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The Effect of Six Months of Topiramate Supplementation Use for Weight Loss on Ambulatory Blood Pressure in Abdominally Obese Males

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# THE EFFECT OF SIX MONTHS OF TOPIRAMATE SUPPLEMENTATION USE FOR WEIGHT LOSS ON AMBULATORY BLOOD PRESSURE IN ABDOMINALLY OBESE MALES

By

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University of Ottawa

August, 2006

*Your file Votre référence*
*ISBN: 978-0-494-18462-2*
*Our file Notre référence*
*ISBN: 978-0-494-18462-2*

**Abstract**

**Objective:** To examine the effect of six months of Topiramate (TPM) supplementation use for weight loss on ambulatory blood pressure (ABP) in abdominally obese males.

**Methods:** Sixty-eight abdominally obese males (Waist circumference >100 cm) with a BMI >27 and < 35 kg/m$^2$ were assigned to the TPM or placebo group using a randomized pretest-posttest control group design with no behavioral modification. This was followed by a 12-week titration period and a 12-week stabilization period with a dosage up to 400 mg/d. Ambulatory blood pressure was monitored at baseline and at six months using the Spacelabs Medical Model 90207-31.

**Results:** Topiramate supplementation group showed a significant decrease in systolic (5.2 ± 9.79; p=0.006, -4.6 ± 10.90; p=0.011 and -6.9 ± 8.31; 0.003 mmHg) and diastolic (-3.7 ± 6.13; p =0.006, -3.3 ± 7.08; p=0.033 and -4.3 ± 7.13; p=0.006 mmHg) 24-hr, daytime and nighttime ABP respectively. However, after performing an ANCOVA to control for the significant weight loss observed in the TPM supplementation group (-3.19 ± 5.72 kg; p=0.006), systolic/diastolic 24-hr (p=0.233/0.147), daytime, (p=0.313/0.276) and nighttime (p= 0.108/0.187) changes in ABP were similar between the TPM and placebo group. Furthermore, change in systolic 24-hr ABP was significantly correlated to changes in % body fat (r=0.54; p=0.025), body fat mass (r=0.51; p=0.039) and total abdominal adipose tissue (r=0.46; p=0.043), whereas change in diastolic 24-hr ABP was significantly correlated to changes in total abdominal adipose tissue (r=0.51; p=0.043). Change in visceral adipose tissue (VAT) was not significantly related to changes in systolic/diastolic ABP (r=0.46/0.41; p=0.075/0.113) respectively.

**Discussion:** These results suggest that the reduction in ABP observed in the TPM is mainly secondary to the reduction in body weight, especially the reduction in fat mass and total abdominal adipose tissue and not by the mechanistic abilities of the drug.

**Key words:** Topiramate, Ambulatory Blood Pressure, Visceral Adipose Tissue, Weight Loss

**Acknowledgements**

I would like to take this time to thank the many individuals who have supported the completion of this project. First and foremost, I would like to thank Dr. Denis Prud'homme. This experience has been enjoyable, largely due to your constant support. You have taught me the fundamentals of research and critical thinking, while keeping everything in perspective. I would also like to thank Dr. Glen Kenny and Dr. Eric Doucet for serving on my committee. Your comments and suggestions have been invaluable to this learning experience. In addition, I would like to thank Dr. Ollie Jay for the assistance in the statistical analysis.

Further, I would like to thank Marie Fortier who always made sure that I was taken care of no matter what problems had arisen. Finally, I would like to take this opportunity to thank my family and friends for their invaluable support throughout the past two years. The last few years have been mentally tough and I am forever grateful for you being there.

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**List of Abbreviations**

| | |
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| **ABP** | Ambulatory Blood Pressure |
| **Acrp30** | Adiponectin |
| **AMPA** | Alphaamino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| **AUC** | Area Under the Curve |
| **BMI** | Body Mass Index |
| **BP** | Blood Pressure |
| **CAD** | Coronary Artery Disease |
| **CT Scan** | Computed Tomography |
| **CVATT** | Critical Visceral Adipose Tissue Threshold |
| **DBP** | Diastolic Blood Pressure |
| **DSAT** | Deep Subcutaneous Adipose Tissue |
| **FA** | Fatty Acid |
| **FFA** | Free Fatty Acids |
| **FM** | Fat Mass |
| **GABA** | Gamma Aminobutyric Acid |
| **HDL** | High Density Lipoprotein |
| **IR** | Insulin Resistance |
| **LDL** | Low Density Lipoprotein |
| **MSNA** | Muscle Sympathetic Neural Activation |
| **NO** | Nitrogen Oxide |
| **OGTT** | Oral Glucose Tolerance Test |
| **SAT** | Subcutaneous Adipose Tissue |
| **SSAT** | Superficial Subcutaneous Adipose Tissue |
| **T2DM** | Type 2 Diabetes |
| **TPM** | Topiramate |
| **VAT** | Visceral Adipose Tissue |

# Chapter 1: Obesity Review

## 1.1 Definitions and Prevalence of Obesity and Hypertension

The World Health Organization defines an individual as overweight when they have a body mass index (BMI) > 25 kg/m² and an individual is obese with a BMI > 30 kg/m². Obesity has risen rapidly in Canada, the United States and all over the world ranging from developed to underdeveloped nations (Flegal et al., 2002; Katzmarzyk, 2002). In Canada, obesity has risen over a 13-year period from 5.6% in 1985 to 14.8% in 1998; translating to 3.3 million Canadians being classified as obese (Katzmarzyk, 2002). While in the United States over the past 15 years, 60% of American adults are either overweight or obese (Flegal et al., 2002; Popkin & Gordon-Larsen, 2004) and the number of those who are considered severely obese (BMI >40 kg/m²) has increased by nearly 200% (Freedman et al., 2002). Obesity is thought to affect approximately 250 million people globally, and this number is expected to continue to rise (Seidell, 2000). Obesity has become the major and primary cause of preventable morbidity and mortality leading to 300,000 premature deaths a year in the United States (Flegal et al., 2002; US Department of Health and Human Services, Office of the Surgeon General, 2001). Increased weight in the population can be partly explained by the western diet, which consists of foods high in saturated fats, sugar, refined foods and low in fibre and/or to a sedentary lifestyle (Ogden et al., 2002; Popkin & Gordon-Larsen, 2004). Further, increased weight gain is associated with aging and a lower socioeconomic status (Bouchard, 2000). Finally, genetic predisposition and poor nutrition skills taught at an early age may be an important predecessor to obesity (Bouchard & Tremblay, 1997). Lyon and Hirschhorn (2005) state that obesity genotypes are complex genetic traits that can be attributed to 30 to 70% of

body mass in humans and that based on an individuals DNA, they may be more susceptible to becoming obese through altered hormone function or other related disorders.

The Canadian Minister of Health (Ujjal Dosanjh) estimates that 5 million Canadians are hypertensive and that 40% of them are not aware of their state (Heart and Stroke Foundation, 2005). Further, essential hypertension is now the most common reason for medical office visits in the United States (Hing et al., 2006). Normal blood pressure (BP) ranges between 120-140/80-90 mmHg, with health consequences (ie. congestive heart failure, stroke, heart attack, peripheral artery disease, aneurysms and kidney failure) ranging anywhere from 135/85 mmHg and higher. There are many possible mechanisms that can increase BP; however an association with abdominal obesity through the link of insulin resistance (IR) is the main focus of this study.

### 1.2 Health Problems Associated with Obesity and Health Care Costs

Obesity can lead to a number of health problems. Obese individuals are more susceptible to coronary artery disease (CAD), hypertension, dyslipidemia, type 2 diabetes (T2DM), cancer, sleep apnea and many other disorders (Flegal et al., 2002; Ogden et al., 2002). Increased weight is particularly disturbing for an individual because a 10-20 pound gain in individuals increases the risk of a heart attack by a factor of 1.65 and 1.25 in men and women respectively who are in the normal/high range of body weight (BMI >25) (Willet et al., 1995; Galanis et al., 1998). The cost of obesity and the associated health problems has also risen in the United States from $99 billion in 1995, to $117 billion in the year 2000 (US Department of Health and Human Services, Office of the

Surgeon General, 2001), while direct medical costs related to obesity in Canada in 1997 was $1.8 billion (Katzmarzyk, 2002).

## 1.3 Obesity Versus Central Obesity

Lipids can be stores in three different areas of the body. They may be stored as subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and in areas known as ectopic fat (liver, skeletal muscle, heart, beta cells located in the pancreas and in the other bodily organs). Abdominal obesity predominantly consists of subcutaneous and visceral adipose tissue. Subcutaneous adipose tissue is located beneath the skin and above the muscle wall, while VAT is composed of the omentum (the major component), peritoneum (attached to the stomach and links it with other abdominal organs) and the mesenteric (round ligament surrounding the bowel at the mid-gut level). It is located beneath the abdominal muscles and composes up to 20 percent of fat storage in men and approximately 5-8 percent in women (Freedland, 2004).

French physician, Jean Vague (1947) recognized over 50 years ago that android (central) obesity increases the risk of developing metabolic diseases compared to gynoid obesity phenotype (lower obesity). Numerous studies have supported this initial finding and have demonstrated that abdominal obesity; especially VAT is associated with insulin resistance (IR) (Lemieux, 2001).

### *1.3.1 Increased Lipolytic Activity in Visceral Adipose Tissue*

One of the potential explanations of the cardiovascular complications associated with VAT may be linked to its lipolytic activity. Visceral adipose tissue has a higher rate of lipolysis as explained by an increase in the β -adrenoceptor pathway (via $ß_1$-, $ß_2$-, and $ß_3$-adrenoceptors), leading to a higher sensitivity to catecholamines, as well as reduced $\alpha$-

adrenoceptor (inhibition via $\alpha_2$-adrenoceptors) component (Jensen et al., 1989). β-adrenergic receptors in VAT has been shown in obese subjects to have increased sensitivity to $ß_3$-adrenoceptor stimulation, mediating a cascade reaction that up regulates cyclic AMP formation, stimulating cAMP-dependent protein kinase that activates hormone sensitive lipase (Lönnqvist et al., 1995). Thus, hydrolyzing triglycerides to glycerol and increasing free fatty acid (FFA) release. Furthermore, in a study comparing the lipolytic sensitivity of VAT between males and females showed no difference to $ß_1$- or $ß_2$-adrenoceptor–specific agonists, but the lipolytic $ß_3$-adrenoceptor sensitivity was 12 times higher and the antilipolytic $\alpha_2$-adrenoceptor sensitivity was 17 times lower in men (Lönnqvist et al., 1997).

### *1.3.2 Antilipolytic Effect of Insulin in Visceral Adipose Tissue*

Insulin displays a prominent effect on lipolysis in adipose tissue (Marin et al., 1992). It acts as an antilipolytic hormone in the body, inhibiting fatty acid (FA) and glycerol release. The binding of insulin activates the insulin receptor on the adipose tissue by autophosphorylating on the tyrosine residue (White & Kahn, 1994). The tyrosine kinase receptor is then activated by autophosphorylation, thus allowing the receptor to tyrosine phosphorylate intracellular substrates, such as insulin receptor substrate-1 (IRS-1) (a protein that is one of the earliest down-stream constituent of the insulin receptor signally pathway) (White & Kahn, 1994; Zierath et al., 1998). A protein that docks to IRS-1 is phosphatidylinositol 3-Kinase (PI 3-Kinase), which leads to an increase in PI-3-Kinase activity (Fry, 1994). A study by Lam et al. (1994) *in vitro* using rat adipocytes and wortmannin (a PI 3-Kinase inhibitor) inhibits lipolysis in adipose tissue, thus contributing to the antilipolytic effect of insulin and suggesting that PI 3-kinase is involved in insulin

signaling. In addition, Bolinder et al. (1983) observed a 3-fold increase in the antilipolytic effect of insulin in SAT compared to VAT during human in *vitro* experimentation. This study also showed that the affinity for the receptor by insulin is significantly lower in omental fat then in SAT in lean subjects. Furthermore, insulin-reduced receptor autophosphorylation is more pronounced in SAT than in the omental adipose tissue as seen *in vitro* experimentation in adipose tissue of humans (Zierath et al., 1998). At maximal insulin stimulation, almost 100% of the insulin receptor autophosphorylation in SAT was observed with only 2/3 of the VAT being autophosphorylated. A possible explanation is the difference in IRS-1 tyrosine autophosphorylation between the two cell types. Further, insulin induced tyrosine phosphorylation of IRS-1 was reduced in omental cells, as well as a 50% reduction in IRS-1 protein expression. Despite the protein expression of PI-3 kinase was similar between SAT and VAT, the ability of insulin to increase PI-3 kinase to stimulate phosphotyrosine enzymatic activity of PI-3-Kinase was reduced in omental cells. Thus, potentially reducing the insulin receptor phosphorylation in VAT compared to subcutaneous adipose tissue (Zierath et al., 1998). This reduction in insulin sensitivity, as well as the increased sensitivity to catecholamines could explain how a higher lipolytic effect occurs in visceral adipose tissue.

### *1.3.3 Increased Deposition of Visceral Adipose Tissue*

Despite VAT highly lipolytic activity, most viscerally obese individuals continually increase their VAT depots without behavioural intervention (Pascot et al., 1999). Therefore, to counteract the high rate of lipolysis, there must be times of increased lipid deposition. Lundgren et al. (2004) performed a biopsy of omental and SAT depots in 18 lean and obese nondiabetic subjects. The omental VAT was shown to double the amount

of glucose uptake via insulin compared to subcutaneous adipose tissue. An explanation of this may have been an increased expression of GLUT-4 that was approximately 4 times higher in omental depots.

A study by Marin et al. (1992), demonstrated that subjects given isotopically labelled FA, followed by a biopsy (24 hours later during abdominal surgery), showed that most of the accumulation of the radioactive FA were found as triglycerides in the omental depots (approximately 50% higher rate of uptake), compared to abdominal subcutaneous adipose tissue. These two investigations (Marin et al., 1992: Lundberg et al., 2004) have shown an increased rate in lipid deposition in VAT compared to SAT and the differences in metabolic activity between VAT and SAT may contribute to the confounding effects of visceral obesity.

### *1.3.4 Comparison Between Subcutaneous and Visceral Adipose Tissue*

A study by Gabriely et al. (2002) compared the removal of SAT and VAT (approximately 18% of total body fat) in rats. They observed a significant increase in hepatic and peripheral insulin sensitivity was only observed in the rats that had VAT removed. In addition, there was a significant decrease in insulin plasma levels following VAT removal. Miyazaki et al. (2002) has also showed a strong correlation between VAT/ body fat mass (FM) and peripheral/hepatic insulin resistance. Furthermore, a study performed in abdominally obese women (waist circumference >100 cm) showed no significant change in plasma glucose, insulin levels, IR, BP or plasma adiponectin (Acrp30) levels, following a liposuction intervention of subcutaneous adipose tissue (Klein et al., 2004). Thus, displaying the important role of VAT in abnormal metabolic function.

Despite the numerous investigations supporting that VAT is closely associated with IR, others have showed that abdominal SAT is the best predictor of insulin resistance (Frayn, 2000; Garg & Misra, 2004). A possible explanation for these contradicting findings is the difference in adipose tissue metabolism between superficial (SSAT) and deep (DSAT) in the abdominal region. Recent data has shown that SSAT has no impact on IR, while DSAT was associated with peripheral and hepatic IR in type 2 diabetics (Kelley et al., 2000; Miyazaki et al., 2002). In a study by Basu et al. (2001), it was observed that DSAT was inversely correlated with insulin-mediated glucose uptake. However, when VAT was considered as a factor in the multivariate analysis, DSAT was no longer a predictor of insulin resistance.

Furthermore, VAT may influence SAT metabolic behaviours. A study by Mauriege et al. (1999) determined that $\beta$-adrenoceptor sensitivity was increased in SAT cells in individuals who had higher VAT accumulation ($162 \pm 29$ cm$^2$; $n = 18$) compared to those with low VAT depots ($101 \pm 21$ cm$^2$; $n = 18$). High levels of VAT led SAT adipocytes to be more sensitive to beta-adrenergic lipolysis, which may lead to advanced impairment of insulin action leading to further conditions associated with metabolic obesity. Thus, leading to the argument that visceral and subcutaneous abdominal obesity may coincide to enhance SAT lipolysis and release of peripheral free fatty acids (Freedland, 2004). In conclusion, the link between abdominal VAT, SAT and IR is still inconclusive and future investigations need to be conducted.

### *1.3.5 Visceral Adipose Tissue Threshold*

Since it has been shown that an increase in VAT is associated with metabolic abnormalities, it is imperative to determine what amount of VAT impairs metabolic

function. A paradigm proposed by Eric Freedland (2004) suggests a critical visceral adipose tissue threshold (CVATT) that helps explain the large intra-individual variation that may contribute to the metabolic syndrome. This CVATT may help explain why relatively lean individuals display features of the metabolic syndrome, as well as those individuals who are obese display normal metabolic phenotypes. This review suggests how a relatively small weight gain can lead to abnormal metabolic responses, as well as how a small reduction in body weight (by means of VAT) can dramatically improve the metabolic profile. Since this is a relatively new theory, other investigators have tried to determine what is the CVATT that increases the risk of developing CAD and other metabolic abnormalities. A study by Williams et al. (1996) determined that values >110 $cm^2$ of intra abdominal fat led to a higher risk in pre and post menopausal women, while a study by Nicklas et al. (2003) determined that VAT levels >106 $cm^2$ showed elevated risk for metabolic abnormalities, with a greater risk with values >163 $cm^2$ in middle and older age women. Despres and Lamarche (1993) observed VAT >100 $cm^2$ in young men and pre-menopausal women led to significant alterations in CAD risk profile and further deterioration when values are >130 $cm^2$. Finally, Hunter et al. (1994) found that males with VAT area >131 $cm^2$ had an increase risk for coronary artery disease. Even if there is a variation between the CVATT (100 to 163 $cm^2$), there is a consensus that individuals with VAT area between 100 and 130 $cm^2$ are at an increase risk of CAD and other metabolic disorders.

### 1.4 Metabolic Syndrome

Obesity, especially abdominal obesity, has been associated with a frequent condition known as the metabolic syndrome, which affects approximately 25.8% of Canadians as

predicted by researchers at the Heart and Stroke Foundation of Canada (Anand et al., 2003). The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults determined five phenotypes define the metabolic syndrome, with normal values in parenthesises (Ford et al., 2002).

1) Abdominal waist circumference of >102 cm and >88 cm in men and women respectively *(< 94 cm and < 80 cm)*,
2) Fasting glucose > 6.1 mmol/L *(< 5.5 mmol/L)*,
3) Hypertriglyceridemia >1.69 mmol/L *(1.7 mmol/L)*,
4) High density lipoprotein (HDL) cholesterol values of < 0.8 mmol/L and < 1.0 mmol/L in men and women respectively *(>1.0 mmol/L and > 1.2 mmol/L)* and
5) Blood pressure (BP) >130/85 mmHg *(120/80 mmHg)*.

The presence in an individual, of three of the five phenotypes defines the metabolic syndrome. Even if the metabolic syndrome phenotype criteria are just above the high-normal value of the population range, it is the combination of these phenotypes that leads to the increased metabolic dysfunction and a possible adverse event. An individual with the metabolic syndrome has almost twice the risk of an occurrence of a cardiovascular incident (Bloch & Basile, 2004). It has also been shown in the same study that the number of phenotypes someone may demonstrate of the metabolic syndrome is a positive indicator of the risk of a cardiovascular event.

### *1.4.1 Potential Mechanism Linking Visceral Adipose Tissue to the Metabolic Syndrome*

Despite the relationship between VAT and IR, accumulating evidence has indicated IR as the common pathogenic factor among metabolic syndrome indicies. However, the precise mechanism for these relationships is still unknown.

The portal theory is a possible link between VAT and the metabolic syndrome. The basis behind the portal theory is the lipolytic activity of VAT will increase the delivery of FFA to the adjacent portal vein, leading to hepatic insulin resistance (Hirsch et al., 1989). A study to support this increased FFA availability was performed by Nielsen et al. (2004), using a sophisticated tracer method in combination with mathematical modeling and technically demanding catheritzation procedures to evaluate regional leg and splanchnic FFA metabolism. They were able to determine the relative contribution of FFA's released from VAT into the portal and systemic circulations in lean and obese men and women. Results from this investigation showed that the FFA's released from VAT depots (232 ± 15 and 130 ± 10 $cm^2$) respectively in obese male and women subjects) into the hepatic portal vein during lipolysis increased with larger amounts of visceral adipose tissue. However, this study reported a large inter-individual variation contribution regarding the FFA release from VAT, ranging from 0% to 45% of total FFA's delivered to the liver, via VAT and the hepatic portal vein. Furthermore, some subjects with as little as 10 $cm^2$ of VAT released more FFA's compared to some subjects with over 300 $cm^2$ of visceral adipose tissue. In addition, the comparative amount of portal vein FFA's from VAT was much less than from lipolysis of SAT depots (266 ± 17 and 339 ± 22 $cm^2$ in obese men and women respectively for abdominal SAT and 10.6 ± 0.7 and 15.5 ± 0.8 kg

for leg SAT in men and women), as seen in *figure 1.* Emphasizing the notion that FFA from VAT is not as important as SAT in supplying FFA to the liver, although it may be an important risk factor in developing hepatic IR in some individuals. Finally, the amount of FFA's from the liver (6% in lean and 14% in obese) being delivered to the systemic circulation, compounded with the fact that most FFA's are from lipolysis of SAT, few FFAs released from VAT are delivered to skeletal muscle. Despite the fact that there is only a minimal increase in FFA from VAT delivered to the muscle, it is not precisely known how it affects IR in skeletal muscle (Klein, 2004). As suggested by Klein (2004), the results of this study shows that even if there is VAT FFA release, it is impossible to predict which individuals will have a greater increase of VAT FFA flux based on body composition and body fat distribution alone. However, to summarize, abdominally obese individuals generally will contribute higher levels of FFA to the liver, potentially linking VAT to the development of the cluster of effects associated with the metabolic syndrome.

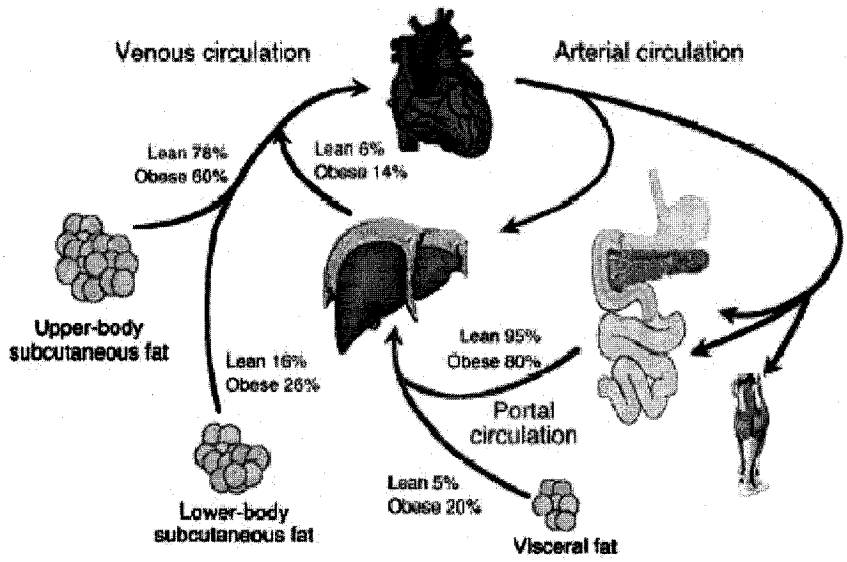


**Figure 1:** Approximate contributions of free fatty acids from subcutaneous and visceral adipose tissue to the portal circulation in lean and obese subjects. Data is based from Nielsen et al., 2004 (Adapted from Klein, 2004, Copied under license from Access Copyright ©. Further reproduction prohibited)

### *1.4.2 Potential Role of Insulin Resistance in the Development of the Metabolic Syndrome*

Excess VAT is also known to be associated with decreased insulin sensitivity, as shown by the results of the euglycemic hyperinsulinemic glucose clamp studies, as well as with a reduced rate of FFA re-esterification (Gastaldelli et al., 2002). Furthermore, excess VAT has shown a delayed clearance of triglycerides following a high fat meal, therefore leading to another means in how VAT contributes to the deterioration in the plasma lipid-lipoprotein profile (Couillard et al., 1998). The decrease in insulin sensitivity associated with VAT also leads to a higher plasma glucose level, followed by an increase in production of insulin by the pancreas, leading to a hyperinsulinemic state. In addition, the high plasma level of FFA decreases the hepatic re-uptake of insulin, which also partly explains the rise in plasma insulin and the hyper-insulinemic state (Matsuzawa, 1998; Watanabe & Tochikubo, 2003). Hyperinsulinism heightens the kidneys' capabilities to reabsorb sodium and stimulate the sympathetic nervous system, creating a state that increases the risk of developing hypertension (Tochikubo et al., 1994; Lefebvre et al., 2003). It has also been shown that IR found in visceral obesity and in a hyperinsulinemic state correlates with casual and ambulatory blood pressure (ABP). However, they were not independent predictors of BP, providing additional proof to the clustering effects of the metabolic syndrome (Lefebvre et al., 2003). With time, insulin secretion by the pancreas could decrease, creating glucose intolerance. If the glucose-insulin metabolism continues to worsen (ie. IR and plasma fasting glucose increase), impaired glucose tolerance will eventually lead to T2DM and increase the risk of

coronary artery disease through complications of the metabolic syndrome (Tochikubo et al., 1994).

### 1.5 Intramuscular Adipose Tissue and Insulin Resistance

It is well known that adipose tissue is also stored in the muscle and it has been discovered within the last ten years that the triglyceride content of muscle is related to IR independent of overall adiposity (Goodpaster & Brown, 2005). Triglyceride accumulation (as lipid droplets) can be located within the muscle or between the muscle fibers, with obesity leading to an increase intracellulary of lipid droplets (Pan et al., 1997; Goodpaster et al., 2000). Boden et al. (2001) studied healthy individuals before and 4 hours after increasing plasma FFA's' by lipid plus heparin infusions. They observed that an acute increase in plasma FFA led to increased intramuscular adipose tissue (IMAT) and a development of IR 3 to 4 hours after FFA increase. Thus, suggesting that intra muscular formation of FFAs' is a pathway in developing IMAT insulin resistance. Furthermore, Santomauro et al. (1999) in subjects who have glucose intolerance and chronically elevated FFA levels demonstrated that by lowering FFA overnight with Acipmox (an antilipolytic drug) reduced IR; displaying the link between plasma FFA level and IR in intramuscular adipose tissue. It is imperative to note that triglycerides themselves are not shown to negatively affect insulin action, but other lipid species and metabolites (by products of triglyceride formation) such as diaglycerol (Itani et al., 2002), fatty acyl CoA species and ceramides (Goodpaster & Brown, 2005). During the synthesis of muscle triglycerides, lipid metabolites are formed, which act on signalling pathways that are known to be defective in type 2 diabetes (Schmitz-Peiffer, 2000; Goodpaster & Brown, 2005). Excess triglyceride formation in IR muscle may lead to a rise in

diaglycerol, activating protein kinase C. This leads to inhibition of tyrosine kinase activity of the insulin receptor and tyrosine phosphorylation of insulin receptor substrate-1, leading to a reduced insulin action (Griffin et al., 1999).

It has also been shown that a defective FA oxidation in skeletal muscle also leads to lipid storage and possibly insulin resistance (Kelley et al, 2002). Once in the sarcoplasm, the long-chain FA is translocated into the mitochondria, via the rate-limiting enzyme complex carnitine palmitoyltransferase, to initiate FFA oxidation in the muscle (McGarry & Brown, 1997). However, complex carnitine palmitoyltransferase activity is reduced in obese individuals with IR skeletal muscle (Goodpaster & Brown, 2005). Furthermore, Kelley et al. (2002) performed a percutaneous biopsy on the vastus lateralis muscle during fasting conditions in lean and obese non-diabetics, as well as obese diabetics. It was observed that the skeletal muscle mitochondria were 30% smaller in the obese and T2DM subjects compared to the lean group. There was also a diminished level of insulin-stimulated glucose metabolism and low levels of FA oxidation during fasting conditions observed in the diabetic group. This may be supported by the observation of a decrease in NADH:$O_2$ oxidoreductase and citrate synthase activity in the T2DM subjects compared to the healthy lean and obese groups. This coincides with the results of Simoneau et al. (1995), in which insulin sensitivity was positively associated with high skeletal muscle FA oxidation as revealed by the significant correlation with increased citrate synthase activity. These observations propose that in muscle with high IMAT, FA is directed towards lipid accumulation and not FA oxidation, suggesting a possible mechanism to increase insulin resistance.

