

B. PAIN OR DISTRESS - NONE OR MINOR
Chronic studies that DO NOT involve survival surgery, induction of painful or stressful disease conditions, or pain or distress in excess of that associated with routine injections or blood collection. Included are induction or transplantation of tumors in animals (so long as the tumors do not cause pain and the animals are terminated prior to becoming seriously ill), administration of mildly toxic substances or drugs that cause no significant disease or distress, and antibody production as long as significant disease does not result and antigen booster doses do not include Complete Freund's Adjuvant (CFA).

C. PAINFUL PROCEDURES WITH ANESTHESIA/ANALGESIA
a. Survival surgical procedures.
b. Painful or potentially painful non-surgical procedures; e.g. bone marrow taps, injections into particularly sensitive areas such as foot pads, cardiac punctures, or traumatic procedures such as burns (burns may be category D, depending on severity).

D. MODERATE DISTRESS OR PAIN GENERALLY WITHOUT ANESTHESIA/ ANALGESIA/ TRANQUILIZERS
Induction of moderately distressful or painful disease conditions (examples: arthritis, administration of toxic chemicals, infectious challenges, immunosuppression resulting in infectious disease, peritonitis, severe inflammation, especially of weight bearing surfaces or resulting in external sores), whole body irradiation, stress models, septic shock, hypotensive shock, moderate painful stimuli (examples: low level electrical shock or heat), survival surgical procedures that have the potential to result in long term distressful illness (organ transplants, for example), induction of cardiac ischemia, booster immunizations with CFA, tumor induction or animal cultures that cause significant distress or pain, sight deprivation, restraint for periods longer than 12 hours.

E. INTENSE SUSTAINED OR REPEATED PAIN WITHOUT ANESTHESIA/ANALGESIA
Direct stimulation of CNS pain tracts, nociceptor stimulation by physical or chemical means that causes severe pain (e.g., corneal abrasions), or any category C (see above) procedure if performed without chemical relief of pain.

Investigator Assurance

Check all boxes that apply.

☐ The information provided in this protocol form accurately reflects the intended use of animals for this research activity. Significant changes in procedures will not be undertaken without prior notification and approval of the Maryville College IACUC.

☐ All persons involved in the use of animals on this protocol have been informed of the experimental objectives and methods. Each has received training in the execution of animal-related procedures he/she will perform prior to participation in the protocol, and will participate in any educational or training programs deemed appropriate or necessary by the Maryville College IACUC.

☐ I agree to follow the provisions of the Animal Welfare Act and the guidelines of the National Institutes of Health on the care and use of laboratory animals.

☐ I agree to use anesthesia, analgesia and tranquilization to relieve pain or distress whenever use of these agents will not jeopardize the scientific validity of the data. I have specifically consulted with the Maryville College IACUC regarding any experiments that are classified in pain/distress categories C, D, or E.

☐ I will take appropriate steps to avoid exposure of persons working with these animals to any biohazard agents used in the study.

For any unchecked box above, explain the reason it does not apply.

Purpose of the Study: Briefly describe your proposed research project (or attach a research proposal). Be sure to include a justification for the species and number.

The purpose of this study is to examine the efficacy of two readily available treatment tools in the management of the growing canine obesity disease: pharmaceutical therapy with dirlotapide or dietary intervention through caloric restriction. This study will identify factors associated with canine obesity in one particular East Tennessee small animal veterinary practice, and compare the outcome of treatment protocols, to see if reduced food intake alone is enough to treat obesity, or if medicating obese patients with dirlotapide promotes significant weight loss. The reality of owner compliance shall also be assessed to see if follow up increases likelihood of successful diet management and return visits.

Potential Scientific Benefits: State potential value of study with respect to human or animal health, advancement of knowledge, or good of society.

Since obesity is such a prevalent and growing health concern, and there are numerous other secondary medical complications in both people and companion animals, exploring the efficacy of available treatment options could be greatly beneficial in furthering knowledge in this area.

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