## 1.6 Hypertension, Insulin Resistance and Endothelial Dysfunction

Shepherd (1990) suggested that endothelial cell dysfunction is the primary reason for the increase in systemic vascular resistance that leads to an increase in blood pressure. In normal endothelial cells there is a production and release of vascular smooth muscle relaxing and growth-inhibiting factors. However, through metabolic changes and increased muscle sympathetic activity, structural changes will occur in the arteries, reducing the size of the lumen, increasing the vasoconstriction response, as well as limiting vasodilation (Shepherd, 1990).

Hyperinsulinemia, frequently observed in abdominal obese individuals, used to be proposed as the main link between insulin sensitivity and increased BP values (Reaven, 1988). Berne et al. (1992) studied 16 non-obese men who underwent hyperinsulinemia-euglycemic clamp and nerve recordings. It was observed that hyperinsulinemia increased sympathetic activity conducting vasoconstrictor signals to the skeletal muscle. This has been supported in other human models, as acute hyperinsulinemia triggers sympathetic activation in skeletal muscle tissue (Rowe et al., 1981; Vollenweider et al., 1993). It is predicted that insulin directly acts upon the central sympathetic motor neurons to increase muscle sympathetic activation (Berne et al., 1992). Sowers et al. (1982) suggested enhanced sympathetic activity may play a role in elevated BP levels in the obese. Norepinephrine plasma levels, a neurotransmitter and hormone that is involved in muscle sympathetic activation has been associated with an increase in blood pressure. During this investigation and others (Anderson et al., 1991), norepinephrine plasma levels were significantly elevated following hyperinsulinemic conditions. However, there was no

change in BP in the study performed by Berne et al. (1992), which was contradictory to the significant increase in BP observed by Anderson et al. (1991).

Scherrer et al. (1994) determined that body fat is a major factor in the resting rate of muscle sympathetic activation, and it may be related to a potential mechanism in cardiovascular complications in obese subjects. It accounts for approximately 50% of inter individual variation in the rate of muscle sympathetic nerve activity (MSNA), while also showing positive correlation to vascular resistance in calf muscle. This is supported by an investigation by Vollenweider et al. (1994) that showed a difference in MSNA and blood flow in lean and obese individuals following a 2-hr hyperinsulinemic-euglycemic clamp. Obese subjects had a 2.2 times higher fasting rate of MSNA and higher resting basal levels of insulin, while only showing minor vasodilatory and sympathetic effect following euglycemic hyperinsulinemia. This is in contrast to the lean group that showed double MSNA and an increased blood flow by 30%. Thus, presenting that obesity is associated with a change in response to hyperinsulinemia and MSNA, as well as insulin being a main promoter that generates sympathetic activation and vasodilation (Vollenweider et al., 1994). Other studies have shown that insulin leads to vasodilation and not vasoconstriction (Laakso et al., 1990). Chronic hyperinsulinemia in dogs' leads to a decrease in BP providing further support that insulin plays a role in vasodilation (Brands et al., 1991). Furthermore, chronic hyperinsulinemia in patients with insulinoma is not associated with an increase in blood pressure (Sawicki et al., 1992). Therefore, hyperinsulinemia may not be the central factor in relation to an increase in BP and that IR may be a better predictor.

Ferrannini et al. (1997) in a study relating to obesity and BP elevation came to the conclusion that BP (systolic and diastolic) is strongly related to IR and not to hyperinsulinemia in non-diabetic, normotensive Europeans. They determined that systolic and diastolic BP was. 1.7 and 2.3 mmHg higher for each 10-unit increase in IR (ie. a 10 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ decrease in the insulin sensitivity index). Insulin resistance is related to metabolic syndrome indicies (hypertension, abdominal obesity and an increase in fasting plasma glucose) and is associated with a blunted insulin-induced vasodilatation (Heise et al., 1998). Another study in obese children showed that a decrease in BP and triglyceride levels, independent of weight change, was correlated to decrease in a HOMA (Homeostasis Model Assessment) score (Reinehr et al., 2005). A HOMA is used to predict beta cell function and insulin sensitivity. Proof of the relationship has been observed in various clinical settings in which there is reciprocity between an improvement in IR and endothelial dysfunction (Satoh, 2003; Natali, 2004). Therefore, adding additional support to the argument that IR may be the central cause behind the development of hypertension.

An epidemiological study has shown that hypertension and IR are related in human morbidity and mortality, suggesting a possible interactive mechanism (Isomaa et al., 2001). Endothelial derived nitric oxide (NO) synthase (a rate limiting enzyme for the potent vasodilator nitric oxide) regulates arterial pressure and is defective in hypertensive patients. Scherrer et al. (1994) performed a study to monitor the effects of NO inhibition in the wake of hyperinsulinemia. NG-monomethyl-L-arginine (an inhibitor of endothelium derived NO synthase) was infused into the brachial arteries of healthy subjects, causing an increase in blood pressure following a 2-hr hyperinsulinemic (6

pmol/kg per min) euglycemic clamp. Thus, showing insulins' vasodilatory effects are mediated by NO and that impairment of insulin-induced NO release may be associated with abnormal vascular function and may lead to hypertension in IR states. To add further proof of insulin's ability to facilitate endothelial-mediated vasodilation, investigations imitating IR (wortmannin) was pursued (Zeng & Quon, 1996; Vincent et al., 2003). These investigations showed that endothelial-mediated vasodilation was impaired. Insulin was not able to activate the key enzyme (nitric oxide synthase) responsible for NO production, explaining the decrease in NO production, which is vital in vascular functions to promote vasodilation (Vincent et al., 2003; Cerosismo & DeFronzo, 2006). In numerous studies involving pharmaceutical reagents (infusion of NG-monomethyl-L-arginine after ibuprofen) that block NO synthesis, it was observed that abnormal vascular responses appear as seen in pre diabetics, T2DM and individuals with cardiovascular risk factors (Joannides et al., 1995; Engelke et al., 1996). Finally, greater than 90% of T2DM and pre-diabetics who are at high risk of cardiovascular disease and who have endothelial dysfunction, have moderate to severe IR: supporting the essential effects of NO and the vital importance of insulin (DeFronzo, 1988). However, the exact molecular mechanism responsible for the association between IR and abnormal vascular function has yet to be discovered, although the link with NO seems to play a vital role. (Cerosismo & DeFronzo, 2006). Thus, underlying an important mechanism in the relation to IR and an increase in blood pressure.

The relationship between IR and NO endothelial dysfunction is only one mechanism, albeit a major role in relation to an increase in blood pressure. Structural changes may occur following chronic IR in the arterial vessels, thus reducing the lumen area and

potentially creating a vasoconstrictor response. In dyslipidemic individuals, (associated with IR) hypertriglyceridemia and elevated low-density lipoprotein (LDL) plasma levels may lead to endothelial dysfunction by triggering the inflammatory response that involves the adhesion of leukocytes (monocytes and lymphocytes) to the endothelial cells (Cerosismo & DeFronzo, 2006). Hemodynamic and metabolic degradation occurs via the excess formation of reactive oxygen and reactive nitrogen species. In the mitochondria, these free radicals reduce the enzymatic capacity and NO is diminished to nitrate formation (Aulak et al., 2004). Eventually, there is impaired vasodilation and loss in capability to inhibit vasoconstriction. It has been shown by Heitzer et al. (2001) in a study of 281 patients with CAD that endothelial dysfunction and enhanced oxidative stress predict the risk of cardiovascular events. In a follow up (up to four and a half years) to this investigation, 91 individuals experienced a cardiovascular event (ie. heart attack, stroke, coronary or peripheral bypass surgery, ischemic stroke or coronary angioplasty). These individuals had a lower vasodilator response to acetylcholine compared to the rest of the sample, but a higher response to the effect of vitamin C (a powerful antioxidant).

### 1.7 Adipocytokines; Adiponectin, Leptin and Tumor Necrosis Factor-Alpha

White adipose tissue plays an important role as an endocrine organ, as it releases hormones known as adipocytokines. These hormones, otherwise known as adipokines may play a role in insulin resistance, atherosclerosis, hypertension and obesity. Furthermore, these hormone levels change with a gain in body weight that will adversely affect bodily functions. Despite the growing number of newly discovered adipocytokines, the focus will be on the well known Acrp30, leptin and tumor necrosis factor alpha (TNF-

α) in this review, as all three can be linked to insulin and other abnormal metabolic functions. Despite the fact that these hormones were not measured in the original investigation, they may play a role as important determinants in regards to insulin action and/or blood pressure regulation. Therefore, a brief review on the function of these hormones is warranted.

### *1.7.1 Adiponectin*

Adiponectin has different forms of the protein; however the high molecular weight Acrp30 is the most biologically active form. Adiponectin enhances insulin sensitivity at the liver and decreases hepatic glucose output. It may also promote glucose and FFA oxidation in the skeletal muscle (Mojiminiyi et al., 2006). It appears that Acrp30 is a major factor in insulin action and its levels are decreased in type 2 diabetics. Further, it is the highest predictor of IR and the metabolic syndrome (Hara et al., 2006). In a study of Pima Indians, Stefan et al. (2002) determined that low plasma Acrp30 concentrations was cross-sectionally associated with an increased basal and reduced rate of insulin-stimulated tyrosine phosphorylation of the insulin receptor in skeletal muscle. Thus, showing Acrp30 plays an important role in insulin sensitivity. However, hyperinsulinemia seems to play an important role in the down regulation of Acrp30 expression, as the phosphoinositide-3-kinase/Foxo1-dependent pathway has been shown to suppress the adiponectin receptor via insulin. Therefore, decreasing Acrp30 plasma levels and supporting the inverse relationship of Acrp30 with insulin (Tsuchida et al., 2004). There are still many missing links; therefore further research needs to be done on the complex relationship between insulin and adiponectin to determine which hormone suppresses or activates the other.

Adiponectin seems to play many roles in bodily functions. A predicted model shows that Acrp30 affects the production of very low-density lipoprotein at the liver. Therefore, lower amounts of Acrp30, as seen in obese and IR individuals, may cause an increase in plasma triglyceride levels (Weiss et al., 2003). Close association between Acrp30 and IMAT indicates it primarily acts on skeletal muscle to increase oxidation of FFAs', reducing triglyceride content. A possible mechanism as seen in obese mice models shows the increased insulin sensitivity by activating the insulin-receptor substrate 1-associated phosphatidositol 3-kinase to improve FFA clearance and probably increasing FA oxidation, and lowering triglyceride plasma levels (Maeda et al., 2002). With a decrease in plasma Acrp30, IR may occur at the level of the receptors.

To summarize, Acrp30 is inversely related to obesity, as obese individuals have lower amounts of Acrp30, while lean individuals have high amounts of Acrp30. It has been shown that plasma Acrp30 is positively related to insulin sensitivity, independent of body composition and body fat distribution, while having a strong inverse relationship with triglyceride levels, IMAT and fasting insulin levels (Weiss et al., 2003).

### *1.7.2 Leptin*

Obesity is associated with elevated levels of an adipocytokine known as leptin. Leptin was originally viewed as an anti-obesity hormone. However, it is now known to signal energy sufficiency and not excess (Vettor et al., 2005). This hormone mainly acts on the hypothalamus, where it reduces appetite, and increases sympathetic outflow to active tissues such as the kidneys and peripheral vascular system.

Leptin resistance may occur in obese individuals. The defects in leptin signalling, blockade in neuronal circulation or transport across the blood-brain barrier may cause this

condition, however the exact mechanism is unknown (Vettor et al., 2005). Banks et al. (2004) suggests that leptin resistance occurs across the blood-brain barrier by a defect in leptin transport. They showed that obese mice were unable to respond to leptin when administered peripherally, however they responded to centrally administered leptin. Furthermore, it is predicted that leptin resistance may play a critical role in cardiovascular complications. In an investigation by Haynes (2005), it was observed that leptin has a selective leptin resistance (a resistance to the anorexic and weight reducing actions of leptin remain, however there is a preservation of its sympatho-excitatory and pressure actions (Franks et al., 2005)) in obesity. This combined with hyperleptinemia, leads to an increase in relative kidney sodium retention by shifting the renal-pressure natriuresis curve. In addition to those with hyperleptinemia, there may be an increase in norepinephrine turnover in adipose tissue that may increase sympathetic activity and vasoconstriction, leading to higher blood pressure (Awdah & Syamic, 2004). It has also been shown that leptin induces a potent vasoconstrictor known as endothelin-1 and mitogen (Mendoza-Nunez et al., 2006). Furthermore, it has been observed that leptin promotes angiogenesis, modifying the endothelial cell proliferation in atherosclerosis (Quehenberger et al., 2002; Iglarz & Schiffrin, 2003; da Silva et al., 2004). However, a study that involved recombinant leptin therapy in obese subjects showed a slight reduction in BP following subcutaneous injections of 20 mg/d for 12 weeks without a significant weight loss (Zelissen et al., 2005). Therefore, these mechanisms may explain the increase in BP observed in hyperleptinemic state individuals, and leptin resistance may be a key factor in hypertension that needs further investigation.

The link between hyperleptinemia, leptin resistance and IR is still controversial. It has been shown that leptin treatment increases insulin sensitivity in normal, diabetic and hyperinsulinemic rats, as well as correcting the diabetic phenotypes in the adult ob/ob (leptin deficient) mice (Muzzin et al., 1996). However, other studies have shown that leptin reduces insulins action. A study by Benomar et al. (2005), showed that induced hyperleptinemia by leptin infusion changed insulin signaling in the liver of rats, thus contributing to insulin resistance. A potential mechanism may be explained at the cellular level as insulin and leptin have been shown to interact at the same molecular pathways (ie. STAT-3, MAP-kinase and IRS/PI-3-kinase) and that leptin impairs insulin receptor phosphorylation (Perez et al., 2004; Benomar et al., 2005). Despite the complex relationship, it seems as though leptin increases insulin sensitivity in leptin deficient animals, but decreases insulin sensitivity in animals that portray the symptoms of hyperleptinemia and leptin resistance. Further investigations must be pursued to explain this link.

### *1.7.3 Tumor Necrosis Factor-Alpha*

Tumor necrosis factor-alpha is expressed as a 26 kD cell that undergoes cleavage to produce the biologically active 17-kD soluble form. It is positively correlated with BMI, percentage of body fat and hyperinsulinemia and it is reduced with weight loss (Bruun et al., 2003; Ronti et al., 2006)). It was the first adipocytokine to be proposed as a link between obesity and IR in obese type 2 diabetics (Katsuki et al., 1998). In a study by Uysal et al. (1997), they investigated mice with a null mutation in the gene coding for TNF-$\alpha$ and they discovered that this led to mice with lower levels of circulating FFA and were protected from obesity induced IR at the level of the receptor in muscle and adipose

tissues. Furthermore, Hotamisligil et al. (1994) in cell cultures showed that the addition of TNF-$\alpha$ decreased insulin-stimulated autophosphorylation of the insulin receptor, thus showing TNF-$\alpha$ directly interferes with the biological actions of insulin, thus enhancing the state of insulin resistance. Furthermore, Ruan et al. (2002) studied male Wistar rats by infusing TNF-$\alpha$ into a mesenteric vein. A one day treatment decreased insulin sensitivity and caused a 70% increase in plasma FFA and a decrease of 46% in Acrp30. This was supported in an additional study that showed TNF-$\alpha$ decreased mRNA levels of adiponectin (Ruan et al., 2002). Thus, showing TNF-$\alpha$ antagonizes insulins action, partly through a reduced Acrp30 expression and increased plasma FFA levels, via inducing lipolysis. Finally, Boyle (2004) showed *in vivo and in vitro* studies that thiazolidinedione (an adjunctive therapy drug used for T2DM increasing insulin sensitivity) inhibited TNF-$\alpha$ action role in decreasing insulins action.

### 1.8 Benefits of Weight Loss

The association of disease with abdominal obesity, IR and hypertension are conclusive and there is a much needed concern for weight reduction in this population group. Weight loss of 5 to 10% of ones body weight in the obese can improve ones health, while a 1 kg weight loss is associated with a .45 mm Hg decrease in systolic and diastolic blood pressure (Blackburn, 1995; Bray et al., 2003). A 5-7% weight loss sustained for an average of 2.8 years can reduce the risk of type 2 diabetics by 58 % (Knowler et al., 2002). Diet and/or physical activity remain the staple procedure for weight loss in most individuals (NHLBI Obesity Initiative Task Force, 1998; Ross et al., 2004). It is estimated that by controlling obesity, 48% of those with hypertension could become normotensive (El-Atat et al., 2003). Further, by increasing energy expenditure

through physical activity and exercise, significant health benefits are achieved by creating a decrease in body fat and blood pressure (Jakicic & Otto, 2006). A single bout of exercise creates a decrease in systolic BP (5-8 mmHg) in normotensive and hypertensive subjects for 11-12 hours and a decrease in diastolic BP (6-8 mmHg) for 4-8 hours (Park et al., 2005). During a period of weight reduction, there are many metabolic changes that occur. This review will focus on the reduction of weight loss in relation to BP, VAT, IR, IMAT, endothelial function, NO and adipocytokine hormones.

### *1.8.1 Weight Loss and Blood Pressure*

Su et al. (1995) performed a study that compared the effects of weight loss (Approximately 7.5 kg / 10% of baseline body weight) by reducing caloric intake by 1000 kcal/day and the inclusion of light exercise in normotensive and hypertensive obese men and women. The hypertensive group reduced their systolic BP by 14 ± 3 mmHg compared to the normotensive group of 12 ± 3 mmHg, while the hypertensive group reduced their diastolic BP by 12 ± 2 mmHg compared to the normotensive group of 7 ± 3 mmHg. Thus, showing that subjects who are originally hypertensive, will show a greater reduction in BP following weight loss compared to their normotensive counterparts. A study by Blumenthal et al. (2000) on men and women with mild hypertension (130-180/85-110), observed that those in the exercise and caloric restriction group reduced their body weight by 7.9 ± 6.0 kg and decreased their BP by 7 and 5 mmHg for systolic and diastolic respectively, whereas the exercise without caloric restriction group, who lost 1.8 ± 2.8 kg, showed a decreased BP by 4 mmHg for systolic and diastolic blood pressure. In a pharmaceutical weight loss intervention study using orlistat (120 mg three times daily), exercise (not monitored) and caloric restriction (total daily energy

expenditure minus 600 kcal/d) in normotensive obese subjects, displayed a reduction in body weight of 8.0 ± 9.0 kg and a BP reduction of 7 ± 10 and 6.8 ± 7 mmHg systolic and diastolic BP respectively (Schneider et al., 2005). Miller et al. (2002) reported a change in ABP and casual BP measurements following a 5.5 ± 1.8 kg weight loss. The subjects were hypertensive (130-170/ 80-100), overweight/obese (BMI = 33.5 ± 5.8) and were taking a single hypertensive medication. They reported a reduction in ambulatory systolic BP of –10.5 ± 8.3 compared to casual systolic BP of –7.4 (SD not reported). Ambulatory diastolic BP was reduced by –5.9 ± 5.9 compared to casual diastolic BP of –5.7 (SD not reported). In conclusion, based on the results of these studies, weight loss may be associated with a decrease in blood pressure.

### *1.8.2 Weight Loss and Visceral Adipose Tissue*

Visceral adipose tissue reduction is associated with improvement in the metabolic profile as previously described in former sections. Weight loss studies have shown that preferential weight loss of VAT over SAT occurs following a negative energy balance state. A study by van der Kooy et al. (1993) displayed that a caloric restrictive diet in 96 obese male and female subjects showed a greater proportional reduction of VAT (40% in men and 33% in women) compared to the SAT (29% in men and 26% in women). In another study by Goodpaster et al. (1999) following a 15 kg weight reduction by caloric restriction, VAT was reduced by 40% compared to 30% in regards to SAT in abdominal obese male and female adults. Finally, a study by Ross et al. (2000) determined that an 8% weight loss by caloric deficit or exercise induced (-700 kcal/d for both diet and exercise) was associated with similar reductions in abdominal fat, VAT and waist circumference, as well as a similar VAT/SAT ratio was observed. Thus, reinforcing the

notion that in a negative energy balance, there is a preference in reduction of VAT that is regardless of exercise or diet intervention. Furthermore, in the same investigation, an exercise group without weight loss (caloric supplementation) showed a significant decrease in VAT over the control group, suggesting that exercise could influence body fat distribution. Ross et al. (1997) reported eight studies that examine the effects of caloric restriction on visceral adipose tissue. A reduction of approximately 2-3 % of VAT (around 3 to 4 $cm^2$) was observed for every kilogram of weight loss. Thus, a 12 kg weight loss would result in a 30-35 % reduction in visceral adipose tissue. However, Ross and Janssen (2001) have stated that it is not possible to establish a dose-response relationship of VAT reduction in relation to exercise. In conclusion, it has been shown that weight loss predominantly favours a reduction in VAT, therefore potentially explaining the health benefits that are associated with weight loss.

### *1.8.3 Weight Loss and Insulin Resistance*

A reduction in weight by caloric deficit and/or increased energy expenditure through physical activity is associated with a reduction in insulin resistance. As mentioned previously, IR is associated with abdominal obesity, particularly accumulation of visceral adipose tissue. A study by Goodpaster et al. (1999), using a 15 kg weight reduction by caloric restriction, improved insulin sensitivity from 5.9 ± 0.4 to 7.3 ± 0.5 mg · FFM– 1 · min– 1 following a euglycemic insulin infusion clamp. The association between VAT reduction and improvement insulin sensitivity was significantly correlated towards one another. However, Laaksonen et al. (2003) performed a study on abdominally obese men and women following a very-low calorie diet for nine weeks. They showed only a significant correlation between reduction in abdominal SAT ($r=-0.57$; $p=0.017$) and total

abdominal fat (r=-0.51; p=0.035), but not VAT (r=0.11; p=0.68) in relation to the significant improvement in the insulin sensitivity index (using the validated quantitative insulin sensitivity check index) from 0.331 ± 0.022 to 0.359 ± 0.031; p<0.001). Furthermore, Ross et al. (2000) showed that glucose disposal in mg/kg of muscle per minute significantly increased in the exercise with weight loss (11.2 to 18.4) and diet induced weight loss groups (13.0 to 18.6) compared to control samples (15.4 to 14.4). Thus, the results of these studies show that a reduction in body weight is associated with an improvement in IR, non prejudicial towards the weight reduction occurring via caloric deficit or increased physical activity. However, the association between SAT and VAT reduction in relation to insulin sensitivity needs to be further investigated.

### *1.8.4 Weight Loss and Endothelial Function*

Endothelial dysfunction is closely associated with obesity and is considered as an early part of the atherosclerotic process (Sciacqua et al., 2003). It can lead to impaired vasodilation, as mentioned in a previous section in association with insulin resistance. Studies have shown that weight loss improves endothelial vasodilation, via an increase in brachial artery flow-mediation (Hamdy et al., 2003; Sciacqua et al. 2003). Sciacqua et al. (2003) performed a study in 76 obese subjects who lost at least 10% of their body weight by caloric deficit and physical activity. Injections of Acetylcholine (a neural transmitter that mimics vagal nerve stimulation) pre and post weight loss showed a significant increase in vasodilation in forearm blood flow (p< 0.0001). Furthermore, the only significant independent predictor of Acetylcholine stimulated forearm blood flow was the relationship with a decrease in insulin resistance (44.6% of the variation following a multivariate regression). Thus, suggesting that weight loss endothelial vasodilation is

improved via an increase in insulin sensitivity and through the increased availability of nitrogen oxide. Higashi et al. (1999) conducted a study involving exercise without weight loss to improve endothelial dysfunction. They showed that long-term physical activity in mild essential hypertensive patients produced lower systolic and diastolic BP, as well as improvement in endothelial function. This improvement was related to an increased release in NO, as been supported by previous investigations. They suggested that exercise protects the endothelium through reducing plasma norepinephrine, thus stimulating acetylcholine NO release. In conclusion, these studies have shown that weight reduction, long term exercise and a combination of both shows improvements in endothelial function, via the increased release of NO, thus potentially leading to better control of blood pressure.

### *1.8.5 Weight Loss and Intramuscular Adipose Tissue*

Intramuscular adipose tissue is associated with obesity and insulin resistance. Furthermore, a reduction in body weight may show a decrease in intramuscular adipose tissue. A study on the effects of weight loss by approximately 15 kg in obese and obese T2DM subjects showed a decrease in 23 and 41% respectively in IMAT from baseline values (Goodpaster et al., 2000). Gray et al. (2003) suggested that a reduction in IMAT enhances insulin sensitivity in morbidly obese subjects who underwent gastric bypass surgery. These subjects showed a 47% reduction in BMI, a 93% decrease in HOMA model and a 30% decrease in intramuscular adipose tissue. However, weight loss achieved by diet and exercise does not always lead to a decrease in intramuscular adipose tissue (Malenfant et al., 2002; He et al., 2004). He et al. (2004) observed a decrease in the size of the lipid droplets in the IMAT and not an overall reduction. Thus, with an increase

in mitochondrial activity following an intervention of exercise combined with weight loss, it was suggested that it is the size of the IMAT droplet that underlies IR in the skeletal muscle of obese individuals. Further investigations need to be pursued to determine the role of IMAT reduction in relation to IR and weight loss.

### *1.8.6 Weight Loss and Adipocytokines*

Adipocytokine levels have been shown to change following a weight loss program. Monzillo et al. (2003) performed a 26-week caloric restriction and moderate physical activity intervention in twenty-four obese subjects with normal and impaired glucose tolerance, as well as T2DM (BMI between 30-40). After a 6.9-± 0.1 kg weight loss, a significant reduction occurred in all leptin groups (27.8 ± 3 vs. 23.6 ± 3 ng/mL, $p = 0.01$), while a significant increase of Acrp30 occurred only in the diabetic group (7.3±1 vs. 9.4±2 $\mu$g/mL, p=0.01). These results coincided with a significant increase in insulin sensitivity index (2.9 ± 0.4 vs. 1.85 ± 0.3 x $10^{-4} \cdot min^{-1} \cdot (mU/mL)^{-1}$, $p < 0.001$). A study by Hotta et al. (2000) showed weight reduction significantly increased Acrp30 levels in diabetics and non-diabetic obese individuals, however there was a more of an increase in the diabetic group. Finally, a weight loss (>10 %) study (Xenachis et al., 2001) in 48 morbid obese subjects following a very low calorie diet (800 kcal/d) for ten weeks, reduced leptin serum levels by 50% and TNF-$\alpha$ by 48%. However, TNF-$\alpha$ has not always shown a significant decrease following weight reduction (Monzillo et al., 2003). Bastard et al. (2000) observed that a 3 kg weight loss in obese women demonstrated no significant changes in TNF-$\alpha$. Further investigations need to be pursued to investigate the relationship between adipocytokines, weight loss and their role in metabolic function.

### *1.8.7 Weight Re-gain*

Despite the numerous studies that have shown behavioural intervention through physical activity and caloric restriction can create a weight reduction; the real challenge lies in keeping the weight off. This was shown in a follow up study of 77 obese women who participated in a 48-week diet and behaviour modification program (Wadden et al., 1998). These women lost an average of 13.5 kg following the intervention, among them; 35-55% gained their weight back in a year. This example helps to represent difficulties of obese individuals to integrate a healthy lifestyle that will help to maintain the weight loss. Therefore, pharmaceutical intervention may possibly be the next approach in the battle against obesity.

## 1.9 Pharmaceutical Reagents

There are currently two drugs that have been approved by the Federal Drug Agency that are being used in the treatment of obesity (Sjostrom et al., 1998; Bray et al., 1999). The first of these drugs is Sibutramine, commercially known as MERIDIA. This drugs acts centrally to decrease food intake and increase thermogenesis. It blocks the reuptake of serotonin and norepinephrine at the post-synaptic neuron (Mcneely & Goa, 1998). This drug has proven in several studies to be effective in weight loss, showing that subjects have been able to lose 5-8% of their body weight from baseline values, independently from behavioural approach (Mcneely & Goa, 1998; Bray et al., 1999; Kim et al., 2003; Ryan, 2004). However, since norepinephrine plasma levels are elevated, it may cause an increase in heart rate and/or blood pressure (Bray et al., 1999; Kim et al., 2003). Sibutramine treated patients have shown a significant increase in systolic BP by 1.7 to 8.4%, while showing a significant increase in diastolic BP by 3.8 to 8%. Patients showing

a increase in BP (≥10 mmHg) or heart rate (≥10 bpm) are recommended to discontinue use, while caution must be given in administering Sibutramine to patients with controlled hypertension and is contraindicated to patients with unstable or poorly controlled hypertension. However, not all subjects experience an increase in BP, therefore individuals should be monitored on a case-by-case basis (*Canadian pharmacists association. compendium of pharmaceuticals and specialties: The Canadian drug reference for health professionals.* 2005).

Orlistat (XENICAL) is another long-term obesity reagent that acts peripherally. It is an inhibitor of the gastrointestinal enzyme pancreatic lipase by forming a covalent bond with the active serine site, inhibiting it to hydrolyze triglycerides into the absorbable free-fatty acids and monoglycerides (Zhi et al., 1994) It decreases the amount of fat absorbed by about 30% with the administration of 120 mg 3 times a day. Non-absorbed fat is then excreted without being digested. Concerns in regard to this drug is the gastrointestinal adverse events and the reduction of uptake of the fat-soluble vitamins A, D, E and K, however the latter has yet to be proven and can be minimized by taking a multivitamin two hours before or after the ingestion of Orlistat. Also, a diet lower in fat will minimize the amount of gastrointestinal distress. It has been shown that hypertensive, obese subjects when supplemented with Orlistat have significantly decreased their body mass by 8% compared to the placebo group by 4%, when following a mild caloric reduction over a 56-week period (Sharma & Golay, 2002). Significant changes were also observed in systolic BP (–9.4 vs –4.6 mmHg) and in diastolic BP (-7.7 vs. –5.6 mmHg). In another long term study accompanied by a hypocaloric diet (deficit of 600 kcal/d), orlistat treated groups showed a significantly larger decrease than the placebo group in fasting plasma

glucose and insulin levels after two years (Sjostrom et al., 1998) However, as seen with Sibutramine, Orlistat treated patients also stabilize their weight loss at the six-month mark (Zhi et al., 1994).

### 1.10 Topiramate

Topiramate (*Appendix 1*) (Topamax) (TPM) is a sulfamate-substituted monosaccharide neurotherapeutic agent approved by over 75 countries worldwide for the treatment of selective seizure disorders (Reife et al., 2000; Topiramate (topamax) tablets, 2002; Wilding et al., 2004). During the treatment of these individuals, it was observed that weight loss was a side effect (Topiramate (topamax) tablets, 2002). Bray et al. (2003) was the first to present data on weight loss in humans with supplementation of Topiramate. In a healthy obese population, a significant decrease in weight, as well as BP was observed during a 24-week testing period in the TPM groups. There was a greater weight loss in the two groups with the higher supplementation of Topiramate (192 and 384 mg/d). All of these subjects followed the Johnson and Johnson lifestyle and weight managerial program known as "PATHWAYS TO CHANGE". The subjects reduced their caloric maintenance quota by 600 kcal/d.

A second study conducted by Wilding et al. (Wilding et al., 2004) included 1289 subjects with a BMI between 27 and 50 kg/m$^2$ including patients with controlled hypertension and/or dyslipidaemia. During the study they observed a significant weight loss and BP reduction in the TPM groups, with the two higher dosages (192 & 256 mg/d) resulting in a greater BP reduction compared to the lower dose (96 mg/d). Improvements in fasting plasma glucose and insulin levels were also observed. The study was originally scheduled to last two years, but the sponsor ended the trial because they were developing

a slow released method of the drug to decrease the frequency of side effects such as paresthesia, lack of concentration, depression and metabolic acidosis. Despite the trial being cut short, it was observed that there was a continual weight loss up to the 60$^{th}$ week (14 month).

Astrup et al. (2004) performed a study on obese individuals who achieved a weight loss of 8% using a behavioral tool intervention, as well as a caloric intake between 800 to 1000 kcal/d for eight weeks, followed by TPM supplementation. Throughout the duration of the study, subjects met with clinical staff members one-to-one to discuss topics such as diet, nutrition, physical activity, psychosocial structuring and support. After the eight-week intervention trial, subjects were placed on a caloric restriction of 600 kcal/d less then their daily energy expenditure and randomly divided into three groups (placebo, 96mg/d and 192mg/d). It was observed that the subjects in the placebo group started to regain some of their weight back after the 24$^{th}$ week, while those in the TPM groups continued to lose weight up to week 44. It was also observed that drug efficacy was similar between the 96 and 192 mg/d dose. This observation is especially appealing because there is less side affects reported with lower TPM dosages (Astrup et al., 2004). Although all groups experienced a reduction in systolic BP and diastolic BP from baseline up to week 44, the 96 mg/d and 192 mg/d groups showed a significantly greater systolic BP reduction compared to the placebo group. However, there was no significant difference in regards to diastolic BP for the 96 mg/d group compared to the placebo, despite the 96 mg/d group showing a higher decrease in diastolic blood pressure. This study provides more evidence regarding TPMs' ability to be used as a long-term weight

maintenance drug and improve metabolic and physiologic complications associated with obesity.

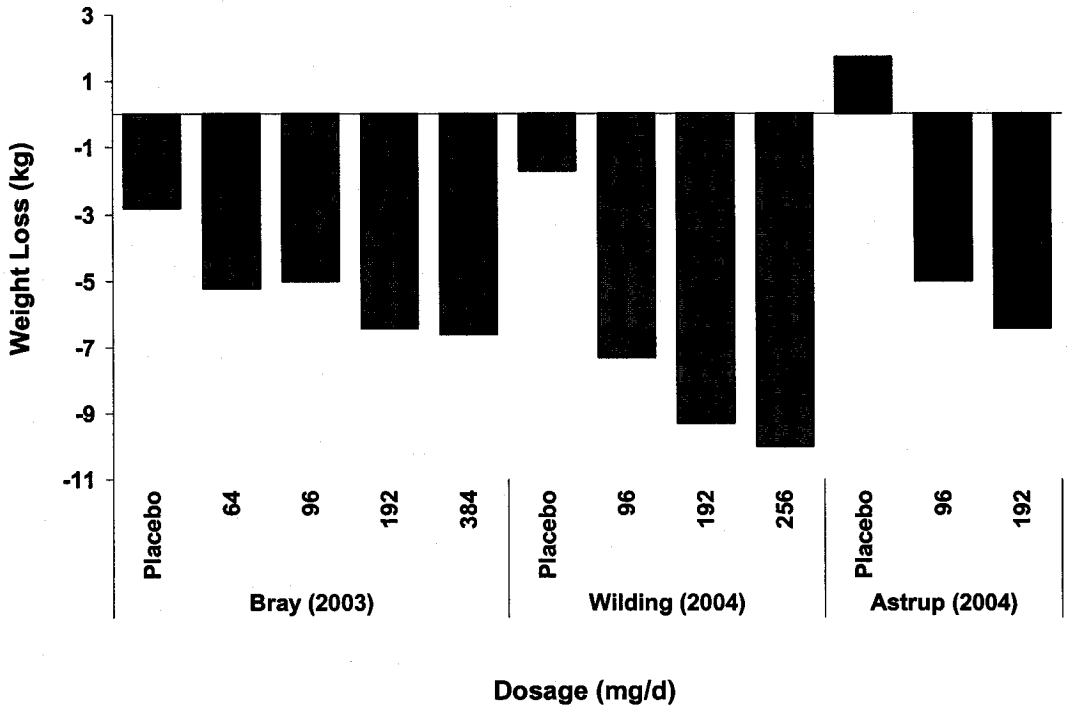


**Figure 2:** Effect of Topiramate dosage on weight loss

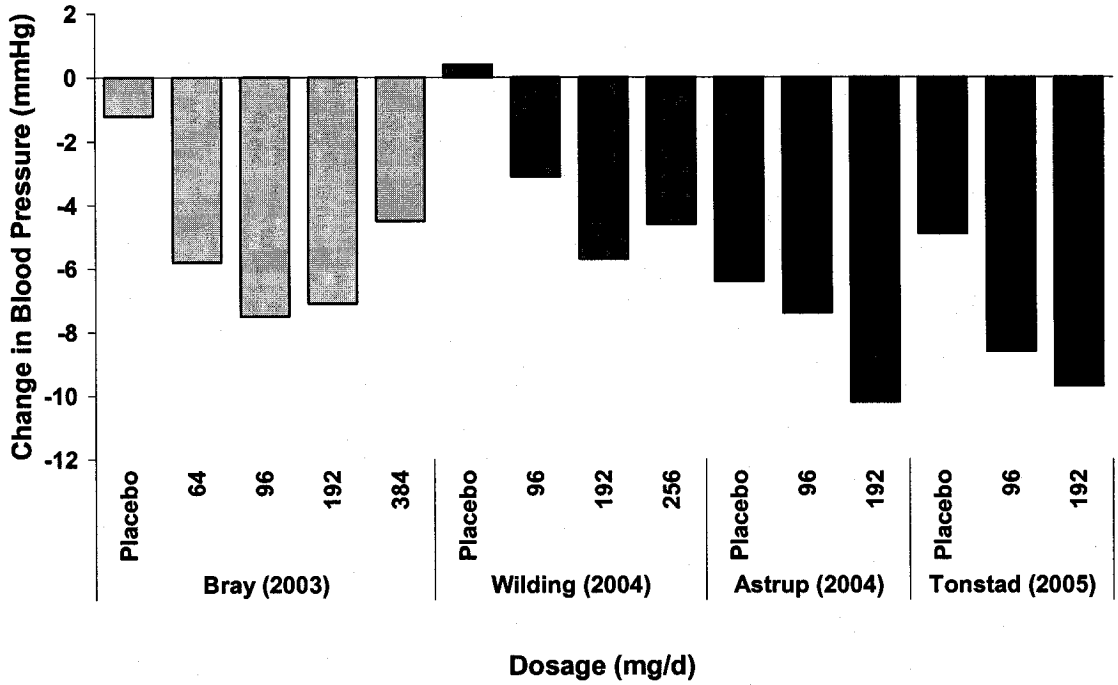


**Figure 3:** Effect of Topiramate dosage on resting systolic blood pressure

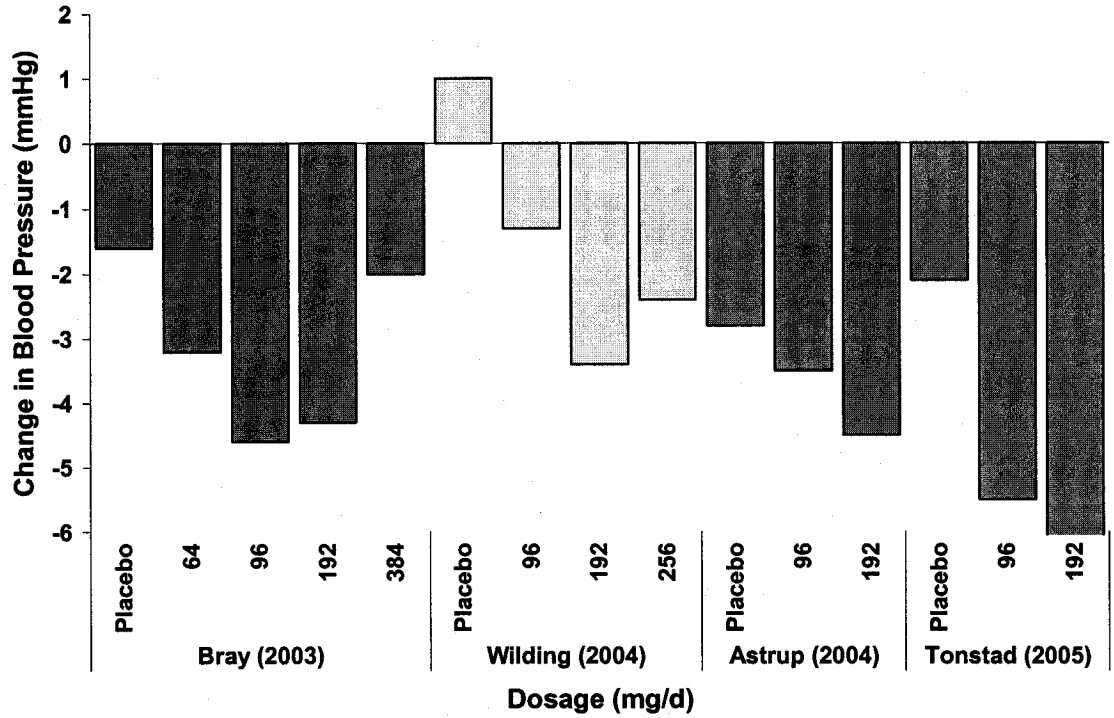


**Figure 4:** Effect of Topiramate dosage on resting diastolic blood pressure

**Table 1:** Studies reporting the effects of Topiramate on weight loss and metabolic indicies

| Authors | Design | # Subjects and criteria | Dosage (mg/d) | Weight loss and lipid profile | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Weight | Chol. | TG | LDL | HDL |
| **Bray et al.** 2003 | Randomized-Double Blind for 24-weeks (titration varied depending on dosage) | 385: 18-75 years of age health, obese subjects with a BMI of ≥30 to < 50 kg/m² or ≥27 to <50 kg/m² if subject had controlled hypertension and/or dyslipidemia. | Placebo | → | | | | |
| | | | 64 | ↓ | | | | |
| | | | 96 | ↓ | | | | |
| | | | 192 | ↓ | | | | |
| | | | 384 | ↓ | | | | |
| **Wilding et al.** 2004 | Randomized, double-blind placebo-controlled study (8 week titration, maintenance up to 83 weeks) | 1289: 18-75 years of age with a BMI of ≥30 to < 50 kg/m² or ≥27 to <50 kg/m² if subject had controlled hypertension and/or dyslipidemia. | Placebo | → | ↑ | → | ↑ | ↑ |
| | | | 96 | ↓ | ↓ | → | ↓ | ↑ |
| | | | 192 | ↓ | → | → | → | → |
| | | | 256 | ↓ | → | → | ↓ | → |
| **Astrup et al.** 2004 | Randomized, double-blind, placebo-controlled study to 44 weeks (8 week titration-36-week maintenance) following ≥ 8% reduction of initial body weight | 293 subjects were analyzed for efficacy: 18-75 years of age with a BMI of ≥30 to < 50 kg/m². Subjects were eligible with controlled hypertension and/or dyslipidemia | Placebo | → | → | → | → | → |
| | | | 96 | ↓ | ↓ | ↓ | → | → |
| | | | 192 | ↓ | ↓ | ↓ | → | ↑ |
| **Tonstad et al.** 2005 | Randomized, double-blind, placebo-controlled trial (8 week titration, maintenance 28 weeks) | 531: 18-75 years of age with a BMI of ≥27 to <50 kg/m². Stage 1 or 2 essential hypertension at enrollment. Sitting SBP between 140-190 mmHg and / or a sitting DBP between 90-110 mmHg. | Placebo | → | → | → | → | → |
| | | | 96 | ↓ | → | ↓ | → | → |
| | | | 192 | ↓ | → | → | → | → |

↓ Significant decrease
→ No change
↑ Significant increase

### *1.10.1 Potential Mechanisms of Topiramate in Relation to Weight Loss and/or Blood Pressure*

Topiramate affects the central nervous system, thereby contributing to its antiepileptic properties (White, 2003). It has multiple biochemical/ pharmacologic effects that may

explain the varying range of nervous system functions. It is a weak carbonic anhydrase inhibitor that probably enhances the side effect paresthesia (Wilding et al., 2004). Another possible side effect of being a carbonic anhydrase inhibitor is that it may cause metabolic acidosis by indirectly affecting the excitatory and inhibitory pH-dependent neurotransmitter system (Ozer & Altunkaya, 2004) However, the mechanism of how TPM affects weight loss is still yet to be determined (Astrup et al., 2004; Wilding et al., 2004). Two potential mechanisms that may create a negative energy balance associated with TPM supplementation are a decrease in appetite and a decrease in efficiency of energy utilization. Both of these have been shown in a variety of animal models (Picard et al., 2000).

*1.10.1.1Topiramate and Energy Efficiency*

Investigations in female Sprague-Dawley rats were supplemented with TPM have shown an increase in brown adipose tissue lipoprotein lipase activity, suggesting that TPM could activate brown adipose tissue thermogenesis (Richard et al., 2000; Richard et al., 2002). However, adult humans have limited amounts of brown adipose tissue in the body, limiting the importance of this discovery in relation to human weight loss. Topiramate also increases skeletal and cardiac lipoprotein lipase activity, potentiating a possible mechanism in energy expenditure (Richard et al., 2000). Furthermore, TPM enhances the expression of uncoupling proteins 2 and 3 in skeletal muscle and adipose tissue in Osborne-Mendel rats, thus decreasing energy efficiency (York et al., 2000).

Despite the support that TPM influences the efficiency of energy utilization in a variety of animals, limited studies have been performed on humans. A recent sub-analysis of the data for the present study by Tremblay et al. (submitted) has shown that TPM

showed no effect on energy expenditure (as measured by indirect calorimetry) in abdominally obese males. However, it was shown that the subjects reduced their energy intake and that could be a significant factor by which TPM produces a negative energy balance.

*1.10.1.2 Topiramate and Food Consumption*

One of its pharmaceutical alterations that may influence food consumption is TPM ability to positively influence the activity of gamma aminobutyric acid (GABA) at the GABA-A receptors, a property which enhances its anticonvulsive effect (White, 2003). GABA is the major inhibitory neurotransmitter in the brain. It acts as an anti-stress, anti-anxiety, muscle relaxant, while helping to display a calming effect upon 25-40% of brain synapses while allowing the cell to hyperpolarize inhibiting nerve activity (Owens et al., 1999). Topiramate binds to allosteric GABA-A receptors through a non-benzodiazepine mechanism and second-messenger system (White et al., 2000). Bray et al. (2003) have suggested that the modulation of GABA receptors may appear to be a potential mechanism for weight loss. However, other anticonvulsant drugs such as valproate and benzodiazepine that enhance the activity of GABA-A receptor have shown to promote weight gain (Ketter et al., 1999), leading to the speculation that with supplementation of TPM, enhancement of GABA-A receptors would favor a positive energy balance. Microinjections of the GABA-A receptor agonist muscimol into the hypothalamic subnuclei, paraventricular nucleus, ventromedial nucleus and lateral hypothalamus stimulates food intake in rat models (Tsujii & Bray, 1991; Pu et al., 1999; Sheng et al., 2006). Furthermore, NPY neurons in the arcuate nucleus co-express agouti related protein and GABA, in which both have been shown to act with NPY to enhance feeding

(Kalra & Kalra, 2004). However, a study by Pu et al. (1999) suggest that GABA and NPY may act through distinct receptors and second messenger systems to stimulate food intake, following NPY and muscimol injections into the paraventricular nucleus in rat models. In addition, Cowley et al. (2001) has shown that GABA may inhibit the appetite-suppressing peptide proopiomelancortin neurons (suggesting they display the GABA-A receptors), adding strength to the notion that GABA will enhance feeding. Future investigations are warranted to determine the specific mechanism how supplementation of TPM associates with GABA to either act as an orexigenic or as an anorectic agent. However, it is suggested that the action of TPM on the GABA system is not predominant in regards to creating a negative energy balance.

Topiramate is also an antagonist at the alphaamino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate type glutamate receptor, but not at the methyl-aspartate receptor (Rogawski & Porter, 1990; Gibbs et al., 2000). Glutamate is the predominant excitatory neurotransmitter in the brain (Robinson, 1998) and it is suggested that the inhibition of glutamate will cause a decrease in appetite (Ketter et al., 1999). Animal models show that by microinjecting glutamate or glutamate agonists (excitatory amino acids, kainic acid and AMPA) into the lateral hypothalamus, stimulation of an increase in food occurs in satiated rats (Stanley et al., 1993). Further, Ketter et al. suggest (1999) anticonvulsant drugs such as TPM might contribute to suppress appetite and regain control to prevent over eating. This may potentially explain the role of TPM in binge eating disorders.

Another possible reasoning that may decrease energy intake is one of the possible side effects of Topiramate. Since it can alter the taste of food, cause gastrointestinal

irritation and possible nausea in some individuals, it is natural occurrence for these subjects to eat less. However, Tremblay et al. (submitted) have shown that eating traits such as perceived hunger, fullness, desire to eat and prospective food consumption were not significantly different from the placebo group following TPM supplementation.

*1.10.1.3 Topiramate and Blood Pressure Reduction*

To date, there have been no studies performed that focus on the mechanism involved in blood pressure reduction following TPM supplementation. However, studies have been performed that may be related to this parameter (Bray et al., 2003; Wilding et al., 2004; Astrup et al., 2004). Topiramate is also known to be an effective drug in the treatment of bipolar disorders (White, 2003). During an acute manic situation, there are higher catecholamine levels. Supplementation of TPM is expected to decrease the release of catecholamines by displaying state-dependent blockade of voltage-dependent sodium or calcium channels (White, 2003). Since higher plasma levels of norepinephrine are associated with an increase in BP (as seen in obese and hypertensive (Chobanian et al. 1978) patients), the decrease caused by TPM may provide as a potential mechanism of how BP is reduced in subjects supplemented with Topiramate.

Another aspect of how TPM may affect the reduction of BP is with the previously described relationship with insulin resistance. After controlling for weight loss, Wilkes et al. (2005) have showed that TPM treated female Zucker diabetic fatty rats produced lower fasting glucose levels, as well as a 30% increase in glucose disposal following a euglycemic-hyperinsulinemic clamp. Further, TPM treated rats showed 30 to 60% increased hepatic glucose output suppression and increased FA suppression from 40 to 75%. However, insulin sensitivity was only observed in adipocytes and not muscle when

tissue samples were studied *ex vivo* or *in vitro*. Therefore, the *in vivo* actions of TPM seem to be exerted through adipose tissue. Wilkes et al. (2005) explains that the potential reason the insulin sensitizing effect of TPM in muscle strips was not detectable during *ex vivo* and *in vitro* is that TPM may allow insulin-resistant adipocytes to communicate *in vivo* to other targeted insulin tissues. Adipocytokines or another mediator that is not preserved when removed from the *in vivo* environment may help perform this action. Further, TPM may improve insulin sensitivity by promoting lower plasma FFA as observed between the treatment and control group, signifying that TPM treatment improves insulins' antilipolytic effects (Wilkes et al, 2005). Either way, with an increase in insulin sensitivity, decreased plasma glucose and FFA levels, it can be speculated that the reduction in blood pressure may be related to mechanistic abilities of TPM supplementation.

In summary, three studies (Bray et al., 2003; Astrup et al., 2004; Wilding et al., 2004) have shown a reduction in body weight and in resting BP with the supplementation of Topiramate. However, no studies have measured ABP following TPM supplementation in abdominally obese men. Further, the original investigation in this retrospective analysis was the first to document a change in abdominal obesity following TPM supplementation.

### 1.11 Advantages of Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring is considered a more accurate measurement of BP due to its' ability to account for circadian variation and white coat hypertension (McGrath, 2002). Furthermore, ABP has a greater ability in assessing the antihypertensive effect when BP reduction occurs, while reducing the placebo effect on

BP to low levels (Coats, 1996). This is beneficial as an important clinical application as nighttime BP is thought to be a better prediction of coronary artery disease (Staessen et al., 1998). Ambulatory blood pressure measurement has also been associated with accumulation of visceral adipose tissue. Studies in abdominally obese men (Lefebvre et al., 2003) and women (Faria et al., 2002) have showed VAT was positively correlated with ambulatory systolic blood pressure.

Since ABP considers the circadian variation and that nighttime BP is consistently lower than daytime values, normal values will differ. Normality measurements for ABP have been based upon calculations from larger and smaller cohorts of subjects previously defined as normotensive by casual BP measurements. The PAMELA study was one of these cohorts that displayed the upper limit of normal BP to be 140/90 mmHg by casual BP measurement. These same values corresponded to a 24-h ABP of 119-126/75-80 mmHg and 125-132/80-85 mmHg for daytime ambulatory blood pressure. Further, the difference between casual and ABP increased in line with increasing casual BP measurements ($r=0.79$ and 0.66 respectively for systolic and diastolic BP) (Mancia et al., 1995). Another study by Staessen et al. (1993) determined that upper limit of normality by casual BP measurements was 140/90 mmHg, compared to ABP measurements of 133/82 mmHg in the $95^{th}$ percentile of the normotensive group. Sica (2005) determined that abnormal values for ABP to be > 130/80 mmHg for the 24-hour period, > 135/85 mmHg for daytime and > 120/75 mmHg for nighttime. These studies have shown ABP measurements are consistently lower, than casual BP measurements and that it has to be taken into consideration when determining hypertension.

# Chapter II: Research Project

## 2.1 Research Question and Objectives

The research question and primary objective for this study is to determine the effect of six months of TPM supplementation use for weight loss on ABP in abdominally obese males. Secondary objectives are to determine the association between changes in insulin area under the curve (AUC), glucose AUC, change in body weight, body fat free mass, % body fat, body fat mass, total abdominal fat, abdominal subcutaneous and VAT changes in relation to 24-hr systolic and diastolic ambulatory blood pressure.

## 2.2 Hypothesis

The primary hypothesis of this study is that the TPM treatment group will show a greater decrease in ABP then the placebo. The secondary hypothesis is that the reduction of ABP will be related to the decrease in visceral adipose tissue. Finally, the TPM treatment group will show a greater improvement in metabolic syndrome indicies compared to the placebo group.

## 2.3 Rationale and Significance of the Study

The health problems associated with obesity have risen dramatically in the past 20 years. Abdominally obesity (predominantly VAT accumulation) is closely related to IR, thus increasing the risk of the metabolic syndrome. These abdominally obese individuals are at a higher risk of health related disorders such as coronary artery disease, hypertension, dyslipidemia, T2DM, some forms of cancer, sleep apnea and many other related disorders. Non-pharmaceutical treatments of obesity have limited long-term effect on body weight. The original investigation was sought out to produce a novel anti-obesity

agent, however TPM trials have been discontinued in the battle against obesity due to adverse events. Nonetheless, it still may be beneficial to determine if TPM has an antihypertensive effect in abdominally obese males (abdominally obese males were specified in the original investigation due to the increased accumulation of VAT in this population group). This may then be related to other population groups such as those affected with mood disorders that may use TPM in addition to their other medications. The effect of TPM on ABP has also not been investigated. Ambulatory blood pressure monitoring, as mentioned in the previous section, is a superior method over casual BP measurements. Furthermore, it has not been determined if the change in BP is due to the reduction in weight loss or due to an antihypertensive effect created by Topiramate. This retrospective analysis will add to the literature of TPM mechanistic abilities in regards to BP control.

### 2.4 Assumptions, Limitations and Delimitations

The proposed study assumes that the subjects answered the questionnaires accurately and cooperated fully for the set of guidelines throughout the duration of the testing. It is also assumed that all testing methods such as ABP monitoring, hydrostatic weighing, computed tomography (CT) scan and oral glucose tolerance test (OGTT) were valid and all experimenters assisting in the project conducted the testing and collected the data in a professional manner

A limitation was the inclusion of only male subjects with abdominal obesity, hindering the ability to create a general consensus for the population.

# Chapter III: Methodology

## 3.1 Retrospective Analysis

This investigation uses a secondary data collection to answer the hypothesis proposed. Even though the original methodology was designed to determine the change in abdominal obesity with the supplementation of TPM, there was a substantial amount of secondary data that was collected and it is from here the basis of this investigation can occur.

## 3.2 Description of the Study

This investigation was originally led by Dr. Denis Prud'homme, who was the first principal investigator in this R.W. Johnson funded project; The Safety and Efficacy of Topiramate (RWJ-17021-000) in Males with Abdominal Obesity: A 6 Month Double-Blind Randomized Placebo-Controlled Study with a 6 Month Open-Label Extension (Protocol TOPMST-OBMA-001; Phase 2).

## 3.3 Selection of Subjects

Sixty-eight males with abdominal obesity (Waist circumference >100 cm) were recruited for this investigation. All of these subjects were volunteers and were recruited by advertising in local newspapers. The following were the inclusion factors for the original study:

1. Male subjects ages between 25 to 55.
2. BMI >27 and < 35 kg/m$^2$.
3. Waist circumference >100 cm.
4. Stable weight (varying no more than 4 kg) for two months prior to study.

5. Sedentary (< 1 session of moderate physical activity lasting 30 minutes/week).
6. Dyslipidemic with:

    a) triglyceride levels >1.9 mmol/L and <4.5 mmol/L

    b) total cholesterol level <6.2 mmol/L

    c) LDL-cholesterol levels <4.1 mmol/L

    d) HDL-cholesterol concentration <1.2 mmol/L
7. Not have smoked for six months or more prior to the study.
8. Not consume more than 9 drinks a week of alcohol
9. Be legally capable of giving consent and must understand what their participation in this study entails, the potential risks and benefits, as well as their freedom to withdraw from the study at any time without any prejudice to subsequent medical arrangement, and sign an informed consent.

The exclusion factors were:

1. Endocrine diseases (hypothyroidism, hyperthyroidism) or other physical causes of obesity.
2. Significant hepatic liver function tests (LFTs >2 times the upper limit of normal) or renal disease (serum creatinine >2.0 micro mol/L)
3. History of schizophrenia, psychotic, or major affective disorder.
4. Epilepsy.
5. History of eating disorders (i.e. Bulimia nervosa or anorexia nervosa).
6. Cardiovascular disease requiring medication or limiting physical activity.
7. Fasting plasma glucose >7.0 mmol/L as defined by the National Diabetes data group.

8. Hypertension requiring medication or a systolic BP > 160 mmHg and/or diastolic BP >95 mmHg without medication.
9. Taking medication that could interfere with the mechanism of action or metabolism of Topiramate within three months prior to enrolment (Appendix 2).
10. Taking mediation known to alter blood pressure, plasma lipids, plasma glucose and/or insulin, within 28 days of enrolment.
11. Any severe systemic illness
12. Hypersensitivity or contraindications to the study drug.
13. Surgery planned during the investigation.
14. A problem of alcohol abuse.
15. Unlikely to cooperate fully in the study
16. History of nephrolithrosis.
17. Participated in an investigational study or received and experimental drug or used an experimental medical device within three months of enrolment.
18. Cancer or other illness that precludes survival.

### 3.4 Research Protocol

The subjects were randomly assigned to the Topiramate or placebo group. This investigation used a randomized pre-test/post-test control group design. The study group were then gradually introduced to the drug over a 12 week titration period to 200 mg b.i.d. or their maximum tolerated dose (up to 400 mg/d). They were given 25 mg/d the first week, which was then increased by 25 mg every week until 200 mg/ d was reached. The dose was then increased by 50 mg every week until the desired dosage was reached. This was followed by a 12-week stabilization period in the TPM group followed by a

gradual withdrawal. However, most of the subjects did not reach the recommended dosage and continued the study at their maximum tolerated dosage. The distribution of subjects' daily dosage is present in *Table 2.* The dose of 200 mg/d b.i.d. was recommended by the Janssen Ortho Company. This was based on the results of weight loss seen in epileptic patients, as the average recommended dosage for treatment is 400 mg/d with the maximum being 1 g/d. Subjects were not exposed to any dietary restrictions or behavioral intervention. This was a double blind experiment method, in which neither the subjects nor the investigators administering the drug know who is getting the drug or the placebo. This double blind method is used to eliminate the error of experimental bias. Adverse events were documented during the experiment by a physician.

**Table 2:** Distribution of subjects by daily dose

| | Placebo (N=35) | | | Topiramate (N=33) | | |
|---|---|---|---|---|---|---|
| **Dose (mg)** | **Average Daily Dose N (%)** | **Maximum Dose N (%)** | **Last Maintained Dose N (%)** | **Average Daily Dose N (%)** | **Maximum Dose N (%)** | **Last Maintained Dose N (%)** |
| **≤ 100** | 4 (11) | 1(3) | 2(6) | 13(39) | 7(21) | 11(33) |
| **101-200** | 3(9) | 5(14) | 4(11) | 12(36) | 12(36) | 11(33) |
| **201-300** | 28(80) | 1(3) | 2(6) | 8(24) | 5(15) | 2(6) |
| **≥ 301** | 0(0) | 28(80) | 27(77) | 0(0) | 9(27) | 9(27) |
| **N** | 35 | 35 | 35 | 33 | 33 | 33 |
| **Mean** | 252.74 | 351.7 | 338.3 | 148.9 | 219.4 | 201.0 |
| **SD** | ± 78.21 | ± 102.11 | ± 106.75 | ± 92.57 | ± 125.58 | ± 133.90 |
| **Median** | 389.3 | 400.00 | 400.00 | 118.00 | 175.00 | 175.00 |
| **Range** | 50.0, 300.0 | 75.0, 400.0 | 75.0, 400.0 | 25.3, 300.0 | 28.6, 400.0 | 25.0, 400.0 |

All of the subjects returned on a bi-weekly basis to have weight, BP and AE monitored, while the other measurements were performed as present in *Table 3.* Upon the six-month, all of the subjects were placed in an open-label study (subjects and investigators know what they are taking) in which all of the subjects were introduced to

the drug at the same rate as the double blind study. However, data analyzed for this report was only from the double-blind phase of this study.

**Table 3:** Time and event schedule for subjects in the study

| | Screening | Baseline | Every 2 weeks During the titration period | Month 3 | Month 6 |
|---|---|---|---|---|---|
| **Informed consent** | x | | | | |
| **Medical history** | x | | | | |
| **Inclusion/ Exclusion Criteria** | x | x | | | |
| **Weight and BP, Physical Examination** | x | x | | | x |
| **Waist Circumference** | | | | | |
| ***ABP and Pulse Rate Monitoring** | x | x | | | x |
| **Anthropometric Measurements** | | x | | x | x |
| **Hydrostatic weighing** | | x | | x | x |
| **Computed tomography** | | x | | x | x |
| **Glucose, insulin, glucose tolerance test** | | x | | x | x |
| **Adverse Events[2]** | | x | x | x | x |
| **Dispense/collect medications** | | x | x | x | x |

* ABP- Ambulatory Blood Pressure

[2] It is to be noted that all subjects were encouraged to address adverse events (side affects) to the study physician.

(Adapted from Protocol TOPMAT-OBMA-001)

## 3.5 Data Collection

### *3.5.1 Anthropometric Measurements*

Weight, height and BMI were determined following the procedures of the National Institute of Health conference (Lohman et al., 1988) on the standardization of anthropometric measurements. The waist and hip circumference was measured following the recommendations of van der Kooy and Seidell (van der Kooy, K. & Seidell, 1993; Seidell, 2000).

### *3.5.2 Body Composition Measurements*

#### *3.5.2.1 Computed Tomography*

The abdominal adipose tissue was measured using a CT scan performed at baseline and six months during the study. The CT scan was performed on a Siemens Somatom DRH scanner (Erlangen, FRG) using the procedures described by Sjostrom et al. (1986). The subjects were examined in supine position with their arms stretched above the head. Three CT scans were performed using a radiograph of the skeleton as the reference to establish the position of the scans at the nearest mm at L4-L5. Total and VAT areas were calculated by delineating with a graph pen the areas and then computing the adipose surfaces using an attenuation range of -190 to –30 HU for adipose tissue (Sjostrom et al., 1986). Visceral adipose tissue was measured by outlining the muscle wall that surrounds the abdominal cavity. Subcutaneous adipose tissue was calculated by subtracting total abdominal fat minus the visceral adipose tissue (Ferland et al., 1989). The digital image that was generated was analyzed with National Health Institute-image software (version 1.55, NIH, Bethesda, MD). Adipose tissue areas were then calculated based on the method described by Lemieux (Lemieux, 1999) and has been validated by Lemieux et al. (1999). During this trial, the CT scanner at the study site became inoperative and was replaced. Therefore, some subjects had their baseline and six-month CT measurements of VAT performed on different CT scan machines. As a result, to reduce possibility of error, a reread of all CT images was performed.

#### *3.5.2.2 Hydrostatic Weighing*

Body density was obtained from the mean of six measurements with the hydrostatic weighing technique (Behnke et al., 1974). Before immersion into the hydrostatic tank, the

helium dilution method of Meneely and Kaltreider (1949) was used to determine the pulmonary residual volume. The percentage of total body fat was determined from body density with the equation determined by Siri (1956). Body FM and fat-free mass were estimated from body weight and the derived percentage of body fat.

### *3.5.3 Blood Pressure*

Resting BP was measured at baseline and every month throughout experimentation by casual blood pressure methods with a sphygmometer. Measurements were taken after the subjects have been sitting and resting for at least three minutes. Three measurements were taken and the mean BP was calculated. Ambulatory blood pressure was measured by Spacelabs Medical, Model # 90207-31 that was attached to the subjects arm to monitor BP every half hour during the day (Between 8:00 am to 10:00 pm) and every hour during the evening (Between 10:00 pm and 8:00 am) during a 24-hour period at baseline and at six months. Subjects were asked to carry out normal activities throughout the day and were instructed to keep the arm at rest during measurements. The mean of the day, night and total 24-hour measurements were calculated. During the original investigation, validation of Spacelabs Medical, Model # 90207-31 was not performed. However, validation was performed on this particular model by O'Brien et al. (1991), in which it was recommended in resting individuals according to the British Hypertension Society protocol.

### *3.5.4 Plasma Glucose and Insulin*

Subjects arrived early in morning following a 12-hour fast to complete an Oral Glucose Tolerance Test. They rested comfortably in a semi-reclined position and two blood samples were obtained in 15 minutes for fasting glucose and insulin

determinations. The subjects drank 300 mL solution containing 75 g of glucose in 3 minutes. Blood samples were collected in tubes containing ethylenediaminetetraacetic acid and Trasylol (Miles Pharmaceutics, Rexdale, Ontario, Canada) through a venous catheter from an antecubital vein at 15, 30, 45, 60, 90, 120, 150 and 180 minutes following the ingestion of glucose. Plasma glucose was assayed enzymatically using a Beckman Glucose Analyzer II (Vitros 950, Johnson & Johnson, Clinical Diagnostics Inc, Rochester, NY, USA) whereas plasma insulin concentration will be measured by radioimmunoassay with polyethylene glycol separation (Despres et al., 1996).

### *3.5.5 Plasma Lipids*

For measurement of plasma lipoprotein, blood samples were collected from an antecubital vein into Vacutainer tubes containing ethylenediaminetetraacetic acid. Samples were taken in the morning after a 12-hour fast while the subjects were in a supine position. Plasma was separated immediately after blood collection by centrifugation at 3000 rpm for 10 minutes at 4°C. Triglyceride and cholesterol concentrations were determined enzymatically in total plasma on a RA-1000 Auto-Analyzer (Technicon Instruments Corporation, Tarrytown, NY). Each plasma sample was then separated by a 12-hour ultracentrifugation (50, 000 rpm) in a Beckman 50.3 Ti rotor (Palo Alto, CA) at 4°C, in 6 mL Beckmans Quickseal tubes, which yielded 2 fractions: the TOP fraction containing VLDL ($d<1.006$ g/mL) and the BOTTOM fractions: consisting of triglyceride-poor lipoproteins ($d>1.006$ g/mL). The high density lipoprotein fraction was obtained after precipitation of LDL in the infranatant ($d>1.006$ g/mL) with heparin and MnCl2.

### 3.6 Statistics

Sample size was determined by ensuring that there was over 80% power, with a two-sided Type I error rate of 0.05. The estimate was based on a 3-month double-blind study of fenfluramine and placebo in a similar population of viscerally obese men (Prud'homme et al., 1997). An unpaired t-test was used to compare means of baseline characteristics of subjects in the safety population. The safety population received at least one dose of study drug, allowing for safety information from the beginning of treatment to be available.

Double Blind Modified intent-to-treat were the 67 subjects (n = 35 placebo and 32 treatment) randomized who received at least one dose of study drug, and provided at least one evaluation. An intent-to-treat analysis of the efficacy endpoints was conducted by using the last observation carried forward method. The completer population (29 placebo and 20 treatment) was the subjects who had at least 161 days of exposure to the study drug. An efficacy analysis was performed using both the completer and modified intent-to-treat population. Analyses presented based on the double-blind completer population used only data collected within 6 days after the last double-blind study drug dose.

Comparison between the placebo and treatment group was determined by using a two-sided unpaired t-test from baseline at month six. An Analysis of Covariance was performed to control for weight loss and to determine if the significant reduction of systolic and diastolic ABP was associated with Topiramate.

Two separate Simple Pearson correlation were performed using the primary endpoints of 24-hr systolic and diastolic ABP and each of the secondary efficacy endpoints of

insulin AUC, glucose AUC, change in bodyweight, body fat free mass, % body fat, body FM, total abdominal fat, abdominal subcutaneous and VAT in the completer population.

# Chapter IV: Results

## Participants

A total of 68 participants were randomized (N=35 placebo and 33 Treatment), with 48 completing the double-blind phase (n=29 placebo and 20 Treatment). The baseline characteristics of the subjects are shown in *Table 4.*

**Table 4:** Demographic and baseline characteristics of the modified intent to treat population

| | Placebo (n=35) | TPM (n=32) |
|---|---|---|
| **Age (years)** | 42.6 ± 7.75 | 43.5 ± 7.28 |
| **White (%)** | 97 | 100 |
| **Weight (kg)** | 97.6 ± 11.67 | 97.0 ± 8.43 |
| **BMI (kg/m²)** | 31.7 ± 2.64 | 31.2 ± 2.62 |
| **Systolic Blood Pressure (mmHg)** | 113.4 ± 11.19 | 114.4 ± 10.74 |
| **Diastolic Blood Pressure (mmHg)** | 79.7 ± 7.59 | 77.5 ± 7.65 |
| **Glucose (mmol/L)** | 5.8 ± 0.49 | 5.9 ± 0.53 |
| **Triglycerides (mmol/L)** | 2.6 ± 1.03 | 2.5 ± 0.90 |
| **Total Cholesterol (mmol/L)** | 4.9 ± 0.68 | 4.9 ± 0.67 |
| ***Visceral Adipose Tissue (cm²)** | 216.55 ± 53.66 | 234.05 ± 67.49 |
| ***Total Abdominal Adipose Tissue (cm²)** | 551.05 ± 93.66 | 574.32 ± 106.22 |
| ***Subcutaneous Adipose Tissue (cm²)** | 334.51 ± 100.82 | 340.72 ± 85.23 |
| **% Body Fat (using hydrostatic weighing)** | 30.93 ± 4.20 | 31.09 ± 4.40 |

Data are mean ± standard deviation
* N=31 subjects for TPM group

## Changes in Body Weight

Topiramate supplementation group showed a significant decrease in body weight (p=0.006), total body FM (p=0.002), percent total body fat (p=0.008) and fat-free body mass (p=0.011) *(Table 5)*. After six months, the TPM group lost on average 3.0 ± 4.48 kg of FM compared to 0.0 ± 2.52 kg in the placebo group. The percentage of total body fat showed a decrease of 2 ± 3.32 % compared to 0.1 ± 1.89 % in the placebo and fat free body mass showed a decrease of 1.3 ± 2.41 kg compared to a gain of 0.2 ± 1.75 kg in the placebo group. Topiramate subjects also significantly decreased their BMI by 1.2 ± 1.99 kg/m² (p=0.003) compared to 0.0 ± 0.97 kg in the placebo group.

**Table 5:** Changes in body composition from baseline to 6 months in the modified intent to treat population of TPM compared to the placebo group

| | Placebo (N=35) | Topiramate (N=32) | P Value |
|---|---|---|---|
| **Body Weight (kg)** | | | |
| *N* | 35 | 32 | |
| ***Baseline Mean*** | 97.6 ± 11.67 | 97.0 ± 8.43 | |
| ***Month 6 Mean (SD)*** | 97.6 ± 12.40 | 93.8 ± 11.16 | |
| ***Mean Change (SD)*** | -0.04 ± 3.02 | -3.19 ± 5.72 | 0.006 |
| **Body Mass Index** | | | |
| *N* | 33 | 29 | |
| ***Baseline Mean*** | 31.8 ± 2.63 | 32 ± 2.66 | |
| ***Month 6 Mean (SD)*** | 31.8 ± 2.80 | 30.8 ± 3.43 | |
| ***Mean Change (SD)*** | 0.0 ±0.97 | -1.2 ± 1.99 | 0.003 |
| **Total Body Fat Mass (kg)** | | | |
| *N* | 31 | 25 | |
| ***Baseline Mean*** | 30 ± 5.81 | 31.2 ± 5.82 | |
| ***Month 6 Mean (SD)*** | 30 ± 6.09 | 28.1 ± 7.25 | |
| ***Mean Change (SD)*** | 0.0 ± 2.52 | -3.0 ± 4.48 | 0.002 |
| **Percent Total Body Fat (%)** | | | |
| *N* | 31 | 25 | |
| ***Baseline Mean*** | 30.5 ± 3.74 | 31.8 ± 4.12 | |
| ***Month 6 Mean (SD)*** | 30.4 ±3.87 | 29.8 ± 5.12 | |
| ***Mean Change (SD)*** | -0.1 ± 1.89 | -2.0 ± 3.32 | 0.008 |
| **Fat Free Body Mass (kg)** | | | |
| *N* | 31 | 25 | |
| ***Baseline Mean*** | 68.1 ± 7.50 | 66.3 ± 5.56 | |
| ***Month 6 Mean (SD)*** | 68.3 ± 7.73 | 65.1 ± 6.43 | |
| ***Mean Change (SD)*** | 0.2 ± 1.75 | -1.3 ± 2.41 | 0.011 |

## Changes in Abdominal Adipose Tissue

No change in area of VAT was observed in the TPM group (-4.4 ± 67.88 $cm^2$) compared to an increase of +13.3 ± 42.41 $cm^2$ in the placebo group (p=0.237). However, a significant decrease of -32.7 ±45.06 $cm^2$; p=0.024 was detected in SAT in the TPM group compared to a decrease of -9.2 ± 30.07 $cm^2$ in the placebo group. This leads to a significant decrease in total area of abdominal tissue in the TPM group of -37.1 ± 96.15 $cm^2$; p=0.046) compared to an increase in the placebo group of 4.1 ± 52.02 $cm^2$ (*Table 6).*

**Table 6:** Changes in abdominal adipose tissue from baseline to 6 months in the modified intent to treat population

| | Placebo | Topiramate | P Value |
|---|---|---|---|
| **Area of Total Abdominal Adipose Tissue ($cm^2$)** | | | |
| ***N*** | 31 | 25 | |
| ***Baseline Mean*** | 553.3 ± 96.20 | 587.8 ± 93.31 | |
| ***Month 6 Mean (SD)*** | 557.5 ± 105.71 | 550.6 ± 134.56 | |
| ***Mean Change (SD)*** | 4.1 ± 52.02 | -37.1 ± 96.15 | 0.046 |
| **Area of Abdominal Subcutaneous Adipose Tissue ($cm^2$)** | | | |
| ***N*** | 31 | 25 | |
| ***Baseline Mean*** | 334.6 ± 104.47 | 349.7 ± 86.88 | |
| ***Month 6 Mean (SD)*** | 325.3 ± 94.75 | 315.9 ± 94.67 | |
| ***Mean Change (SD)*** | -9.2 ± 30.07 | -32.7 ± 45.06 | 0.024 |
| **Area of Abdominal Visceral Adipose Tissue ($cm^2$)** | | | |
| ***N*** | 31 | 25 | |
| ***Baseline Mean*** | 218.8 ± 55.23 | 238.1 ± 61.59 | |
| ***Month 6 Mean (SD)*** | 232.1 ± 55.75 | 234.7 ± 76.74 | |
| ***Mean Change (SD)*** | 13.3 ± 42.41 | -4.4 ± 67.88 | 0.237 |

## Changes in Metabolic Indicies

The lipid profile in the TPM group showed no significant changes in total cholesterol, triglycerides, HDL, LDL and total/HDL cholesterol ratio levels compared to the placebo group (*Table 7).*

**Table 7:** Changes in lipid profile from baseline to 6 months in the modified intent to treat population

| | Placebo | Topiramate | P Value |
|---|---|---|---|
| **Total Cholesterol (mmol/L)** | | | |
| *N* | 32 | 31 | |
| ***Baseline Mean (SD)*** | 4.89 ± 0.68 | 4.89 ± 0.67 | |
| ***Month 6 Mean (SD)*** | 4.87 ± 0.825 | 4.67 ± 0.710 | |
| ***Mean Change (SD)*** | -0.02 ± 0.484 | -0.21 ± 0.507 | 0.122 |
| **Triglycerides (mmol/L)** | | | |
| *N* | 32 | 31 | |
| ***Baseline Mean*** | 2.65 ± 1.03 | 2.53 ± 0.90 | |
| ***Month 6 Mean (SD)*** | 2.38 ± 0.906 | 2.18 ± 0.688 | |
| ***Mean Change (SD)*** | -0.27 ± 0.963 | -0.35 ± 0.754 | 0.726 |
| **HDL-Cholesterol (mmol/L)** | | | |
| *N* | 32 | 31 | |
| ***Baseline Mean*** | 0.88 ± 0.14 | 0.84 ± 0.16 | |
| ***Month 6 Mean (SD)*** | 0.89 ± 0.145 | 0.83 ± 0.163 | |
| ***Mean Change (SD)*** | 0.01 ± 0.139 | 0.00 ± 0.114 | 0.784 |
| **LDL-Cholesterol (mmol/L)** | | | |
| *N* | 32 | 31 | |
| ***Baseline Mean*** | 2.87 ± 0.65 | 2.98 ± 0.61 | |
| ***Month 6 Mean (SD)*** | 2.98 ± 0.712 | 2.90 ± 0.753 | |
| ***Mean Change (SD)*** | 0.11 ± 0.502 | -0.08 ± 0.353 | 0.077 |
| **Total-to-HDL Cholesterol Ratio** | | | |
| *N* | 32 | 31 | |
| ***Baseline Mean*** | 5.66 ± 1.00 | 6.02 ± 1.26 | |
| ***Month 6 Mean (SD)*** | 5.57 ± 0.940 | 5.72 ± 0.935 | |
| ***Mean Change (SD)*** | -0.09 ± 0.898 | -0.30 ± 0.802 | 0.327 |

Results of the OGTT as presented in *Table 8*, showed a significant decrease in glucose AUC of –54.1 ± 214.79 min*mmol/L; p=0.045 in the TPM group compared to an increase in the placebo group of 58.66 ± 171.87 min*mmol/L. However, insulin AUC was not significantly decreased in the TPM group (-9367.95± 45355.94 min*pmol/L; p= 0.297) compared to the placebo group (950.36 ± 22277.82 min*pmol/L).

**Table 8:** Changes in glucose and insulin area under the curve during the oral glucose tolerance test from baseline to month 6 in the modified intent to treat population

| AUC for: | Placebo | Topiramate | P value |
|---|---|---|---|
| **Glucose (min*mmol/L)** | | | |
| *N* | 28 | 22 | |
| ***Baseline Mean*** | 1413.78 ± 219.92 | 1490.59 ± 219.73 | |
| ***Month 6 mean (SD)*** | 1472.44 ± 344.39 | 1436.49 ± 188.86 | |
| ***Mean Change (SD)*** | 58.66 ± 171.87 | -54.1 ± 214.79 | 0.045 |
| **Insulin (min*pmol/L)** | | | |
| *N* | 28 | 22 | |
| ***Baseline Mean*** | 111717.50 ± 52573.73 | 103009.90 ± 47504.47 | |
| ***Month 6 mean (SD)*** | 112667.80 ± 55870.14 | 93642 ± 35327.85 | |
| ***Mean Change (SD)*** | 950.36 ± 22277.82 | -9367.95± 45355.94 | 0.297 |

Note: Only subjects with both baseline and post baseline values are included.

## Changes in Blood Pressure

We observed a significantly ABP reduction in the TPM group than the placebo in the intent-to-treat population. Systolic ABP decreased by -5.2 ± 9.79; p=0.006, -4.6 ± 10.90; p=0.011 and -6.9 ± 8.31; 0.003 mmHg in 24 hr, daytime and evening respectively, compared to an increase in the placebo of +2.1 ± 6.52, +2.6 ± 6.63 and +1.8 ± 9.03 mmHg. Diastolic ABP showed a -3.7 ± 6.13; p =0.006, -3.3 ± 7.08; p=0.033 and -4.3 ± 7.13; p=0.006 mmHg decrease, while the placebo showing an increase of +1.0 ± 4.91, +0.9 ± 5.66 and +1.8 ± 6.64 mmHg (*Table 9).* However, after performing an analysis of covariance to control for weight loss, systolic 24-hr (p=0.233), daytime, (p=0.313) and nighttime (p= 0.108) ABP were not different than the placebo group. Furthermore, diastolic 24-hr (p=0.147), daytime (p=0.276) and evening (p=0.187) ABP were not different between the two groups. The change in ABP in the TPM treatment group and the placebo group in the completer population are present in *figures 5 and 6.*

**Table 9:** 24-hour Blood Pressure from baseline to 6 month in the modified intent to treat population

| | Placebo | Topiramate | Non-Controlled for Weight Loss P Value | *Controlled for Weight Loss P Value |
|---|---|---|---|---|
| **Systolic Blood Pressure (mmHg)** | | | | |
| **24-hour** | | | | |
| ***N*** | 24 | 19 | | |
| ***Baseline Mean*** | 125.6 ± 7.79 | 125.2 ± 9.77 | | |
| ***Month 6 mean (SD)*** | 127.2 ± 7.40 | 119.9 ± 8.95 | | |
| ***Mean Change (SD)*** | 2.1 ±6.52 | -5.2 ± 9.79 | 0.006 | 0.233 |
| **Daytime** | | | | |
| ***N*** | 24 | 19 | | |
| ***Baseline Mean*** | 128.6 ± 8.19 | 127.8 ± 10.24 | | |
| ***Month 6 mean (SD)*** | 130.6 ± 7.73 | 123.3 ± 9.44 | | |
| ***Mean Change (SD)*** | 2.6 ± 6.63 | -4.6 ± 10.90 | 0.011 | 0.313 |
| **Evening** | | | | |
| ***N*** | 24 | 18 | | |
| ***Baseline Mean*** | 114.4 ± 8.60 | 116.5 ± 8.38 | | |
| ***Month 6 mean (SD)*** | 115.8 ± 8.37 | 109.6 ± 8.91 | | |
| ***Mean Change (SD)*** | 1.8 ± 9.03 | -6.9 ± 8.31 | 0.003 | 0.108 |
| **Diastolic Blood Pressure mmHg** | | | | |
| **24-hr** | | | | |
| ***N*** | 25 | 18 | | |
| ***Baseline Mean*** | 78.9 ± 6.62 | 77.3 ± 6.12 | | |
| ***Month 6 mean (SD)*** | 79.9 ± 7.11 | 73.5 ± 5.52 | | |
| ***Mean Change (SD)*** | 1.0 ± 4.91 | -3.7 ± 6.13 | 0.006 | 0.147 |
| **Daytime** | | | | |
| ***N*** | 25 | 18 | | |
| ***Baseline Mean*** | 81.6 ± 7.62 | 79.7 ± 6.69 | | |
| ***Month 6 mean (SD)*** | 82.5 ± 7.63 | 76.4 ± 5.93 | | |
| ***Mean Change (SD)*** | 0.9 ± 5.66 | -3.3 ± 7.08 | 0.033 | 0.276 |
| **Nighttime** | | | | |
| ***N*** | 25 | 18 | | |
| ***Baseline Mean*** | 69.4 ± 6.96 | 69.2 ± 6.69 | | |
| ***Month 6 mean (SD)*** | 71.2 ± 7.23 | 64.9 ± 6.34 | | |
| ***Mean Change (SD)*** | 1.8 ± 6.64 | -4.3 ± 7.13 | 0.006 | 0.187 |

* P value after performing ANCOVA to control for weight loss

*Note: numbers vary due to completion of tests*

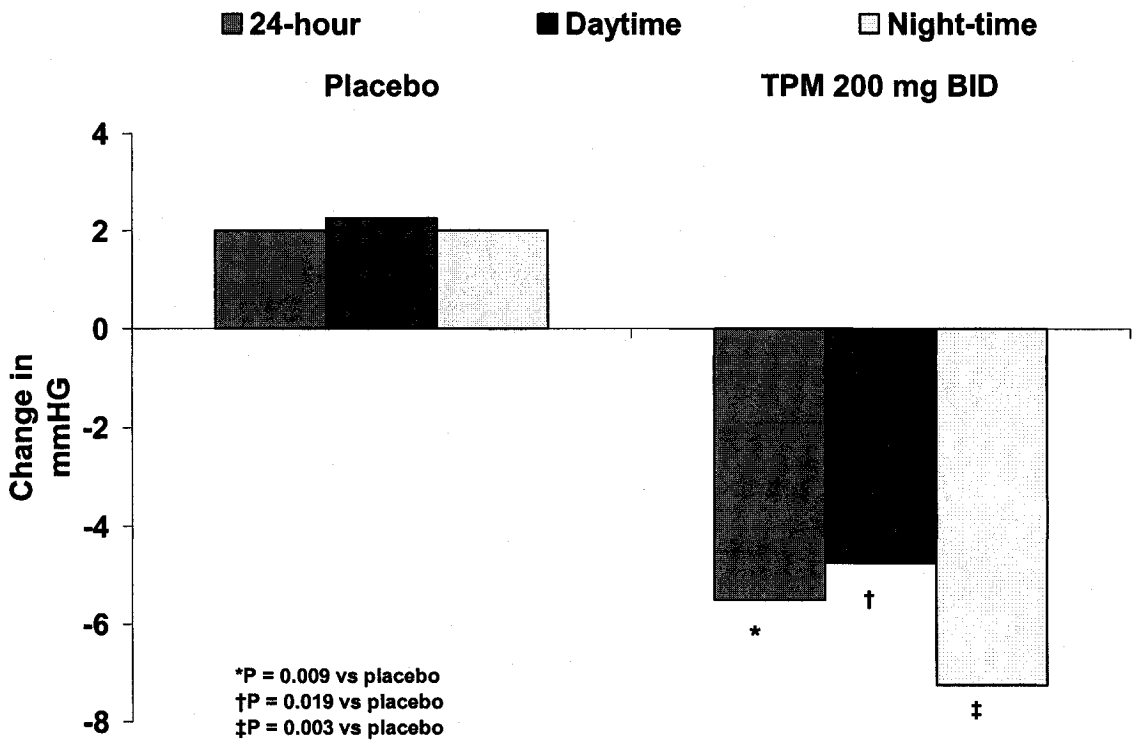


**Figure 5:** Change in ambulatory systolic blood pressure measurements in completer population

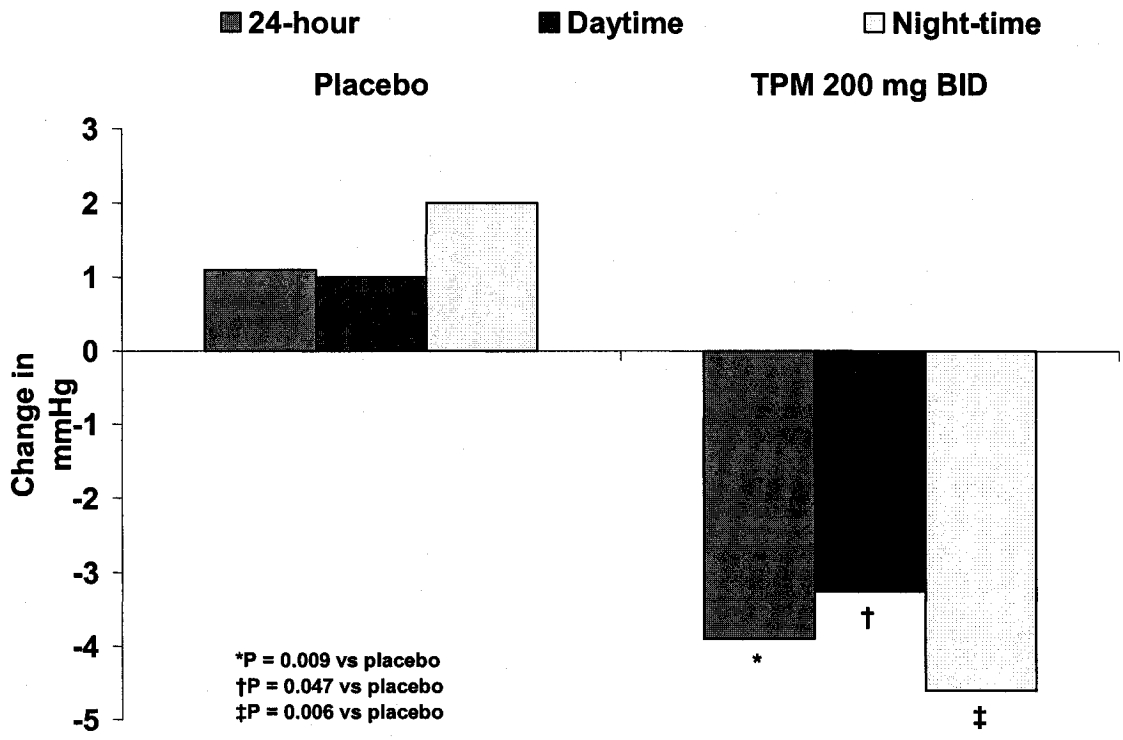


**Figure 6:** Change in ambulatory diastolic blood pressure measurements in completer population

**Associations Between Change in Systolic and Diastolic 24-hr ABP, Body Composition and Metabolic Indicies**

Change in systolic 24-hr ABP was significantly correlated to changes in % body fat (r=0.54; p=0.025), body fat mass (r=0.51; p=0.039) and total abdominal adipose tissue (r=0.46; =0.043) (*Table10)*. However, only changes in total abdominal adipose tissue (r=0.51; p=0.043) was significantly correlated with diastolic 24-hr ambulatory blood pressure. In addition, there was a trend between the changes in glucose AUC (r=0.48; p=0.052) and diastolic 24-hr ambulatory blood pressure (*Table 11)*.

**Table 10:** Correlation between change in systolic 24-hr ambulatory blood pressure (ABP) and changes in body composition and metabolic indicies in the completer population

| | 24-hr Systolic ABP | | | | |
|---|---|---|---|---|---|
| **Changes In:** | **Placebo** | | **Topiramate** | | |
| | **n** | **r** | **n** | **r** | **P value** |
| **Insulin AUC** | 24 | -0.07 | 17 | 0.26 | 0.312 |
| **Glucose AUC** | 24 | 0.20 | 17 | 0.36 | 0.156 |
| **Body Weight** | 24 | 0.20 | 17 | 0.43 | 0.083 |
| **Body Fat Free Mass** | 24 | 0.21 | 17 | 0.19 | 0.475 |
| **Body Fat %** | 24 | -0.03 | 17 | 0.54 | **0.025** |
| **Body Fat Mass** | 24 | 0.07 | 17 | 0.51 | **0.039** |
| **Total Abdominal Adipose Tissue** | 24 | 0.26 | 16 | 0.51 | **0.043** |
| **Abdominal Subcutaneous Adipose Tissue** | 24 | 0.31 | 16 | 0.38 | 0.152 |
| **Abdominal Visceral Adipose Tissue** | 24 | 0.03 | 16 | 0.46 | 0.075 |

*p value= significance of correlation in relation to TPM treatment group only. There was no significance related to the placebo group.
**$p \leq 0.05$

**Table 11:** Correlation between change in diastolic 24-hr ambulatory blood pressure (ABP) and changes in body composition and metabolic indicies in the completer population

| | 24-hr Diastolic ABP | | | | |
|---|---|---|---|---|---|
| **Changes In:** | **Placebo** | | **Topiramate** | | |
| | **N** | **r** | **n** | **r** | **p value** |
| **Insulin AUC** | 25 | -0.27 | 17 | 0.29 | 0.254 |
| **Glucose AUC** | 25 | -0.11 | 17 | 0.48 | 0.052 |
| **Body Weight** | 25 | .001 | 17 | 0.46 | 0.061 |
| **Body Fat Free Mass** | 25 | -0.03 | 17 | 0.34 | 0.189 |
| **Body Fat %** | 25 | -0.02 | 17 | 0.46 | 0.066 |
| **Body Fat Mass** | 25 | -0.01 | 17 | 0.45 | 0.072 |
| **Total Abdominal Adipose Tissue** | 25 | 0.22 | 16 | 0.51 | **0.043** |
| **Abdominal Subcutaneous Adipose Tissue** | 25 | 0.31 | 16 | 0.45 | 0.081 |
| **Abdominal Visceral Adipose Tissue** | 25 | -0.00 | 16 | 0.41 | 0.113 |

p value= significance of correlation in relation to TPM treatment group only. There was no significance related to the placebo group
**$p \leq 0.05$

**Adverse Events**

More TPM treated subjects (30%) withdrew from the study due to adverse events compared to the placebo treated group (14%) (*Table 12).* Paraesthesia was the most common side effect occurring in 55% of the TPM group, while only occurring in 11% in the placebo treated group. Other side effects included fatigue, difficulty with concentration, taste perversion, upper respiratory tract infection, dry mouth and somnolence. Symptoms usually went away as the body adapted to the medication. It was observed that all but one (upper respiratory tract infection) of the adverse events that led to subject withdrawal was considered possibly, probably or very likely drug-related.

**Table 12:** Most common adverse events for safety population

| Symptom | Placebo (N=35) (%) | Topiramate (N=33) (%) |
|---|---|---|
| **Paresthesia** | 4 (11) | 18 (55) |
| **Fatigue** | 10 (29) | 11 (33) |
| **Difficulty with Concentration** | 1 (3) | 10 (30) |
| **Upper respiratory Tract Infection** | 1 (3) | 7 (21) |
| **Taste Perversion** | 3 (9) | 6 (18) |
| **Dry Mouth** | 1 (3) | 6 (18) |
| **Somnolence** | 3 (9) | 5 (15) |

# Chapter V: Discussion

This investigation showed a significant reduction in 24-hr, daytime and nighttime systolic and diastolic ABP in the TPM supplementation group. However, when controlled for weight loss, no significant differences in ABP were found between the TPM and the placebo group. Furthermore, only changes in % body fat, body FM and total abdominal adipose tissue was significantly correlated to 24-hr systolic ABP, while only total abdominal adipose tissue was significantly correlated with 24-hr diastolic ambulatory blood pressure.

This was the first study on the treatment of obesity in which TPM was not combined with a behavioural intervention program and is the only study performed exclusively in abdominally obese males. Previous investigations have all showed that subjects treated with TPM combined with behavioural interventions showed a significant decrease in body weight and resting BP compared to a placebo (Bray et al., 2003; Astrup et al., 2004; Wilding et al., 2004). The results of this investigation coincide with a significant decrease in body weight and a reduction in ambulatory blood pressure.

The non-significant change in ABP between placebo and treatment group (when controlled for weight loss) led to believe that weight loss, especially decrease in fat mass and total abdominal adipose tissue, explain the associate ABP reduction. It has been shown in numerous studies that a reduction in body weight is associated with a decrease in blood pressure (Su et al., 1995; Blumenthal et al., 2000; Miller et al., 2002). In epidemiological studies, a 1 kg weight loss is associated with a .45 mmHg decrease in systolic and diastolic blood pressure (Blackburn, 1995; Bray et al., 2003). However, in this investigation, FM loss and % body fat reduction were significantly correlated to a

reduction in systolic ambulatory blood pressure. Furthermore, it appeared that the body fat distribution seems to be an important correlate of a reduction in ambulatory blood pressure. In fact, decrease in total abdominal adipose tissue was correlated with a reduction in systolic and diastolic ambulatory blood pressure.

The absence of correlation between the change in VAT and ABP is and not surprising because of the non-significant VAT reduction observed in the present study, despite significant weight loss, BMI, total body FM and % body fat reduction. It has been shown that in a state of negative energy balance, there is a preference in reduction of visceral adipose tissue (van der Kooy et al., 1993; Goodpaster et al., 1999; Ross et al., 2000). Further, Ross et al. (1997) reported eight studies that examined the effects of caloric restriction on visceral adipose tissue. They determined that a reduction of 2-3 % of VAT occur for every kilogram of weight loss. However, in the present investigation, only a reduction of 4.4 ± 67.88 $cm^2$ occurred, when it would be predicted that an 11-12 $cm^2$ reduction should occur in comparison to previous investigations. A possible explanation of this occurrence may be related to the mechanistic abilities of TPM and the lipolytic activity of visceral adipose tissue. Supplementation of TPM is expected to decrease the release of catecholamines by displaying state-dependent blockade of voltage-dependent sodium or calcium channels (White, 2003). Visceral adipose tissue has a higher rate of lipolysis as explained by an increase in the $\beta$-adrenoceptor pathway (via $ß_1$-, $ß_2$-, and $ß_3$-adrenoceptors), leading to a higher sensitivity of catecholamines (Jensen et al., 1989). $\beta$-adrenergic receptors in VAT has been shown in obese subjects to have increased sensitivity to $ß_3$-adrenoceptor stimulation, mediating a cascade reaction that up regulates cyclic AMP formation, stimulating cAMP-dependent protein kinase that activates

hormone sensitive lipase (Lönnqvist et al., 1995). Thus, hydrolyzing triglycerides to glycerol and increasing FFA release. However, a decrease in catecholamine levels may explain a reduction in VAT lipolytic activity, thus a decreased fat mobilization. In addition, we observed a large inter-individual variation in change in VAT, which may indicate inter-individual susceptibility to TPM as suggested by the incidence of the adverse events. The large dosage range and the small sample size are other factors that could explain the absence of a significant VAT reduction in the TPM group.

The association of VAT and IR being linked with an increase in BP (Ferrannini et al., 1997) led to the secondary hypothesis of this investigation. However, VAT was not significantly reduced in the present study and was not significantly correlated with systolic and diastolic ambulatory blood pressure, thus disproving our hypothesis. On the other hand, a significant reduction occurred in total abdominal fat, as well as abdominal subcutaneous adipose tissue. Recent investigations suggest that abdominal SAT is the best predictor of insulin resistance (Frayn, 2000; Kelley et al., 2000; Miyazaki et al., 2002; Garg & Misra, 2004). In addition, studies have shown only the deeper layer of abdominal SAT is associated with insulin resistance (Kelley et al., 2000; Miyazaki et al., 2002). Thus, the reduction in total abdominal fat and abdominal SAT may explain the significant decrease observed in plasma glucose AUC during the OGTT. Combined with the absence of a significant decrease in insulin AUC during the OGTT, suggests a reduction of insulin resistance. Therefore, the significant correlation observed between changes in systolic and diastolic 24-hr ABP with change in total abdominal adipose tissue may be associated with a reduction in IR as suggested by our OGTT results. Finally, the change in plasma glucose AUC during the OGTT showed a trend to be significantly

correlated with change in diastolic 24-hr ABP, adds supplementary proof to this hypothesis. An improvement in insulin sensitivity has also been shown in TPM treated rat models even when they controlled for weight loss. Wilkes et al. (2005) has shown TPM supplemented Zucker rats have a 30% increase in glucose disposal using a euglycemic-hyperinsulinemic clamp.

The mode of action of how TPM creates a weight reduction is still unclear regardless of its' known association with an effect on the central nervous system (Wilding et al., 2004). Despite the support that TPM influences the efficiency of energy utilization in a variety of animals (Picard et al., 2000; Richard et al., 2000), limited studies have been performed on humans. A recent sub-analysis of the data for the present study by Tremblay et al. (submitted) has shown that TPM showed no effect on energy expenditure (as measured by indirect calorimetry) in this sample of abdominally obese males. However, it was shown that the subjects reduced their energy intake and that could be a significant factor by which TPM produces a negative energy balance. Bray et al. (2003) have suggested the modulation of GABA receptors may appear to be a potential mechanism for weight loss. However, other anticonvulsant drugs such as valproate and benzodiazepine that enhance the activity of GABA-A receptor have shown to promote weight gain (Ketter et al., 1999), leading to the speculation that with supplementation of TPM, enhancement of GABA-A receptors would lead to create a positive energy balance. Microinjections of the GABA-A receptor agonist muscimol into the hypothalamic subnuclei, paraventricular nucleus, ventromedial nucleus and lateral hypothalamus stimulates food intake in rat models (Tsujii & Bray, 1991; Pu et al., 1999; Sheng et al., 2006). Future investigations are warranted to determine the specific mechanism how

supplementation of TPM associates with GABA to either act as an orexigenic or as an anorectic agent. However, it is suggested that the action of TPM on the GABA system is not predominant in regards to creating a negative energy balance.

Topiramate is also an antagonist at the AMPA/kainate type glutamate receptor (Rogawski & Porter, 1990; Gibbs et al., 2000). Glutamate is the predominant excitatory neurotransmitter in the brain (Robinson, 1998) and it is suggested that the inhibition of glutamate will cause a decrease in appetite (Ketter et al., 1999). Animal models show that by microinjecting glutamate or glutamate agonists (excitatory amino acids, kainic acid and AMPA) into the lateral hypothalamus, stimulation of an increase in food occurs in satiated rats (Stanley et al. 1993). Further, Ketter et al. (1999) suggest anticonvulsant drugs such as TPM might contribute to suppress appetite and to prevent over eating.

A drawback of this investigation is the inconsistent individual dosing of TPM, which limits the interpretation of our results. Subjects who discontinued the study had adverse events from dosages as low as 50 mg/d up to the maximal dosage of 400 mg/d, with few subjects reaching the latter. The TPM treated groups had an average daily dose of 148.9 ± 92.57 mg/d compared to the placebo daily dose of 252.74 ± 78.21 mg/d. Fifty-five percent of the TPM treated individuals had symptoms of paresthesia, compared to only 11% of the placebo group. Further, 30% of TPM treated group had symptoms of difficulty of concentration compared to only 3% in the placebo group. These adverse events coincide with other investigations that have shown consistent results with maximal weight loss benefit with 192 mg/d, with these and other increasing side effects at a higher dosage (Bray et al., 2003; Wilding et al., 2004). These side effects have led to previous investigations being cut short to develop a controlled-release formation to minimize the

incidence and prevalence of side effects and increase tolerability. However, TPM has been discontinued as an anti-obesity agent since the analysis of the results of this study.

# Chapter VI: Conclusions and Perspectives

The TPM supplementation group showed significant decrease in 24-hr, daytime and nighttime systolic and diastolic ABP compared to the placebo group. However, when controlled for weight loss, no significant difference in ABP was found between the TPM and the placebo group. Furthermore, change in VAT was not significantly correlated with changes in 24-hr systolic or diastolic ABP, as originally hypothesized. The mechanism of how TPM acts is still poorly understood, however, following this investigation it can be stated that the reduction in ABP with TPM is mainly associated with reduction in body weight, especially the reduction in FM and total abdominal fat and not by the mechanistic abilities of the drug. The change in total abdominal adipose tissue is significantly correlated with the change in 24-hr systolic and diastolic ABP, as well as % body fat and FM being correlated to 24-hr systolic ambulatory blood pressure.

As this study was a retrospective analysis, there were many variables that were unavailable that would be advantageous to this investigation. The first of which is the measurement of the adipocytokine hormones leptin and adiponectin. It is becoming more and more recognized that these hormones play a vital role in body weight and BP control. Secondly, measurement of the catecholamine plasma levels to determine if the non-significant change in VAT would be related to this parameter. Finally, the most inconsistent aspect of this study was the various individual dosages of TPM supplementation that occurred during the treatment period. Since this original study was one of the premiere investigations on TPM related to weight loss, it was not certain what would be an effective, well-tolerated dose.

Despite TPM trials have been discontinued in the battle against obesity; it still is used in the treatment of epilepsy and in conjunction with other medications in patients with mood disorders and schizophrenia. It decreases ABP through weight loss, potentially increases insulin sensitivity and may have other health benefits associated with the drug usage. Therefore, more studies are needed to document the effects of TPM in humans, as well as discover the mechanistic abilities of how TPM creates a negative energy balance, while documenting the potential health benefits associated with the use of TPM in these population groups.

# Chapter VII: References


*Canadian pharmacists association. compendium of pharmaceuticals and specialties: The Canadian drug reference for health professionals.*(2005). Ottawa, Ontario:

Topiramate (topamax) tablets. (2002). *Physicians desk reference* (pp. 2590-2595). Montvale, NJ: Medical Economics Co.

Anand, S. S., Yi, Q., Gerstein, H., Lonn, E., Jacobs, R., & Vuksan, V., et al. (2003). Relationship of metabolic syndrome and fibrinolytic dysfunction to cardiovascular disease. *Circulation, 108*(4), 420-425.

Anderson, E. A., Hoffman, R. P., Balon, T. W., Sinkey, C. A., & Mark, A. L. (1991). Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *The Journal of Clinical Investigation, 87*(6), 2246-2252.

Astrup, A., Caterson, I., Zelissen, P., Guy-Grand, B., Carruba, M., & Levy, B., et al. (2004). Topiramate: Long-term maintenace of weight loss induced by a low-calorie diet in obese subjects. *Obesity Research, 12*(10), 1658-1669.

Aulak, K. S., koeck, T., Crabb, J. W., & et al. (2004). Dyanmics of protein nitration in celss and mitochondria. *American Journal of Physiology, 286*, H30-H38.

Awdah, M. A., & Syamic, A. Y. (2004). Relationship between plasma angiotensinII, leptin and arterial blood pressure. *Saudi Medical Journal, 25*(9), 1193-1198.

Banks, W. A., Coon, A. B., Robinson, S. M., Moinuddin, A., Shultz, J. M., & Nakaoke, R., et al. (2004). Triglycerides induce leptin resistance at the blood-brain barrier. *Diabetes, 53*(5), 1253-1260.

Bastard, J. P., Jardel, C., Bruckert, E., Blondy, P., Capeau, J., & Laville, M., et al. (2000). Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *The Journal of Clinical Endocrinology and Metabolism, 85*(9), 3338-3342.

Basu, A., Basu, R., Shah, P., Vella, A., Rizza, R. A., & Jensen, M. D. (2001). Systemic and regional free fatty acid metabolism in type 2 diabetes. *American Journal of Physiology. Endocrinology and Metabolism, 280*(6), E1000-6.

Behnke, A. R., & Wilmore, J. H. (1974). Evaluation and regulation of body build and composition. *Evaluation and regulation of body build and composition* (pp. 20-37)Prentice Hall.

Benomar, Y., Wetzler, S., Larue-Achagiotis, C., Djiane, J., Tome, D., & Taouis, M. (2005). In vivo leptin infusion impairs insulin and leptin signalling in liver and hypothalamus. *Molecular and Cellular Endocrinology, 242*(1-2), 59-66.

Berne, C., Fagius, J., Pollare, T., & Hjemdahl, P. (1992). The sympathetic response to euglycaemic hyperinsulinaemia. evidence from microelectrode nerve recordings in healthy subjects. *Diabetologia, 35*(9), 873-879.

Blackburn, G. L. (1995). Effect of degree of weight loss on health benefits. *Obesity Research, 3*(Supplementary 2), S211-S216.

Bloch, M. J., & Basile, J. (2004). Analysis of recent papers in hypertension. *The Journal of Clinical Hypertension, 6*(9), 530-531.

Blumenthal, J. A., Sherwood, A., Gullette, E. C., Babyak, M., Waugh, R., & Georgiades, A., et al. (2000). Exercise and weight loss reduce blood pressure in men and women with mild hypertension: Effects on cardiovascular, metabolic, and hemodynamic functioning. *Archives of Internal Medicine, 160*(13), 1947-1958.

Boden, G., Lebed, B., Schatz, M., Homko, C., & Lemieux, S. (2001). Effects of acute changes of plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects. *Diabetes, 50*(7), 1612-1617.

Bolinder, J., Kager, L., Ostman, J., & Arner, P. (1983). Differences at the receptor and postreceptor levels between human omental and subcutaneous adipose tissue in the action of insulin on lipolysis. *Diabetes, 32*(2), 117-123.

Bouchard, C. (2000). *Physical activity and obesity*. Champaign, IL: Human Kinetics.

Bouchard, C., & Tremblay, A. (1997). Genetic influences on the response of body fat and fat distribution to positive and negative energy balances in human identical twins. *The Journal of Nutrition, 127*(5 Suppl), 943S-947S.

Boyle, P. J. (2004). What are the effects of peroxisome proliferator-activated receptor agonists on adiponectin, tumor necrosis factor-alpha, and other cytokines in insulin resistance? *Clinical Cardiology, 27*(7 Suppl 4), IV11-6.

Brands, M. Q., Mizelle, L., Gaillard, C. A., Hildenbrandt, D. A., & Hall, J. E. (1991). The haemodynamic response to chronic hyperinsulinemia in conscious dogs. *American Journal of Hypertension, 4*, 164-168.

Bray, G. A., Hollander, P., Klein, S., Kushner, R., Levy, B., & Fitchet, M., et al. (2003). A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obesity Research, 11*(6), 722-733.

Bray, G. A., Blackburn, G. L., Ferguson, J. M., Greenway, F. L., Jain, A. K., & Mendel, C. M., et al. (1999). Sibutramine produces dose-related weight loss. *Obesity Research, 7*(2), 189-198.

Bruun, J. M., Verdich, C., Toubro, S., Astrup, A., & Richelsen, B. (2003). Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-alpha. effect of weight loss in obese men. *European Journal of Endocrinology / European Federation of Endocrine Societies, 148*(5), 535-542.

Cerosismo, E., & DeFronzo, R. A. (2006). Insulin resistance and endothelial dysfunction: The road map to cardiovascular diseases. *Diabetes/Metabolism Research and Reserve, Feb. 28*

Chobanian, A. V., Garvras, H., Gavras, I., Bresnahan, M., Sullivan, P., & Melby, J. C. (1978). Studies on the activity of the sympathetic nervous system in essential hypertension. *Journal of Human Stress, 4*(3), 22-28.

Chobanian, A. V., Gavras, H., Melby, J. C., Gavras, I., & Jick, H. (1978). Relationship of basal plasma noradrenaline to blood pressure, age, sex, plasma renin activity and plasma volume in essential hypertension. *Clinical Science and Molecular Medicine. Supplement, 4*, 93s-96s.

Coats, A. J. (1996). Benefits of ambulatory blood pressure monitoring in the design of antihypertensive drug trials. *Blood Pressure Monitoring, 1*(2), 157-160.

Couillard, C., Bergeron, N., Prud'homme, D., Bergeron, J., Tremblay, A., & Bouchard, C., et al. (1998). Postprandial triglyceride response in visceral obesity in men. *Diabetes, 47*(6), 953-960.

Cowley, M. A., Smart, J. L., Rubinstein, M., Cerdan, M. G., Diano, S., & Horvath, T. L., et al. (2001). Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature, 411*(6836), 480-484.

da Silva, A. A., Kuo, J. J., Tallam, L. S., & Hall, J. E. (2004). Role of endothelin-1 in bloodpressure regulation in a rat model of visceral obesity and hypertension. *Hypertension, 43*, 383-387.

DeFronzo, R. A. (1988). The triumvirate; beta cell, muscle and liver, a collusion responsible for NIDDM. *Diabetes, 37*, 667-687.

Despres, J. P., & Lamarche, B. (1993). Effects of diet and physical activity on adiposity and body fat distribution: Implications for the prevention of cardiovascular disease. *Nutritional Research Review, 6*, 137-159.

Despres, J. P., Lamarche, B., & Mauriege, P. (1996). Hyperinsulinemia as an independent risk factor for ischemic heart disease. *New England Journal of Medicine, 334*, 952.

El-Atat, F., Aneja, A., Mcfarlane, S., & Sowers, J. (2003). Obesity and hypertension. *Endocrinology and Metabolism Clinics of North America, 32*(4), 823-854.

Engelke, k. A., Halliwill, J. R., & Protcor, D.N. et al. (1996). Contribution of nitric oxide and prostaglandins to reactive hyperemia in the human forearm. *Journal of Applied Physiology, 81*(4), 1807-1814.

Faria, A. N., Ribeiro Filho, F. F., Gouveia Ferreira, S. R., & Zanella, M. T. (2002). Impact of visceral fat on blood pressure and insulin sensitivity in hypertensive obese women. *Obesity Research, 10*(12), 1203-1206.

Ferland, M., Despres, J. P., Tremblay, A., Pinault, S., Nadeau, A., & Moorjani, S., et al. (1989). Assessment of adipose tissue distribution by computed axial tomography in obese women: Association with body density and anthropometric measurements. *The British Journal of Nutrition, 61*(2), 139-148.

Ferrannini, E., Natali, A., Capaldo, B., Lehtovirta, M., Jacob, S., & Yki-Jarvinen, H. (1997). Insulin resistance, hyperinsulinemia and blood pressure: Role of age and obesity. *Hypertension, 30*, 1144-1149.

Flegal, K. M., carroll, M. D., Ogden, C. L., & Johnson, C. L. (2002). Prevalence and trends in obesity among US adults, 1999-2000. *Journal of the American Medical Association, 14*(288), 1723-1727.

Ford, E. S., Giles, W. H., & Dietz, W. H. (2002). Prevalence of the metabolic syndrome among US adults. *The Journal of the American Medical Association, 287*(3), 356-359.

Franks, P. W., Brage, S., Luan, J., Ekelund, U., Rahman, M., & Farooqi, I. S., et al. (2005). Leptin predicts a worsening of the features of the metabolic syndrome independently of obesity. *Obesity Research, 13*(8), 1476-1484.

Frayn, K. N. (2000). Visceral fat and insulin resistance--causative or correlative? *The British Journal of Nutrition, 83 Suppl 1*, S71-7.

Freedland, E. S. (2004). Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: Implications for controlling dietary carbohydrates: A review. *Nutr.Metab.(Lond), 1*(1), 12.

Freedman, D. S., Khan, L. K., Serdula, M. K., Galuska, D. A., & Dietz, W. H. (2002). Trends and correlates of class 3 obesity in the united states from 1990 through 2000. *JAMA : The Journal of the American Medical Association, 288*(14), 1758-1761.

Fry, M. J. (1994). Structure, regulation and function of phosphoinositide 3-kinases. *Biochimica Et Biophysica Acta, 1226*(3), 237-268.

Gabriely, I., Ma, X. H., & Yang, X.M. et al. (2002). Removal of visceral fat prevents insulin resistance and glucose intoerance of aging. an adipokine-mediated process? *Diabetes, 51*, 2951-2958.

Galanis, D. J., Harris, T., Sharp, D. S., & Petrovitch, H. (1998). Relative weight, weight change, and risk of coronary heart disease in the honolulu heart program. *American Journal of Epidemiology, 147*, 379-386.

Garg, A., & Misra, A. (2004). Regional adiposity and insulin resistance. *Journal of Clinical Endocrinology and Metabolism, 33*, 4206-4210.

Gastaldelli, A., Miyazaki, Y., Pettiti, M., Matsuda, M., Mahankali, S., & Santini, E., et al. (2002). Metabolic effects of visceral fat accumulation in type 2 diabetes. *The Journal of Clinical Endocrinology and Metabolism, 87*(11), 5098-5103.

Gibbs, J. W.,3rd, Sombati, S., DeLorenzo, R. J., & Coulter, D. A. (2000). Cellular actions of topiramate: Blockade of kainate-evoked inward currents in cultured hippocampal neurons. *Epilepsia, 41 Suppl 1*, S10-6.

Goodpaster, B. H., & Brown, F. (2005). Skeletal muscle lipid and it's association with insulin resistance: What is the role for exercise? *Exercise and Sport Sciences Review, 33*(3), 150-154.

Goodpaster, B. H., Kelley, D. E., Wing, R. R., Meier, A., & Thaete, F. L. (1999). Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes, 48*(4), 839-847.

Goodpaster, B. H., Theriault, R., Watkins, S. C., & Kelley, D. E. (2000). Intramuscular lipid content is increased in obesity and decreased by weight loss. *Metabolism: Clinical and Experimental, 49*(4), 467-472.

Gray, R. E., Tanner, C. J., Pories, W. J., MacDonald, K. G., & Houmard, J. A. (2003). Effect of weight loss on muscle lipid content in morbidly obese subjects. *American Journal of Physiology. Endocrinology and Metabolism, 284*(4), E726-32.

Griffin, M. E., Marcucci, M. J., Cline, G. W., Bell, K./ Barucci, N., Lee, D., & Goodyear, L.J. Kraegen, E.W., et al. (1999). Free fatt acid-induced insulin resistance is associated with activation of protein kinase ce theta and alterations in the insulin signalling cascade. *Diabetes, 48*, 1270-1274.

Hamdy, O., Ledbury, S., Mullooly, C., Jarema, C., Porter, S., & Ovalle, K., et al. (2003). Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. *Diabetes Care, 26*(7), 2119-2125.

Hara, K., Horikoshi, M., Yamauchi, T., Yago, H., Miyazaki, O., & Ebinuma, H., et al. (2006). Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. *Diabetes Care, 29*(6), 1357-1362.

Haynes, W. G. (2005). Role of leptin in obesity-related hypertension. *Experimental Physiology, 90*(5), 683-688.

He, J., Goodpaster, B. H., & Kelley, D. E. (2004). Effects of weight loss and physical activity on muscle lipid content and droplet size. *Obesity Research, 12*(5), 761-769.

Heise, T., Magnusson, K., Heinemann, L., & Sawicki, P. T. (1998). Insulin resistance and the effect of insulin on blood pressure in essential hypertension. *Hypertension, 32*, 243-248.

Heitzer, T., Schlinzig, T., Krohn, K., Meinertz, T., & Munzel, T. (2001). Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation, 104*(22), 2673-2678.

Higashi, Y., Sasaki, S., Kurisu, S., Yoshimizu, A., Sasaki, N., & Matsuura, H., et al. (1999). Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: Role of endothelium-derived nitric oxide. *Circulation, 100*(11), 1194-1202.

Hing, E., Cherry, D. K., & Woodwell, D. A. (2006). National ambulatory medical care survey: 2004 summary. *Advance Data, (374)*(374), 1-33.

Hirsch, J., Fried, S. K., Edens, N. K., & Leibel, R. L. (1989). The fat cell. *Medical Clinics of North America, 73*, 83-96.

Hotamisligil, G. S., Murray, D. L., Choy, L. N., & Spiegelman, B. M. (1994). Tumor necrosis factor alpha inhibits signaling from the insulin receptor. *Proceedings of the National Academy of Sciences of the United States of America, 91*(11), 4854-4858.

Hotta, K., Funahashi, T., Arita, Y., Takahashi, M., Matsuda, M., & Okamoto, Y., et al. (2000). Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arteriosclerosis, Thrombosis, and Vascular Biology, 20*(6), 1595-1599.

Hunter, G. R., Snyder, S. W., Kekes-Szabo, T., Nicholson, C., & Berland, L. (1994). Intra-abdominal adipose tissue values associated with risk of possessing elevated blood lipids and blood pressure. *Obesity Research, 2*(6), 563-568.

Iglarz, M., & Schiffrin, E. L. (2003). Role of endothelin-1 in hypertension. *Current Hypertension Report, 5*, 144-148.

Isomaa, B., Almgren, P., Tuomi, T., Forsen, B., Lahti, K., & Nissen, M., et al. (2001). Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care, 24*(4), 683-689.

Itani, S. I., Ruderman, N. B., Schmieder, F., & Boden, G. (2002). Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IkappaB-alpha. *Diabetes, 51*(7), 2005-2011.

Jakicic, J. M., & Otto, A. D. (2006). Treatment and prevention of obesity: What is the role of exercise? *Nutrition Reviews, 64*(2 Pt 2), S57-61.

Jensen, M. D., Haymond, M. W., Rizza, R. A., Cryer, P. E., & Miles, J. M. (1989). Influence of body fat distribution on free fatty acid metabolism in obesity. *The Journal of Clinical Investigation, 83*(4), 1168-1173.

Joannides, R., Haefeli, W. E., Linder, L., & et al. (1995). Nitric oxide is reponsible flor flow-dependent dilatation of human peripheral conduit arteries in vivo. *Circulation, 91*, 1314-1319.

Kalra, S. P., & Kalra, P. S. (2004). NPY and cohorts in regulating appetite, obesity and metabolic syndrome: Beneficial effects of gene therapy. *Neuopeptides, 38*, 201-211.

Katsuki, A., Sumida, Y., Murashima, S., Murata, K., Takarada, Y., & Ito, K., et al. (1998). Serum levels of tumor necrosis factor-alpha are increased in obese patients with noninsulin-dependent diabetes mellitus. *The Journal of Clinical Endocrinology and Metabolism, 83*(3), 859-862.

Katzmarzyk, P. T. (2002). The canadian obesity epidemic, 1985-1998. *CMAJ : Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne, 166*(8), 1039-1040.

Kelley, D. E., Menshikova, H. J., & Ritov, V. B. (2002). Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes, 51*(10), 2944-2950.

Kelley, D. E., Thaete, F. L., Troost, F., Huwe, T., & Goodpaster, B. H. (2000). Subdivision of subcutaneous abdominal adipose tissue and insulin resistance. *American Journal of Physiology and Encrinology Metabolism, 278*, E941-E948.

Ketter, T. A., Post, R. M., & Theodore, W. H. (1999a). Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. *Neurology, 53*(5 Suppl 2), S53-67.

Kim, S. H., Lee, Y. M., Jee, S. H., & Nam, C. M. (2003). Effect of sibutramine on weight loss and blood pressure: A meta-analysis of controlled trials. *Obesity Research, 11*(9), 1116-1123.

Klein, S. (2004). The case of visceral fat: Argument for the defense. *The Journal of Clinical Investigation, 113*(11), 1530-1532.

Klein, S., Fontana, L., Young, V. L., Coggan, A. R., Kilo, C., & Patterson, B. W., et al. (2004). Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *The New England Journal of Medicine, 350*(25), 2549-2557.

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., & Walker, E. A., et al. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine, 346*(6), 393-403.

Laakso, M., Edelman, S. V., Brechtel, G., & Baron, A. D. (1990). Decreased effect of insulin to stimulate muscle blood flow in obese men: A novel mechanism for insulin resistance. *Journal of Clinical Investigation, 85*, 1844-1852.

Laaksonen, D. E., Kainulainen, S., Rissanen, A., & Niskanen, L. (2003). Relationships between changes in abdominal fat distribution and insulin sensitivity during a very low calorie diet in abdominally obese men and women. *Nutrition, Metabolism, and Cardiovascular Diseases : NMCD, 13*(6), 349-356.

Lam, K., Carpenter, C. L., Ruderman, N. B., Friel, J. C., & Kelly, K. L. (1994). The phosphatidylinositol 3-kinase serine kinase phosphorylates IRS-1. stimulation by insulin and inhibition by wortmannin. *Journal of Biological Chemistry, 269*(32), 20648-20652.

Lefebvre, I., Despres, J. P., Dumont, M., Almeras, N., Plourde, G., & Prud'homme, D. (2003). The relationship between 24-hour blood pressure monitoring and visceral adiposity in dyslipidemic men. *Unpublished Data,*

Lemieux, S. (2001). Contribution of visceral obesity to the insulin resistance syndrome. *Canadian Journal of Applied Physiology = Revue Canadienne De Physiologie Appliquee, 26*(3), 273-290.

Lemieux, S., Lesage, M., Bergeron, J., Prud'Homme, D., & Despres, J. P. (1999). Comparison of two techniques for measurement of visceral adipose tissue cross-sectional areas by computed tomography. *American Journal of Human Biology : The Official Journal of the Human Biology Council, 11*(1), 61-68.

Lohman, T. G., Roche, A. F., & Martorell, R. (1988). Anthropometry and body composition. *Anthropometric standardization reference manual.* Champaign (IL): Human Kinetics.

Lonnqvist, F., Thome, A., Nilsell, K., Hoffstedt, J., & Arner, P. (1995). A pathogenic role of visceral fat beta 3-adrenoceptors in obesity. *The Journal of Clinical Investigation, 95*(3), 1109-1116.

Lonnqvist, F., Thorne, A., Large, V., & Arner, P. (1997). Sex differences in visceral fat lipolysis and metabolic complications of obesity. *Arteriosclerosis, Thrombosis, and Vascular Biology, 17*(7), 1472-1480.

Lundgren, M., Buren, J., Ruge, T., Myrnas, T., & Eriksson, J. W. (2004). Glucocorticoids down-regulate glucose uptake capacity and insulin-signaling proteins in omental but not subcutaneous human adipocytes. *The Journal of Clinical Endocrinology and Metabolism, 89*(6), 2989-2997.

Lyon, H. N., & Hirschhorn, J. N. (2005). Genetics of common forms of obesity: A brief overview. *The American Journal of Clinical Nutrition, 82*(1 Suppl), 215S-217S.

Maeda, N., Shimomura, I., Kishida, K., Nishizawa, H., Matsuda, M., & Nagaretani, H., et al. (2002). Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nature Medicine, 8*(7), 731-737.

Malenfant, P., Tremblay, A., Doucet, E., Imbeault, P., Simoneau, J. A., & Joanisse, D. R. (2001). Elevated intramyocellular lipid concentration in obese subjects is not reduced after diet and exercise training. *American Journal of Physiology. Endocrinology and Metabolism, 280*(4), E632-9.

Mancia, G., Sega, R., Bravi, C., De Vito, G., Valagussa, F., & Cesana, G., et al. (1995). Ambulatory blood pressure normality: Results from the PAMELA study. *Journal of Hypertension, 13*(12 Pt 1), 1377-1390.

Marin, P., Andersson, B., Ottosson, M., Olbe, L., Chowdhury, B., & Kvist, H., et al. (1992). The morphology and metabolism of intra-abdominal adipose tissue in men. *Metabolism, 41*, 1242-1248.

Matsuzawa, Y. (1998). Insulin intolerance and visceral fat.*15*(9), 55-59.

Mauriege, P., Brochu, M., Prud'homme, D., Tremblay, A., Nadeau, A., & Lemieux, S., et al. (1999). Is visceral adiposity a significant correlate of subcutaneous adipose cell lipolysis in men? *The Journal of Clinical Endocrinology and Metabolism, 84*(2), 736-742.

McGarry, J. D., & Brown, N. F. (1997). The mitochondria carnitine palmitoyltransferase system: From concept to analysis. *Euopean Journal of Biochemistry, 244*, E1130-E1141.

McGrath, B. P. (2002). Ambulatory blood pressure monitoring. *The Medical Journal of Australia, 176*, 588-592.

Mcneely, W., & Goa, K. L. (1998). Sibutramine. A review of its contribution to the management of obesity. *Drugs, 56*, 1093-1124.

Mendoza-Nunez, V. M., Correa-Munoz, E., Garfias-Cruz, E. A., Sanchez-Rodriguez, M. A., Galvan-Duarte, R. E., & Retana-Ugalde, R. (2006). Hyperleptinemia as a risk factor for high blood pressure in the elderly. *Archives of Pathology & Laboratory Medicine, 130*(2), 170-175.

Meneely, G. R., & Kaltreider, N. L. (1949). The Volume of the Lung Determined by Helium Dilution. Description of the Method and Comparison with Other Procedures. *The Journal of Clinical Investigation, 28*(1), 129-139.

Miller, E. R.,3rd, Erlinger, T. P., Young, D. R., Jehn, M., Charleston, J., & Rhodes, D., et al. (2002). Results of the diet, exercise, and weight loss intervention trial (DEW-IT). *Hypertension, 40*(5), 612-618.

Miyazaki, Y., Glass, L., Triplitt, C., Wajcberg, E., Mandarino, L. J., & DeFronzo, R. A. (2002). Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. *American Journal of Physiology. Endocrinology and Metabolism, 283*(6), E1135-43.

Mojiminiyi, O. A., Abdella, N. A., Al Arouj, M., & Ben Nakhi, A. (2006). Adiponectin, insulin resistance and clinical expression of the metabolic syndrome in patients with type 2 diabetes. *Int.J.Obes.(Lond),*

Monzillo, L. U., Hamdy, O., Horton, E. S., Ledbury, S., Mullooly, C., & Jarema, C., et al. (2003). Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. *Obesity Research, 11*(9), 1048-1054.

Muzzin, P., Eisensmith, R. C., Copeland, K. C., & Woo, S. L. (1996). Correction of obesity and diabetes in genetically obese mice by leptin gene therapy. *Proceedings of the National Academy of Sciences of the United States of America, 93*(25), 14804-14808.

Natali, A., Baldeweg, S., Toschi, E., Capaldo, B., Barbaro, D., & Gastaldelli, A., et al. (2004). Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes. *Diabetes Care, 27*(6), 1349-1357.

NHLBI Obesity Initiative Task Force. (1998). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults-the evidence report. *Obesity Research, 9*(Supplementary 2), S51-S209.

Nicklas, B. J., Penninx, B. W., Ryan, A. S., Berman, D. M., Lynch, N. A., & Dennis, K. E. (2003). Visceral adipose tissue cutoffs associated with metabolic risk factors for coronary heart disease in women. *Diabetes Care, 26*(5), 1413-1420.

Nielsen, S., Guo, Z. K., Johnson, C. M., Hensrud, D. D., & Jensen, M. D. (2004). Splanchnic lipolysis in human obesity. *Journal of Clinical Investigation, 113*, 1582-1588.

O'Brien, E., Mee, F., Atkins, N., & O'Malley, K. (1991). Accuracy of the SpaceLabs 90207 determined by the british hypertension society protocol. *Journal of Hypertension, 9*(6), 573-574.

Ogden, C. L., Flegal, K. M., Caroll, M. D., & Johnson, C. L. (2002). Prevalence and trends in overweight amount US children and adolescents, 1999-2000. *The Journal of the American Medical Association, 288*, 1728-1732.

Ogden, C. L., Flegal, K. M., Carroll, M. D., & Johnson, C. L. (2002). Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA : The Journal of the American Medical Association, 288*(14), 1728-1732.

Owens, D. F., Liu, X., & Kriegstein, A. R. (1999). Changing properties of GABA(A) receptor-mediated signaling during early neocortical development. *Journal of Neurophysiology, 82*(2), 570-583.

Ozer, Y., & Altunkaya, H. (2004). Topiramate induced metabolic acidosis. *Anaesthesia, 59*(8), 830.

Pan, D. A., Lillioja, S., Kriketos, M. R., Milner, L. A., Baur, C., & Bogardus, A. B., et al. (1997). Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes, 46*, 983-988.

Park, S., Jastremski, C. A., & Wallace, J. P. (2005). Time of day for exercise on blood pressure reduction in dipping and nondipping hypertension. *Journal of Human Hypertension, 19*(8), 597-605.

Pascot, A., Lemieux, S., Lemieux, I., Prud'homme, D., Tremblay, A., & Bouchard, C., et al. (1999). Age-related increase in visceral adipose tissue and body fat and the metabolic risk profile of premenopausal women. *Diabetes Care, 22*(9), 1471-1478.

Perez, C., Fernandez-Galaz, C., Fernandez-Agullo, T., Arribas, C., Andres, A., & Ros, M., et al. (2004). Leptin impairs insulin signaling in rat adipocytes. *Diabetes, 53*(2), 347-353.

Picard, F., Deshaies, Y., Lalonde, J., Samson, P., & Richard, D. (2000). Topiramate reduces energy and fat gains in lean (fa/?) and obese (fa/fa) zucker rats. *Obesity Research, 8*, 656-663.

Popkin, B. M., & Gordon-Larsen, P. (2004). The nutrition transition: Worldwide obesity dynamics and their determinants. *International Journal of Obesity, 28*, S2-S9.

Prud'homme, D., Dumont, M., Brochum, A., N., Nadeau, A., & Despres, P. (1997). Beneficial effects of a 12-week fenfluramine treatment on the cardiovascular disease risk profile of visceral obese men. *International Journal of Obesity, 21*(Supplementary 2)

Pu, S., Jain, M. R., Horvath, T. L., Diano, S., Kalra, P. S., & Kalra, S. P. (1999). Interactions between neuropeptide Y and gamma-aminobutyric acid in stimulation of feeding: A morphological and pharmacological analysis. *Endocrinology, 140*(2), 933-940.

Quehenberger, P., Exner, M., Sunder-Plassmann, R., & et al. (2002). Leptin induces endothelin 1 in endothelial cells in vitro. *Circulatory Research, 90*, 711-720.

Reaven, G. M. (1988). Role of insulin resistance in human disease: Banting lecture. *Diabetes, 37*, 1595-1607.

Reife, R., Pledger, G., & Wu, S. C. (2000). Topiramate as add-on therapy: Pooled analysis of randomized controlled trials in adults. *Epilepsia, 41*(Supplementary 1), S66-S71.

Reinehr, T., Gideon, D. S., & Werner, A. (2005). Longitudinal analyses among overweight, insulin resistance, and cardiovascular risk factors in children. *Obesity Research, 13*(10), 1824-1833.

Richard, D., Ferland, J., Lalonde, J., Samson, P., & Deshaies, Y. (2000). Influence of topiramate in the regulation of energy balance. *Nutrition (Burbank, Los Angeles County, Calif.), 16*(10), 961-966.

Richard, D., Picard, F., Lemieux, C., Lalonde, J., Samson, P., & Deshaies, Y. (2002). The effects of topiramate and sex hormones on energy balance of male and female rats. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity, 26*(3), 344-353.

Robinson, M. B. (1998). The family of sodium-dependent glutamate transporters: A focus on the GLT-1/EAAT2 subtype. *Neurochemistry International, 33*(6), 479-491.

Rogawski, M. A., & Porter, R. J. (1990). Antiepileptic drugs: Pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. *Pharmacology Review, 42*, 223-286.

Ronti, T., Lupattelli, G., & Mannarino, E. (2006). The endocrine function of adipose tissue: An update. *Clinical Endocrinology, 64*(4), 355-365.

Ross, R., Janssen, I., Dawson, J., Kungl, A. M., Kuk, J. L., & Wong, S. L., et al. (2004). Exercise-induced reduction in obesity and insulin resistance in women: A randomized controlled trial. *Obesity Research, 12*(50), 789-798.

Ross, R. (1997). Effects of diet- and exercise-induced weight loss on visceral adipose tissue in men and women. *Sports Medicine (Auckland, N.Z.), 24*(1), 55-64.

Ross, R., Dagnone, D., Jones, P. J., Smith, H., Paddags, A., & Hudson, R., et al. (2000). Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. *Annals of Internal Medicine, 133*(2), 92-103.

Ross, R., & Janssen, I. (2001). Physical activity, total and regional obesity: Dose-response considerations. *Medicine and Science in Sports and Exercise, 33*(6 Suppl), S521-7; discussion S528-9.

Rowe, J. W., Young, J. B., Minaker, K. L., Stevens, A. L., Pallotta, J., & Landsberg, L. (1981). Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. *Diabetes, 30*(3), 219-225.

Ruan, H., Hacohen, N., Golub, T. R., Van Parijs, L., & Lodish, H. F. (2002). Tumor necrosis factor-alpha suppresses adipocyte-specific genes and activates expression of preadipocyte genes in 3T3-L1 adipocytes: Nuclear factor-kappaB activation by TNF-alpha is obligatory. *Diabetes, 51*(5), 1319-1336.

Ruan, H., Miles, P. D., Ladd, C. M., Ross, K., Golub, T. R., & Olefsky, J. M., et al. (2002). Profiling gene transcription in vivo reveals adipose tissue as an immediate target of tumor necrosis factor-alpha: Implications for insulin resistance. *Diabetes, 51*(11), 3176-3188.

Ryan, D. H. (2004). Clinical use of sibutramine. *Drugs Today, 40*(1), 41-54.

Santomauro, A. T., Boden, G., Silva, M. E., Rocha, D. M., Santos, R. F., & Ursich, M. J., et al. (1999). Overnight lowering of free fatty acids with acipimox improves insulin resistance and glucose tolerance in obese diabetic and nondiabetic subjects. *Diabetes, 48*(9), 1836-1841.

Satoh, N., Ogawa, Y., Usui, T., Tagami, T., Kono, S., & Uesugi, H., et al. (2003). Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. *Diabetes Care, 26*(9), 2493-2499.

Sawicki, P. T., Heinermann, L., Starke, A. A. R., & Berger, M. (1992). Hyperinsulinaemia is not linked with blood pressure elevation in patients with insulinoma. *Diabetologia, 35*, 649-652.

Scherrer, U., Randin, D., Tappy, L., Vollenweider, P., Jequier, E., & Nicod, P. (1994). Body fat and sympathetic nerve activity in healthy subjects. *Circulation, 89*(6), 2634-2640.

Scherrer, U., Randin, D., Vollenweider, P., Vollenweider, L., & Nicod, P. (1994). Nitric oxide release accounts for insulin's vascular effects in humans. *The Journal of Clinical Investigation, 94*(6), 2511-2515.

Schmitz-Peiffer, C. (2000). Signalling aspects of insulin resistance in skeletal muscle: Mechanisms induced by lipid oversupply. *Cellular Signalling, 12*, 583-594.

Schneider, R., Golzman, B., Turkot, S., Kogan, J., & Oren, S. (2005). Effect of weight loss on blood pressure, arterial compliance, and insulin resistance in normotensive obese subjects. *The American Journal of the Medical Sciences, 330*(4), 157-160.

Sciacqua, A., Candigliota, M., Ceravolo, R., Scozzafava, A., Sinopoli, F., & Corsonello, A., et al. (2003). Weight loss in combination with physical activity improves endothelial dysfunction in human obesity. *Diabetes Care, 26*(6), 1673-1678.

Seidell, J. C. (2000). Obesity, insulin resistance and diabetes—a worldwide epidemic. *British Journal of Nutrition, 83*, S5-S8.

Sharma, A. M., & Golay, A. (2002). Effect of orlistat-induced weight loss on blood pressure and heart rate in obese patients with hypertension. *Journal of Hypertension, 20*(9), 1731-1735.

Sheng, G., Chang, G. Q., Lin, J. Y., Yu, Z. X., Fang, Z. H., & Rong, J., et al. (2006). Hypothalamic huntingtin-associated protein 1 as a mediator of feeding behavior. *Nature Medicine, 12*(5), 526-533.

Shepherd, J. T. (1990). Franz volhard lecture. increased systemic vascular resistance and primary hypertension: The expanding complexity. *Journal of Hypertension. Supplement : Official Journal of the International Society of Hypertension, 8*(7), S15-27.

Sica, D. A. (2005). *Ambulatory blood pressure monitoring in 2005*.http://www.medscape.com/viewarticle/520334_1

Simoneau, J. A., Colberg, S. R., Thaete, F. L., & Kelley, D. E. (1995). Skeletal muscle glycolytic and oxidative enzyme capacities are determinants of insulin sensitivity and muscle composition in obese women. *FASEB J., 9*(2), 273-278.

Siri, W. E. (1956). The gross composition of the body. *Advances in Biological and Medical Physics, 4*, 239-280.

Sjostrom, L., Kvist, H., Cederlad, A., & Tylen, U. (1986). Determination of total adipose tissue and body fat in women by computed tomography, 40K and tritium. *American Journal of Physiology, 250*, E736-E745.

Sjostrom, L., Rissanen, A., Andersen, T., Boldrin, M., Golay, A., & Koppeschaar, H. P., et al. (1998). For the european multicentre orlistat study group. randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet, 352*, 167-172.

Sowers, J. R., Whitfield, L. A., Catania, R. A., Stern, N., Tuck, M. L., & Dornfeld, L., et al. (1982). Role of the sympathetic nervous system in blood pressure maintenance in obesity. *The Journal of Clinical Endocrinology and Metabolism, 54*(6), 1181-1186.

Staessen, J. A., O'Brien, E. T., Atkins, N., & Amery, A. K. (1993). Short report: Ambulatory blood pressure in normotensive compared with hypertensive subjects. the ad-hoc working group. *Journal of Hypertension, 11*(11), 1289-1297.

Staessen, J. A., Thijs, L., Gasowski, J., Cells, H., & Fagard, R. H. (1998). Treatment of isolated systolic hypertension in the elderly: Further evidence from the systolic hypertension in europe (syst-eur) trial. *The American Journal of Cardiology, 82*(9B), 20R-22R.

Stanley, B. G., Willett, V. L.,3rd, Donias, H. W., Ha, L. H., & Spears, L. C. (1993). The lateral hypothalamus: A primary site mediating excitatory amino acid-elicited eating. *Brain Research, 630*(1-2), 41-49.

Stefan, N., Vozarova, B., Funahashi, T., Matsuzawa, Y., Weyer, C., & Lindsay, R. S., et al. (2002). Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. *Diabetes, 51*(6), 1884-1888.

Su, H. Y., Sheu, W. H., Chin, H. M., Jeng, C. Y., Chen, Y. D., & Reaven, G. M. (1995). Effect of weight loss on blood pressure and insulin resistance in normotensive and hypertensive obese individuals. *American Journal of Hypertension : Journal of the American Society of Hypertension, 8*(11), 1067-1071.

Tochikubo, O., Miyajima, E., & Ishii, M. (1994). Improvement of multiple coronary risk factors in obese hypertensives by reduction of intra-abdominal visceral fat. *The Japanese Heart Journal, 35*(6), 715-725.

Tonstad, S., Tykarski, A., Weissgarten, J., Ivleva, A., Levy, B., & Kumar, A., et al. (2005). Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension. *The American Journal of Cardiology, 96*(2), 243-251.

Tremblay, A., Chaput, J. P., Berube-Parent, S., Prud'homme, D., Leblanc, C., & Almeras, N., et al. The effect of topiramate on energy balance; a 6 month double-blind randomized placebo-controlled study with a 6 month open-label extension. *Unpublished Data,*

Tsuchida, A., Yamauchi, T., Ito, Y., Hada, Y., Maki, T., & Takekawa, S., et al. (2004). Insulin/Foxo1 pathway regulates expression levels of adiponectin receptors and adiponectin sensitivity. *Journal of Biological Chemistry, 279*(29), 30817-30822.

Tsujii, S., & Bray, G. A. (1991). GABA-related feeding control in genetically obese rats. *Brain Research, 540*(1-2), 48-54.

Unknown. (January, 2002). *International task force on obesity.* Retrieved October/15, 2004 from http://www.iotf.org/

US Department of Health and Human Services, Office of the Surgeon General. (2001). *The surgeon general's call to action to prevent and decrease overweight and obesity.* Rockville, Maryland: US Department of Health and Human Services.

Uysal, K. T., Wiesbrock, S. M., Marino, M. W., & Hotamisligil, G. S. (1997). Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature, 389*(6651), 610-614.

Vague, J. (1947). La differenciation sexuelle, facteur deterimnant des formes de l'obesite. *La Presse Medicale, 4*, 20-34.

van der Kooy, K., & Seidell, J. C. (1993). Techniques for the measurement of visceral fat: A pratical guide. *International Journal of Obesity, 17*, 187-196.

van der Kooy, K., Leenen, R., Seidell, J. C., Deurenberg, P., Droop, A., & Bakker, C. J. (1993). Waist-hip ratio is a poor predictor of changes in visceral fat. *The American Journal of Clinical Nutrition, 57*(3), 327-333.

Vettor, R., Milan, G., Rossato, M., & Federspil, G. (2005). Review article: Adipocytokines and insulin resistance. *Alimentary Pharmacology & Therapeutics, 22 Suppl 2*, 3-10.

Vincent, M. A., Barrett, E. J., & Lindner, J.R. et al. (2003). Inhibiting NOS blocks microvascular recruitment and blunts muscle glucose uptake in response to insulin. *American Journal of Physiology and Endocrinology Metabolism, 285*, E123-E129.

Vollenweider, P., Randin, D., Tappy, L., Jequier, E., Nicod, P., & Scherrer, U. (1994). Impaired insulin-induced sympathetic neural activation and vasodilation in skeletal muscle in obese humans. *The Journal of Clinical Investigation, 93*(6), 2365-2371.

Vollenweider, P., Tappy, L., Randin, D., Schneiter, P., Jequier, E., & Nicod, P., et al. (1993). Differential effects of hyperinsulinemia and carbohydrate metabolism on sympathetic nerve activity and muscle blood flow in humans. *The Journal of Clinical Investigation, 92*(1), 147-154.

Wadden, T. A., Vogt, R. A., Foster, G. D., & Anderson, D. A. (1998). Exercise and the maintenance of weight loss: 1-year follow-up of a controlled clinical trial. *Journal of Consulting and Clinical Psychology, 66*(2), 429-433.

Watanabe, J., & Tochikubo, O. (2003). Relationship between visceral fat accumulation and hypertension in obese men. *Clinical Experimental Hypertension, 25*, 199-208.

Weiss, R., Dufour, S., Groszmann, A., Petersen, K., Dziura, J., & Taksali, S. E., et al. (2003). Low adiponectin levels in adolescent obesity: A marker of increased intramyocellular lipid accumulation. *The Journal of Clinical Endocrinology and Metabolism, 88*(5), 2014-2018.

White, S. (2003). Mechanism of action of new anticonvulsants. *Journal of Clinical Psychiatry, 64*(Supplementary 8), 5-8.

White, H. S., Brown, S. D., Woodhead, J. H., Skeen, G. A., & Wolf, H. H. (2000). Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. *Epilepsia, 41 Suppl 1*, S17-20.

White, M. F., & Kahn, C. R. (1994). The insulin signaling system. *Journal of Biological Chemistry, 269*(1), 1-4.

Wilding, J., Van Gaal, L., Rissanen, A., Vercruysse, F., & Fitchet, M. (2004). A randomized double-blind placebo-controlled study of the long-term efficacy and

safety of topiramate in the treatment of obese subjects. *International Journal of Obesity, 28*, 1399-1410.

Wilkes, J. J., Nelson, E., Osborne, M., Demarest, K. T., & Olefsky, J. M. (2005). Topiramate is an insulin-sensitizing compound in vivo with direct effects on adipocytes in female ZDF rats. *American Journal of Physiology. Endocrinology and Metabolism, 288*(3), E617-24.

Willet, W. C., Manson, J. E., Stampfer, M. J., Colditz, G. A., Rosner, B., & Speizer, F. E., et al. (1995). Weight, weight change, and coronary heart disease in women: Risk within the normal weight range. *The Journal of the American Medical Association, 273*, 461-465.

Williams, M. J., Hunter, G. R., Kekes-Szabo, T., Trueth, M. S., Snyder, S., & Berland, L., et al. (1996). Intra-abdominal adipose tissue cut-points related to elevated cardiovascular risk in women. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity, 20*(7), 613-617.

Xenachis, C., Samojlik, E., Raghuwanshi, M. P., & Kirschner, M. A. (2001). Leptin, insulin and TNF-alpha in weight loss. *Journal of Endocrinological Investigation, 24*(11), 865-870.

York, D. A., Singer, L., Thomas, S., & Bray, G. A. (2000). Effect of topiramate on body weight and body composition of osborne-mendel rats fed a high-fat diet: Alterations in hormones, neuropeptide, and uncoupling-protein mRNAs. *Nutrition (Burbank, Los Angeles County, Calif.), 16*(10), 967-975.

Zelissen, P. M., Stenlof, K., Lean, M. E., Fogteloo, J., Keulen, E. T., & Wilding, J., et al. (2005). Effect of three treatment schedules of recombinant methionyl human leptin on body weight in obese adults: A randomized, placebo-controlled trial. *Diabetes, Obesity & Metabolism, 7*(6), 755-761.

Zeng, G., & Quon, M. J. (1996). Insulin-stimulated production of nitric oxide is inhibited by wortmannin: Direct measurement in vascular endothelial cell. *Journal of Clinical Invstigation, 98*, 894-898.

Zhi, J., Melia, A. T., & Guerciolini, R. (1994). Retrospective population-based analysis of the dose-response (fecal fat exretion) relationship of orlistat in normal and obese volunteers. *Clinical Pharmacology, 56*, 82-85.

Zierath, J. R., Livingston, J. N., Thorne, A., Bolinder, J., Reynisdottir, S., & Lonnqvist, F., et al. (1998). Regional difference in insulin inhibition of non-esterified fatty acid release from human adipocytes: Relation to insulin receptor phosphorylation and intracellular signalling through the insulin receptor substrate-1 pathway. *Diabetologia, 41*(11), 1343-1354.

# Appendix I: Compendium of Pharmaceuticals and Specialties

There is no information on incompatibilities at present and therefore raltitrexed should not be mixed with any other drug.

As with all parenteral drug products, i.v. admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solutions and containers permit.

**Supplied:** Each vial of sterile, lyophilized powder without preservative or bacteriostatic agent contains: raltitrexed 2 mg (as the disodium salt). Nonmedicinal ingredients: dibasic sodium phosphate, mannitol, nitrogen and sodium hydroxide. Single dose vials of 2 mg.

## Topamax® P

*Topiramate*

**Antiepileptic—Migraine Prophylaxis**

Janssen-Ortho

Date of Preparation: March 6, 1997
Date of Revision: May 9, 2005

**Summary Product Information:**

| Route of Administration | Dosage Form/Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Tablet 25 mg, 100 mg, 200 mg | Lactose<br>For a complete listing see Dosage Forms, Composition and Packaging. |
| Oral | Sprinkle capsule 15 mg, 25 mg | None<br>For a complete listing see Dosage Forms, Composition and Packaging. |

**Indications and Clinical Use: Epilepsy:** TOPAMAX (topiramate) is indicated as monotherapy for the management of patients (adults and children six years and older) with newly diagnosed epilepsy.

TOPAMAX (topiramate) is also indicated as adjunctive therapy for the management of patients (adults and children two years and older) with epilepsy who are not satisfactorily controlled with conventional therapy.

**Migraine:** TOPAMAX (topiramate) is indicated in adults for the prophylaxis of migraine headache. Prophylactic treatment of migraine may be considered in situations such as: adults experiencing four or more migraine attacks per month who fail to respond adequately to acute abortive therapy; recurring attacks that significantly interfere with the patient's daily routine; a pattern of increasing migraine attacks over time, with the risk of developing rebound headache from acute abortive therapies; or failure, or contraindication to, or troublesome side effects from acute abortive medications. Continuing therapy should be reviewed every six months. TOPAMAX should not be used in the acute treatment of migraine attacks. Safety and efficacy of topiramate in the management or prevention of cluster headache, hemiplegic, basilar, ophthalmoplegic, or transformed migraine headaches have not been established.

**Geriatrics (>65 years of age):** There is limited information in patients over 65 years of age. (See Warnings and Precautions, Special Populations, Geriatrics [>65 years of age].)

**Contraindications:**

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section.

**Warnings and Precautions: General:** Antiepileptic drugs, including TOPAMAX (topiramate), should be withdrawn gradually to minimize the potential of increased seizure frequency. In adult clinical trials, dosages were decreased by 100 mg/day at weekly intervals.

**Endocrine and Metabolism: Oligohidrosis and Hyperthermia:** Oligohidrosis (decreased sweating) and hyperthermia, infrequently resulting in hospitalization, including fatalities, have been reported in patients treated with topiramate. Oligohidrosis and hyperthermia may have potentially serious sequelae and may be preventable by prompt recognition of symptoms and appropriate treatment. Decreased sweating and elevation of body temperature above normal characterized the cases reported in patients treated with topiramate. Some of the cases were reported after exposure to elevated environmental temperatures.

These reports have primarily involved children. Patients treated with TOPAMAX, especially pediatric patients, should be monitored closely for evidence of decreased sweating and increased body temperature, particularly in hot weather. Proper hydration before and during activities such as exercise or exposure to warm temperatures is recommended.

Caution should be used when TOPAMAX is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity. (See Adverse Reactions, Post-market Adverse Drug Reactions.)

**Metabolic Acidosis:** Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/L at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in pediatric patients). Rarely, patients have experienced decreases to values below 10 mmol/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or certain drugs) may be additive to the bicarbonate lowering effects of topiramate.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mmol/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mmol/L and >5 mmol/L decrease from pretreatment) in these trials was 3% for 400 mg/day, and 0% for placebo. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (<16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut Syndrome or refractory partial onset seizures was 67% for TOPAMAX (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mmol/L and >5 mmol/L decrease from pretreatment) in these trials was 11% for TOPAMAX and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mmol/L and >5 mmol/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and <1% for placebo.

Safety and effectiveness in patients below the age of 2 years have not been established. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia (rickets) and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Chronic metabolic acidosis in pediatric patients can reduce growth rates. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in pediatric or adult populations.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

**Decreases in Serum Potassium with Concomitant Treatment with Hydrochlorothiazide (HCTZ):** In a drug interaction study, a greater decrease from baseline in serum potassium values was seen with concomitant treatment than for either drug alone. At the end of each treatment period, 27% (3/12) of subjects on topiramate treatment alone and 25% (3/12) of subjects on HCTZ treatment alone showed a serum potassium value of <3.6 mEq/L, compared to 61% (14/23) of subjects on concomitant drug treatment. One of the subjects who had hypokalemia with concomitant treatment also had an abnormal ECG (nonspecific ST-T wave changes), which may have been related to the decrease in plasma potassium levels. Caution should be used when treating patients who are receiving TOPAMAX and hydrochlorothiazide concomitantly. (See Drug Interactions.)

**Nutritional Supplementation:** A dietary supplement or increased food intake may be considered if the patient is losing weight while on this medication.

**Hepatic/Biliary/Pancreatic: Decreased Hepatic Function:** In hepatically impaired patients, TOPAMAX should be administered with caution as the clearance of topiramate was decreased compared with normal subjects.

**Neurologic: Central Nervous System Effects:** Adverse events most often associated with the use of TOPAMAX were central nervous system related and were observed in both the epilepsy and migraine populations. In adults, the most significant of these can be classified into three general categories:

i. psychomotor slowing, difficulty with concentration and speech or language problems, in particular, word-finding difficulties,
ii. somnolence or fatigue and
iii. mood disturbances including irritability and depression.

In the controlled epilepsy adjunctive therapy trials, these events were generally mild to moderate, and generally occurred early in therapy. While the incidence of psychomotor slowing does not appear to be dose related, both language problems and difficulty with concentration or attention increased in frequency with increasing dosage in the six double-blind trials, suggesting that these events are dose related (see Adverse Reactions, Post-market Adverse Drug Reactions).

Central nervous system and psychiatric-related events were also more frequently reported in topiramate-treated subjects in the migraine prophylaxis trials. These included: anorexia, dizziness, difficulty with memory, somnolence, language problems, and difficulty with concentration and attention. Most of the events were mild or moderate in severity, some of which led to withdrawal from treatment. (See Adverse Reactions, Migraine).

In the double-blind phases of clinical trials with topiramate in approved and investigational indications, suicide attempts occurred at an incidence of 0.2% (13 reports/7999 patients) on topiramate versus 0 (0 reports/3150 patients) on placebo. One completed suicide was reported in a bipolar disorder trial in a patient on topiramate (see Adverse Reactions, Less Common Clinical Trial Adverse Drug Reactions (<2%) and Post-market Adverse Drug Reactions).

Additional nonspecific CNS effects occasionally observed with TOPAMAX as add-on epilepsy therapy include dizziness or imbalance, confusion and memory problems. Although the duration of the epilepsy monotherapy studies was considerably longer than the epilepsy adjunctive therapy studies, these adverse events were reported at lower incidences in the monotherapy trials.

**Paresthesia:** Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX. Paresthesia was more frequently reported in the migraine prophylaxis and epilepsy monotherapy trials versus the adjunctive therapy trials in epilepsy. The higher incidence in the epilepsy monotherapy studies may have been related to the higher topiramate plasma concentrations achieved in the monotherapy studies. In the majority of instances, paresthesia did not lead to treatment discontinuation.

**Ophthalmologic: Acute Myopia and Secondary Angle Closure Glaucoma:** A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within a few days to 1 month of initiating TOPAMAX therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with TOPAMAX has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TOPAMAX, may be helpful (see Adverse Reactions, Post-market Adverse Drug Reactions).

In all cases of acute visual blurring and/or painful/red eye(s), immediate consultation with an ophthalmologist/emergency room is recommended.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequalae including permanent vision loss.

**Renal: Kidney Stones:** A total of 32/1715 (1.5%) of patients exposed to TOPAMAX during its epilepsy adjunctive therapy development reported the occurrence of kidney stones, an incidence about 10 times that expected in a similar, untreated population (M/F ratio: 27/1092 male; 5/623 female). In double-blind epilepsy monotherapy studies, a total of 8/886 (0.9%) of adults reported the occurrence of kidney stones. In the general population, risk factors for kidney stone formation include gender (male), ages between 20-50 years, prior stone formation, family history of nephrolithiasis, and hypercalciuria. Based on logistic regression analysis of the clinical trial data, no correlation between mean TOPAMAX dosage, duration of TOPAMAX therapy, or age and the occurrence of kidney stones was established; of the risk factors evaluated, only gender (male) showed a correlation with the occurrence of kidney stones. In the pediatric patients studied, there were no kidney stones observed.

Carbonic anhydrase inhibitors, e.g. acetazolamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. Concomitant use of TOPAMAX, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Patients, especially those with a predisposition to nephrolithiasis, may have an increased risk of renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Therefore, adequate hydration is recommended to reduce this risk. None of the risk factors for nephrolithiasis can reliably predict stone formation during TOPAMAX treatment.

**Adjustment of Dose in Renal Failure:** The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with impaired renal function ($CL_{CR}$ <70 mL/min/1.73 m²) or with end-stage renal disease receiving hemodialysis treatments may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function. As with all patients, the titration schedule should be guided by clinical outcome (i.e. seizure control, avoidance of side effects) with the knowledge that patients with known renal impairment may require a longer time to reach steady-state at each dose (see Dosage and Administration, Dosing Considerations).

**Information to Be Provided to the Patient: Pregnant Women:** Patients should be reminded to inform their doctor if they are pregnant or intend to become pregnant while on TOPAMAX therapy.

**Adequate Hydration:** Patients, especially those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation. Patients also should be instructed to increase and maintain fluid intake prior to and during activities such as exercise and exposure to warm temperatures to help prevent complications from decreased sweating.

**Occupational Hazards:** Effects on Ability to Drive and Use Machines: Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on TOPAMAX to gauge whether it adversely affects their mental and/or motor performance.

**Acute Myopia and Secondary Angle Closure Glaucoma:** Patients taking TOPAMAX should be told to immediately contact their doctor and/or go to the Emergency Room if they/their child experience(s) sudden worsening of vision, blurred vision or painful/red eye(s).

**Special Populations:** *Pregnant Women:* Like many other drugs, topiramate was teratogenic in mice, rats, and rabbits. In rats, topiramate crosses the placental barrier.

There are no studies using TOPAMAX in pregnant women. However, TOPAMAX therapy should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to TOPAMAX, with or without other anticonvulsants; however, a causal relationship with TOPAMAX has not been established.

The effect of TOPAMAX on labor and delivery in humans is unknown.

*Nursing Women:* Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since the potential for serious adverse reactions in nursing infants exposed to TOPAMAX exists, the prescriber should decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother and the risks to the infant.

**Pediatrics (<2 years of age):** Safety and effectiveness in children under 2 years of age have not been established.

**Weight Loss in Pediatrics (>2 years of age):** TOPAMAX administration is associated with weight loss in some children that generally occurs early in therapy. Of those pediatric subjects treated in clinical trials for at least a year who experienced weight loss, 96% showed a resumption of weight gain within the period tested. In 2-4 year-olds, the mean change in weight from baseline at 12 months (n=25) was +0.7 kg (range −1.1 to 3.2); at 24 months (n=14), the mean change was +2.2 (range −1.1 to 6.1). In 5-10 year- olds, the mean change in weight from baseline at 12 months (n=88) was +0.7 kg (range −6.7 to 11.8); at 24 months (n=67), the mean change was +3.3 (range −8.6 to 20.0). Weight decreases, usually associated with anorexia or appetite changes, were reported as adverse events for 9% of patients treated with TOPAMAX. The long-term effects of reduced weight gain in pediatric patients are not known.

**Geriatrics (>65 years of age):** There is limited information in patients over 65 years of age. The possibility of age-associated renal function abnormalities should be considered when using TOPAMAX. (See Action and Clinical Pharmacology, Special Populations and Conditions.)

**Monitoring and Laboratory Tests:** It has been observed in clinical trials that topiramate treated subjects experienced an average decrease in serum bicarbonate level of 4 mmol/L and an average increase in serum chloride level of 4 mmol/L. (See Warnings and Precautions, Endocrine and Metabolism.)

**Hypokalemia Observed During Concomitant Treatment With Hydrochlorothiazide:** In a drug interaction study with the diuretic hydrochlorothiazide (HCTZ), the percentage of patients with a serum potassium measurement of <3.6 mEq/L was greater at the end of concomitant treatment than at the end of treatment for either drug alone: 27% (3/11) of subjects on topiramate treatment alone and 25% (3/12) of subjects on HCTZ alone versus 61% (14/22) of subjects on concomitant drug treatment. (See Warnings and Precautions, Endocrine and Metabolism and Drug Interactions.)

**Adverse Reactions: Epilepsy: Adverse Drug Reaction Overview for Monotherapy: Adults:** The most commonly observed adverse events associated with the use of topiramate at dosages of 100 to 400 mg/day in controlled trials in adults with newly diagnosed epilepsy were: paresthesia, fatigue, headache, somnolence, dizziness, upper respiratory tract infection, anorexia, weight decrease, depression, and nausea (see Table 1).

Approximately 19% of the 886 adult patients who received topiramate as monotherapy in controlled clinical trials for patients with newly diagnosed epilepsy discontinued therapy due to adverse events. Adverse events associated with discontinuing therapy included paresthesia (2.6%), somnolence (2.5%), fatigue (2.3%), nausea (2.0%), and psychomotor slowing (1.6%).

**Pediatrics:** The most commonly observed adverse events associated with the use of topiramate at dosages of 100 to 400 mg/day in controlled trials in children with newly diagnosed epilepsy were: upper respiratory tract infection, headache, anorexia, difficulty with concentration/attention, weight decrease, somnolence, paresthesia, fever, and fatigue (see Table 2).

Approximately 10% of the 245 pediatric patients who received topiramate as monotherapy in controlled clinical trials for patients with newly diagnosed epilepsy discontinued therapy due to adverse events. Adverse events associated with discontinuing therapy included difficulty with concentration/attention (2.0%). No pediatric patients withdrew due to psychomotor slowing.

**Clinical Trial Adverse Drug Reactions: Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.**

Table 1: TOPAMAX

Incidence of Treatment-emergent Adverse Events in Monotherapy Trials in Adults[a] Where Rate Was ≥2% in Any Topiramate Group

| Body System/Adverse Event | TOPAMAX Dosage (mg/day) | | |
|---|---|---|---|
| | 50–100 (n=444) | 200–400 (n=329) | 500 (n=113) |
| **Body as a Whole—General Disorders** | | | |
| Fatigue | 18 | 18 | 19 |
| Injury | 9 | 8 | 4 |
| Asthenia | 4 | 5 | 4 |
| Back Pain | 3 | 2 | 5 |
| Pain | 3 | 2 | 5 |
| Chest Pain | 2 | 2 | 3 |

(cont'd)

Table 1: TOPAMAX (cont'd)

Incidence of Treatment-emergent Adverse Events in Monotherapy Trials in Adults[a] Where Rate Was ≥2% in Any Topiramate Group

| Body System/Adverse Event | TOPAMAX Dosage (mg/day) | | |
|---|---|---|---|
| | 50–100 (n=444) | 200–400 (n=329) | 500 (n=113) |
| Fever | 1 | 2 | 3 |
| Syncope | 2 | 1 | 1 |
| Leg Pain | 2 | 2 | 1 |
| Peripheral Edema | 1 | <1 | 2 |
| **Central & Peripheral Nervous System Disorders** | | | |
| Paresthesia | 23 | 39 | 38 |
| Headache | 23 | 16 | 19 |
| Dizziness | 16 | 13 | 13 |
| Hypoesthesia | 5 | 5 | 12 |
| Language Problems | 4 | 5 | 6 |
| Ataxia | 3 | 5 | 4 |
| Speech Disorders/Related Speech Problems | 2 | 3 | 3 |
| Vertigo | 2 | 3 | 4 |
| Tremor | 3 | 2 | 3 |
| Hypertonia | 1 | 2 | 2 |
| Involuntary Muscle Contractions | 1 | 2 | 4 |
| Sensory Disturbances | 1 | 1 | 4 |
| Migraine | 2 | 1 | 1 |
| Abnormal Coordination | 1 | 1 | 3 |
| Convulsions Aggravated | 1 | 0 | 2 |
| Convulsions Grand Mal | <1 | 1 | 2 |
| Gait Abnormal | <1 | <1 | 3 |
| Dyskinesia | 0 | 0 | 2 |
| **Gastrointestinal System Disorders** | | | |
| Nausea | 11 | 12 | 12 |
| Diarrhea | 6 | 8 | 12 |
| Abdominal Pain | 6 | 8 | 7 |
| Dyspepsia | 5 | 5 | 4 |
| Vomiting | 4 | 3 | 2 |
| Constipation | 2 | 3 | 1 |
| Dry Mouth | 1 | 2 | 6 |
| Gastroenteritis | 2 | 1 | 2 |
| Gastritis | 1 | 2 | 2 |
| Tooth Ache | 1 | 1 | 2 |
| Gastrointestinal Disorder NOS | <1 | <1 | 2 |
| Hemorrhoids | <1 | <1 | 2 |
| Stomatitis Ulcerative | <1 | 0 | 2 |
| **Hearing and Vestibular Disorders** | | | |
| Tinnitus | 1 | 2 | 2 |
| **Heart Rate and Rhythm Disorders** | | | |
| Palpitation | 1 | 1 | 4 |
| Tachycardia | 1 | 0 | 2 |
| **Metabolic and Nutritional Disorders** | | | |
| Weight Decrease | 9 | 14 | 18 |

(cont'd)

Table 1: TOPAMAX *(cont'd)*

Incidence of Treatment-emergent Adverse Events in Monotherapy Trials in Adults[a] Where Rate Was ≥2% in Any Topiramate Group

| Body System/Adverse Event | TOPAMAX Dosage (mg/day) | | |
|---|---|---|---|
| | 50–100 (n=444) | 200–400 (n=329) | 500 (n=113) |
| **Muscle-Skeletal System Disorders** | | | |
| Arthralgia | 3 | 4 | 4 |
| Myalgia | 2 | 1 | 2 |
| Muscle Weakness | 1 | 1 | 2 |
| **Platelet, Bleeding & Clotting Disorders** | | | |
| Epistaxis | 1 | 2 | 1 |
| Hematoma | 0 | 0 | 2 |
| **Psychiatric Disorders** | | | |
| Somnolence | 11 | 15 | 19 |
| Anorexia | 8 | 14 | 11 |
| Insomnia | 9 | 8 | 9 |
| Difficulty with Memory NOS | 6 | 10 | 9 |
| Depression | 7 | 10 | 4 |
| Difficulty with Concentration/Attention | 6 | 9 | 8 |
| Nervousness | 6 | 7 | 8 |
| Mood Problems | 5 | 6 | 4 |
| Anxiety | 4 | 6 | 5 |
| Confusion | 4 | 5 | 7 |
| Psychomotor Slowing | 2 | 5 | 8 |
| Cognitive Problems NOS | 2 | 3 | 3 |
| Agitation | 2 | 2 | 3 |
| Emotional Lability | 1 | 3 | 2 |
| Aggressive Reaction | 2 | 1 | 2 |
| Libido Decreased | 1 | 2 | 1 |
| Depression Aggravated | <1 | 2 | 3 |
| Impotence | 1 | 1 | 2 |
| **Reproductive Disorders, Female** | | | |
| Menstrual Disorder | 3 | 1 | 8 |
| Dysmenorrhea | 2 | 2 | 0 |
| Intermenstrual Bleeding | 2 | 1 | 0 |
| Menorrhagia | 1 | 1 | 2 |
| Pregnancy Unintended | 1 | 1 | 2 |
| Mastitis | 0 | 0 | 2 |
| **Reproductive Disorders, Male** | | | |
| Premature Ejaculation | 0 | 0 | 2 |
| **Resistance Mechanism Disorders** | | | |
| Infection Viral | 5 | 9 | 6 |
| Otitis Media | 2 | 1 | 2 |
| **Respiratory System Disorders** | | | |
| Upper Respiratory Tract Infection | 15 | 13 | 10 |
| Pharyngitis | 5 | 5 | 2 |
| Sinusitis | 3 | 4 | 6 |
| Rhinitis | 3 | 3 | 5 |
| Bronchitis | 2 | 2 | 1 |

*(cont'd)*

Table 1: TOPAMAX *(cont'd)*

Incidence of Treatment-emergent Adverse Events in Monotherapy Trials in Adults[a] Where Rate Was ≥2% in Any Topiramate Group

| Body System/Adverse Event | TOPAMAX Dosage (mg/day) | | |
|---|---|---|---|
| | 50–100 (n=444) | 200–400 (n=329) | 500 (n=113) |
| Coughing | 2 | 2 | 2 |
| Dyspnea | 1 | 2 | 1 |
| Pneumonia | 1 | <1 | 3 |
| **Skin and Appendages Disorders** | | | |
| Rash | 3 | 4 | 3 |
| Alopecia | 3 | 3 | 1 |
| Acne | 1 | 3 | 2 |
| Pruritus | 1 | 3 | 1 |
| Increased Sweating | 1 | <1 | 2 |
| Maculopapular Rash | 1 | 0 | 2 |
| **Special Senses Other, Disorders** | | | |
| Taste Perversion | 3 | 5 | 6 |
| **Urinary System Disorders** | | | |
| Urinary Tract Infection | 2 | 2 | 5 |
| Micturition Frequency | 1 | 2 | 4 |
| Dysuria | <1 | 2 | 1 |
| Cystitis | <1 | 2 | 1 |
| Renal Calculus | <1 | 2 | 2 |
| **Vision Disorders** | | | |
| Vision Abnormal | 3 | 4 | 4 |
| Diplopia | 1 | 1 | 2 |

[a] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Table 2: TOPAMAX

Incidence of Treatment-emergent Adverse Events in Monotherapy Trials in Children Ages 6 up to 16 Years[a] Where Rate Was ≥2% in Any Topiramate Group

| Body System/Adverse Event | TOPAMAX Dosage (mg/day) | | |
|---|---|---|---|
| | 50–100 (n=125) | 200–400 (n=106) | 500[b] (n=14) |
| **Body as a Whole—General Disorders** | | | |
| Fatigue | 7 | 10 | 14 |
| Fever | 2 | 11 | 7 |
| Injury | 4 | 2 | 14 |
| Asthenia | 0 | 3 | 7 |
| Back Pain | 2 | 2 | 0 |
| Allergic Reaction | 1 | 1 | 7 |
| Allergy | 0 | 1 | 7 |
| Influenza-like Symptoms | 0 | 0 | 7 |
| **Central & Peripheral Nervous System Disorders** | | | |
| Headache | 27 | 17 | 29 |
| Dizziness | 9 | 8 | 0 |
| Paresthesia | 4 | 11 | 7 |
| Language Problems | 0 | 3 | 7 |
| Convulsions Grand Mal | 2 | 0 | 7 |
| Hypertonia | 0 | 0 | 7 |

*(cont'd)*

Table 2: TOPAMAX *(cont'd)*

**Incidence of Treatment-emergent Adverse Events in Monotherapy Trials in Children Ages 6 up to 16 Years[a] Where Rate Was ≥2% in Any Topiramate Group**

| Body System/Adverse Event | TOPAMAX Dosage (mg/day) | | |
|---|---|---|---|
| | 50–100 (n=125) | 200–400 (n=106) | 500[b] (n=14) |
| Hyperkinesia | 2 | 0 | 21 |
| Migraine | 2 | 1 | 0 |
| Muscle Contractions Involuntary | 1 | 2 | 0 |
| Tremor | 2 | 0 | 0 |
| Vertigo | 0 | 3 | 0 |
| Cramps Legs | 2 | 0 | 0 |
| Gait Abnormal | 2 | 0 | 0 |
| **Collagen Disorders** | | | |
| Auto-antibody Response | 0 | 0 | 7 |
| **Gastrointestinal System Disorders** | | | |
| Diarrhea | 9 | 7 | 7 |
| Vomiting | 8 | 6 | 14 |
| Abdominal Pain | 6 | 4 | 14 |
| Nausea | 4 | 5 | 14 |
| Gastroenteritis | 6 | 0 | 7 |
| Constipation | 1 | 0 | 7 |
| Gastrointestinal Disorder NOS | 0 | 0 | 7 |
| Dyspepsia | 2 | 1 | 0 |
| Tooth Ache | 1 | 1 | 7 |
| **Hearing and Vestibular Disorders** | | | |
| Earache | 2 | 0 | 0 |
| **Metabolic and Nutritional Disorders** | | | |
| Weight Decrease | 5 | 14 | 0 |
| Acidosis | 0 | 0 | 7 |
| **Muscle-Skeletal System Disorders** | | | |
| Arthralgia | 1 | 2 | 7 |
| **Platelet, Bleeding & Clotting Disorders** | | | |
| Epistaxis | 2 | 4 | 14 |
| **Psychiatric Disorders** | | | |
| Anorexia | 13 | 13 | 14 |
| Somnolence | 14 | 9 | 0 |
| Difficulty with Concentration/Attention | 6 | 13 | 7 |
| Insomnia | 5 | 4 | 14 |
| Nervousness | 5 | 6 | 0 |
| Mood Problems | 2 | 8 | 0 |
| Difficulty with Memory NOS | 4 | 2 | 14 |
| Cognitive Problems NOS | 1 | 6 | 0 |
| Psychomotor Slowing | 3 | 3 | 0 |
| Aggressive Reaction | 2 | 3 | 7 |
| Depression | 0 | 5 | 0 |
| Sleep Disorder | 2 | 2 | 0 |
| Personality Disorder (Behaviour Problems) | 2 | 2 | 0 |
| Anxiety | 2 | 1 | 0 |

*(cont'd)*

Table 2: TOPAMAX *(cont'd)*

**Incidence of Treatment-emergent Adverse Events in Monotherapy Trials in Children Ages 6 up to 16 Years[a] Where Rate Was ≥2% in Any Topiramate Group**

| Body System/Adverse Event | TOPAMAX Dosage (mg/day) | | |
|---|---|---|---|
| | 50–100 (n=125) | 200–400 (n=106) | 500[b] (n=14) |
| Confusion | 0 | 3 | 0 |
| Emotional Lability | 2 | 1 | 0 |
| **Red Blood Cell Disorder** | | | |
| Anemia | 1 | 2 | 0 |
| **Reproductive Disorders, Female** | | | |
| Vaginitis | 0 | 0 | 13 |
| Dysmenorrhea | 2 | 2 | 0 |
| Intermenstrual Bleeding | 0 | 2 | 0 |
| **Reproductive Disorders, Male** | | | |
| Testis Disorder | 2 | 0 | 0 |
| **Resistance Mechanism Disorders** | | | |
| Infection Viral | 4 | 7 | 7 |
| Infection | 2 | 6 | 0 |
| Otitis Media | 2 | 1 | 7 |
| **Respiratory System Disorders** | | | |
| Upper Respiratory Tract Infection | 26 | 25 | 21 |
| Pharyngitis | 9 | 5 | 21 |
| Rhinitis | 5 | 6 | 21 |
| Sinusitis | 3 | 6 | 14 |
| Bronchitis | 2 | 4 | 0 |
| Asthma | 2 | 1 | 0 |
| Coughing | 2 | 1 | 0 |
| **Skin and Appendages Disorders** | | | |
| Rash | 3 | 4 | 21 |
| Dermatitis | 1 | 0 | 7 |
| Alopecia | 1 | 3 | 0 |
| Acne | 2 | 0 | 0 |
| Nail Disorder | 2 | 0 | 0 |
| Pruritus | 0 | 2 | 0 |
| Rash Erythematous | 2 | 0 | 0 |
| **Urinary System Disorders** | | | |
| Urinary Incontinence | 2 | 2 | 7 |
| Renal Calculus | 0 | 0 | 7 |
| Micturition Frequency | 0 | 2 | 0 |
| Urinary Tract Infection | 2 | 0 | 0 |
| **Vascular Disorders** | | | |
| Flushing | 1 | 4 | 7 |
| **Vision Disorders** | | | |
| Conjunctivitis | 2 | 2 | 0 |

[a] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[b] Due to n=14 in the 500 mg topiramate group, an incidence of 7% represents one patient.

**Adverse Drug Reaction Overview for Adjunctive Therapy: Adults:** The most commonly observed adverse events associated with the adjunctive use of TOPAMAX (topiramate) at dosages of 200 to 400 mg/day in controlled trials in adults that were seen at greater frequency in patients treated with TOPAMAX and did not appear to be dose related within this dosage range were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, nystagmus, and paresthesia (see Table 3).

The most common dose-related adverse events at dosages of 200 to 1000 mg/day were: nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, and mood problems (see Table 4).

**Pediatrics:** Adverse events associated with the use of TOPAMAX at dosages of 5 to 9 mg/kg/day in worldwide pediatric clinical trials that were seen at greater frequency in patients treated with TOPAMAX were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease (see Table 5).

**Clinical Trial Adverse Drug Reactions: Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.**

Table 3: TOPAMAX

**Incidence of Treatment-emergent Adverse Events in Placebo-controlled, Add-on Epilepsy Trials in Adults[a,b] (Events that occurred in ≥ 2% of patients treated with TOPAMAX and occurred more frequently in patients treated with TOPAMAX than placebo-treated patients)**

| Body System/Adverse Event | Placebo (n=216) | TOPAMAX Dosage (mg/day) 200–400 (n=113) | 600–1000[b] (n=414) |
|---|---|---|---|
| **Body as a Whole** | | | |
| Asthenia | 1.4 | 8 | 3.1 |
| Back Pain | 4.2 | 6.2 | 2.9 |
| Chest Pain | 2.8 | 4.4 | 2.4 |
| Influenza-like Symptoms | 3.2 | 3.5 | 3.6 |
| Leg Pain | 2.3 | 3.5 | 3.6 |
| Hot Flushes | 1.9 | 2.7 | 0.7 |
| **Nervous System** | | | |
| Dizziness | 15.3 | 28.3 | 32.1 |
| Ataxia | 6.9 | 21.2 | 14.5 |
| Speech Disorders/Related Speech Problems | 2.3 | 16.8 | 11.4 |
| Nystagmus | 9.3 | 15 | 11.1 |
| Paresthesia | 4.6 | 15 | 19.1 |
| Tremor | 6 | 10.6 | 8.9 |
| Language Problems | 0.5 | 6.2 | 10.4 |
| Coordination Abnormal | 1.9 | 5.3 | 3.6 |
| Hypoesthesia | 0.9 | 2.7 | 1.2 |
| Abnormal Gait | 1.4 | 1.8 | 2.2 |
| **Gastrointestinal System** | | | |
| Nausea | 7.4 | 11.5 | 12.1 |
| Dyspepsia | 6.5 | 8 | 6.3 |
| Abdominal Pain | 3.7 | 5.3 | 7 |
| Constipation | 2.3 | 5.3 | 3.4 |
| Dry Mouth | 0.9 | 2.7 | 3.9 |
| **Metabolic and Nutritional** | | | |
| Weight Decrease | 2.8 | 7.1 | 12.8 |
| **Neuropsychiatric** | | | |
| Somnolence | 9.7 | 30.1 | 27.8 |
| Psychomotor Slowing | 2.3 | 16.8 | 20.8 |
| Nervousness | 7.4 | 15.9 | 19.3 |
| Difficulty with Memory | 3.2 | 12.4 | 14.5 |
| Confusion | 4.2 | 9.7 | 13.8 |
| Depression | 5.6 | 8 | 13 |
| Difficulty with Concentration/Attention | 1.4 | 8 | 14.5 |
| Anorexia | 3.7 | 5.3 | 12.3 |
| Agitation | 1.4 | 4.4 | 3.4 |
| Mood Problems | 1.9 | 3.5 | 9.2 |
| Aggressive Reaction | 0.5 | 2.7 | 2.9 |
| Apathy | 0 | 1.8 | 3.1 |
| Depersonalization | 0.9 | 1.8 | 2.2 |
| Emotional Lability | 0.9 | 1.8 | 2.7 |
| **Reproductive, Female** | (n=59) | (n=24) | (n=128) |
| Breast Pain, Female | 1.7 | 8.3 | 0 |
| Dysmenorrhea | 6.8 | 8.3 | 3.1 |
| Menstrual Disorder | 0 | 4.2 | 0.8 |
| **Reproductive Disorders, Male** | (n=157) | (n=89) | (n=286) |
| Prostatic Disorder | 0.6 | 2.2 | 0 |
| **Respiratory System** | | | |
| Pharyngitis | 2.3 | 7.1 | 3.1 |
| Rhinitis | 6.9 | 7.1 | 6.3 |
| Sinusitis | 4.2 | 4.4 | 5.6 |
| Dyspnea | 0.9 | 1.8 | 2.4 |
| **Skin and Appendages** | | | |
| Pruritus | 1.4 | 1.8 | 3.1 |
| **Vision** | | | |
| Diplopia | 5.6 | 14.2 | 10.4 |
| Vision Abnormal | 2.8 | 14.2 | 10.1 |
| **White Cell and RES** | | | |
| Leukopenia | 0.5 | 2.7 | 1.2 |

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.
[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Table 4: TOPAMAX

**Incidence (%) of Dose-related Adverse Events From Placebo-controlled, Add-on Epilepsy Trials in Adults**

| Adverse Event | Placebo (n=216) | TOPAMAX Dosage (mg/day) 200 (n=45) | 400 (n=68) | 600–1000 (n=414) |
|---|---|---|---|---|
| Fatigue | 13.4 | 11.1 | 11.8 | 29.7 |
| Nervousness | 7.4 | 13.3 | 17.6 | 19.3 |
| Difficulty with Concentration/Attention | 1.4 | 6.7 | 8.8 | 14.5 |
| Confusion | 4.2 | 8.9 | 10.3 | 13.8 |
| Depression | 5.6 | 8.9 | 7.4 | 13 |
| Anorexia | 3.7 | 4.4 | 5.9 | 12.3 |
| Language Problems | 0.5 | 2.2 | 8.8 | 10.1 |
| Anxiety | 6 | 2.2 | 2.9 | 10.4 |
| Mood Problems | 1.9 | 0 | 5.9 | 9.2 |

In six double-blind clinical trials, 10.6% of subjects (n=113) assigned to a TOPAMAX dosage of 200 to 400 mg/day in addition to their standard AED therapy discontinued due to adverse events, compared to 5.8% of subjects (n=69) receiving placebo. The percentage of subjects discontinuing due to adverse events appeared to increase at dosages above 400 mg/day. Overall, approximately 17% of all subjects (n=527) who received TOPAMAX in the double-blind trials discontinued due to adverse events, compared to 4% of the subjects (n=216) receiving placebo.

Table 5 lists treatment-emergent adverse events that occurred in at least 2% of children treated with 5 to 9 mg/kg/day TOPAMAX in controlled trials that were numerically more common than in patients treated with placebo.

(cont'd)

**Table 5: TOPAMAX**

**Incidence (%) of Treatment-emergent Adverse Events in Worldwide Pediatric Add-on Epilepsy Clinical Trials Experience (2-16 years of Age)[a,b] (Events that occurred in ≥2% of patients treated with TOPAMAX and occurred more frequently in patients treated with TOPAMAX than placebo-treated patients)**

| Body System/Adverse Event | Placebo (n=101) | Topiramate (n=98) |
|---|---|---|
| **Body as a Whole—General Disorders** | | |
| Fatigue | 5 | 16.3 |
| Injury | 12.9 | 14.3 |
| Allergic Reaction | 1 | 2 |
| **Central and Peripheral Nervous System Disorders** | | |
| Gait Abnormal | 5 | 8.2 |
| Ataxia | 2 | 6.1 |
| Hyperkinesia | 4 | 5.1 |
| Dizziness | 2 | 4.1 |
| Speech Disorders/Related Speech Problems | 2 | 4.1 |
| Convulsions Aggravated | 3 | 3.1 |
| Hyporeflexia | 0 | 2 |
| **Gastrointestinal System Disorders** | | |
| Nausea | 5 | 6.1 |
| Saliva Increased | 4 | 6.1 |
| Constipation | 4 | 5.1 |
| Gastroenteritis | 2 | 3.1 |
| **Metabolic and Nutritional Disorders** | | |
| Weight Decrease | 1 | 9.2 |
| Thirst | 1 | 2 |
| **Platelet, Bleeding and Clotting Disorders** | | |
| Purpura | 4 | 8.2 |
| Epistaxis | 1 | 4.1 |
| **Nervous Disorders** | | |
| Somnolence | 15.8 | 25.5 |
| Anorexia | 14.9 | 24.5 |
| Nervousness | 6.9 | 14.3 |
| Personality Disorder (Behaviour Problems) | 8.9 | 11.2 |
| Difficulty with Concentration/Attention | 2 | 10.2 |
| Aggressive Reaction | 4 | 9.2 |
| Insomnia | 6.9 | 8.2 |
| Mood Problems | 6.9 | 7.1 |
| Difficulty with Memory NOS[c] | 0 | 5.1 |
| Emotional Lability | 5 | 5.1 |
| Confusion | 3 | 4.1 |
| Psychomotor Slowing | 2 | 3.1 |
| **Reproductive Disorders, Female** | | |
| Leukorrhea | 0 | 2.3 |
| **Resistance Mechanism Disorders** | | |
| Infection Viral | 3 | 7.1 |
| Infection | 3 | 3.1 |
| **Respiratory System Disorders** | | |
| Upper Respiratory Tract Infection | 36.6 | 36.7 |
| Pneumonia | 1 | 5.1 |
| **Skin and Appendages Disorders** | | |
| Skin Disorder | 2 | 3.1 |
| Alopecia | 1 | 2 |
| Dermatitis | 0 | 2 |
| Hypertrichosis | 1 | 2 |
| Rash Erythematous | 0 | 2 |
| **Urinary System Disorders** | | |
| Urinary Incontinence | 2 | 4.1 |
| **Vision Disorders** | | |
| Eye Abnormality | 1 | 2 |
| Vision Abnormal | 1 | 2 |
| **White Cell and RES Disorders** | | |
| Leukopenia | 0 | 2 |

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.
[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.
[c] Not otherwise specified.

None of the pediatric patients who received TOPAMAX adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse events. In open extensions of the controlled clinical trials, approximately 9% of the 303 pediatric patients who received TOPAMAX at dosages up to 30 mg/kg/day discontinued due to adverse events. Adverse events associated with discontinuing therapy included aggravated convulsions (2.3%), language problems (1.3%), and difficulty with concentration/attention (1.3%).

When the safety experience of patients receiving TOPAMAX as adjunctive therapy in both double-blind and open-label trials (1446 adults and 303 children) was analyzed, a similar pattern of adverse events emerged.

**Less Common Clinical Trial Adverse Drug Reactions (<2%):** Adverse events that occurred less frequently but were considered potentially medically relevant included: taste perversion, cognitive problems (not otherwise specified) and psychosis/psychotic symptoms.

In adult and pediatric patients, nephrolithiasis was reported rarely. Isolated cases of thromboembolic events have also been reported; a causal association with the drug has not been established.

In clinical trials with topiramate, the occurrence rate for all potential cases of oligohidrosis (decreased sweating) was 0.25%.

In clinical trials for topiramate in epilepsy, migraine prophylaxis and other investigational indications (obesity, bipolar disorder and diabetic peripheral neuropathy), suicide-related adverse events* occurred at a rate of 0.8% (84 reports/10 846 patients) in topiramate versus 0.2% (5 reports/3150 patients) in placebo groups. Although the average exposure time for patients on topiramate (approximately 10 months) was longer than for those on placebo (approximately 5 months), these adverse events were reported randomly over the exposure period. Suicide attempts occurred in 0.3% (33 reports/10 846 patients) of the topiramate-treated patients compared to 0% in placebo groups. Of these 33 attempts, one completed suicide was reported in a double-blind bipolar disorder trial and 3 in the open-label phase of the bipolar disorder trials (see Warnings and Precautions, Neurologic, Central Nervous System Effects).

**Migraine: Adverse Drug Reaction Overview:** Table 6 includes those adverse events reported for patients in four multicentre, randomized, double-blind, placebo-controlled, parallel-group migraine prophylaxis clinical trials where the incidence rate in any topiramate treatment group was at least 2% and was greater than that for placebo patients. Most of the adverse events were mild or moderate in severity and most occurred more frequently during the titration period than during the maintenance period.

**Clinical Trial Adverse Drug Reactions:**

**Table 6: TOPAMAX**

**Incidence % of Treatment-emergent Adverse Events in Placebo-controlled Migraine Trials Where Rate Was at Least 2% in Any Topiramate Group and Greater Than the Rate in Placebo-treated Patients[a]**

| Body System/Adverse Event | Placebo (n=445) | TOPAMAX Dosage (mg/day) 50 (n=235) | 100 (n=386) | 200 (n=514) |
|---|---|---|---|---|
| **Body as a Whole—General Disorders** | | | | |
| Fatigue | 11 | 14 | 15 | 19 |
| Injury | 7 | 9 | 6 | 6 |
| Asthenia | 1 | <1 | 2 | 2 |
| Fever | 1 | 1 | 1 | 2 |
| Influenza-like Symptoms | <1 | <1 | <1 | 2 |

* Suicide-related adverse events include suicidal ideation, suicide attempt, suicide and any evidence of self-harm.

(cont'd)

Table 6: TOPAMAX *(cont'd)*

Incidence % of Treatment-emergent Adverse Events in Placebo-controlled Migraine Trials Where Rate Was at Least 2% in Any Topiramate Group and Greater Than the Rate in Placebo-treated Patients[a]

| Body System/Adverse Event | Placebo (n=445) | TOPAMAX Dosage (mg/day) 50 (n=235) | 100 (n=386) | 200 (n=514) |
|---|---|---|---|---|
| Allergy | <1 | 2 | <1 | <1 |
| **Central and Peripheral Nervous System Disorders** | | | | |
| Paresthesia | 6 | 35 | 51 | 49 |
| Dizziness | 10 | 8 | 9 | 12 |
| Hypoesthesia | 2 | 6 | 7 | 8 |
| Language Problems | 2 | 7 | 6 | 7 |
| Involuntary Muscle Contractions | 1 | 2 | 2 | 4 |
| Ataxia | <1 | 1 | 2 | 1 |
| Speech Disorders/Related Speech Problems | <1 | 1 | <1 | 2 |
| **Gastrointestinal System Disorders** | | | | |
| Nausea | 8 | 9 | 13 | 14 |
| Diarrhea | 4 | 9 | 11 | 11 |
| Abdominal Pain | 5 | 6 | 6 | 7 |
| Dyspepsia | 3 | 4 | 5 | 3 |
| Dry Mouth | 2 | 2 | 3 | 5 |
| Vomiting | 2 | 1 | 2 | 3 |
| Gastroenteritis | 1 | 3 | 3 | 2 |
| **Hearing and Vestibular Disorders** | | | | |
| Tinnitus | 1 | <1 | 1 | 2 |
| **Metabolic and Nutritional Disorders** | | | | |
| Weight Decrease | 1 | 6 | 9 | 11 |
| Thirst | <1 | 2 | 2 | 1 |
| **Musculoskeletal System Disorders** | | | | |
| Arthralgia | 2 | 7 | 3 | 1 |
| **Neoplasms** | | | | |
| Neoplasm NOS | <1 | 2 | <1 | <1 |
| **Psychiatric Disorders** | | | | |
| Anorexia | 6 | 9 | 15 | 14 |
| Somnolence | 5 | 8 | 7 | 10 |
| Difficulty with Memory NOS | 2 | 7 | 7 | 11 |
| Difficulty with Concentration/Attention | 2 | 3 | 6 | 10 |
| Insomnia | 5 | 6 | 7 | 6 |
| Anxiety | 3 | 4 | 5 | 6 |
| Mood Problems | 2 | 3 | 6 | 5 |
| Depression | 4 | 3 | 4 | 6 |
| Nervousness | 2 | 4 | 4 | 4 |
| Confusion | 2 | 2 | 3 | 4 |
| Psychomotor Slowing | 1 | 3 | 2 | 4 |
| Libido Decreased | 1 | 1 | 1 | 2 |
| Aggravated Depression | 1 | 1 | 2 | 2 |
| Agitation | 1 | 2 | 2 | 1 |
| Cognitive Problems NOS | 1 | <1 | 2 | 2 |

*(cont'd)*

Table 6: TOPAMAX *(cont'd)*

Incidence % of Treatment-emergent Adverse Events in Placebo-controlled Migraine Trials Where Rate Was at Least 2% in Any Topiramate Group and Greater Than the Rate in Placebo-treated Patients[a]

| Body System/Adverse Event | Placebo (n=445) | TOPAMAX Dosage (mg/day) 50 (n=235) | 100 (n=386) | 200 (n=514) |
|---|---|---|---|---|
| **Reproductive Disorders, Female** | | | | |
| Menstrual Disorder | 2 | 3 | 2 | 2 |
| **Reproductive Disorders, Male** | | | | |
| Ejaculation Premature | 0 | 3 | 0 | 0 |
| **Resistance Mechanism Disorders** | | | | |
| Viral Infection | 3 | 4 | 4 | 3 |
| Otitis Media | <1 | 2 | 1 | 1 |
| **Respiratory System Disorders** | | | | |
| Upper Respiratory Tract Infection | 12 | 13 | 14 | 12 |
| Sinusitis | 6 | 10 | 6 | 8 |
| Pharyngitis | 4 | 5 | 6 | 2 |
| Coughing | 2 | 2 | 4 | 3 |
| Bronchitis | 2 | 3 | 3 | 3 |
| Dyspnea | 2 | 1 | 3 | 2 |
| Rhinitis | 1 | 1 | 2 | 2 |
| **Skin and Appendages Disorders** | | | | |
| Pruritis | 2 | 4 | 2 | 2 |
| **Special Sense Other, Disorders** | | | | |
| Taste Perversion | 1 | 15 | 8 | 12 |
| Taste Loss | <1 | 1 | 1 | 2 |
| **Urinary System Disorders** | | | | |
| Urinary Tract Infection | 2 | 4 | 2 | 4 |
| Renal Calculus | 0 | 0 | 1 | 2 |
| **Vision Disorders** | | | | |
| Vision Abnormal | <1 | 1 | 2 | 3 |
| Blurred Vision[b] | 2 | 4 | 2 | 4 |
| Conjunctivitis | 1 | 1 | 2 | 1 |

[a] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[b] Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for >50% of events coded as vision abnormal, a preferred term.

Of the 1135 patients exposed to topiramate in the placebo-controlled studies, 25% discontinued due to adverse events, compared to 10% of the 445 placebo patients. The most common adverse events associated with discontinuing therapy in the topiramate-treated patients included paresthesia (6.7%), fatigue (4.3%), nausea (4.0%), difficulty with concentration/attention (2.9%), insomnia (2.7%), anorexia (2.1%), and dizziness (2.0%).

In the 6-month migraine prophylaxis controlled trials, the proportion of patients who experienced one or more cognitive-related events was 19% for TOPAMAX 50 mg/day, 22% for 100 mg/day, 28% for 200 mg/day and 10% for placebo. These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase but infrequently began in the maintenance phase.

Table 7 shows adverse events that were dose-dependent.

Table 7: TOPAMAX

Incidence (%) of Dose-related Adverse Events From Placebo-controlled Migraine Trials[a]

| Adverse Event | Placebo (n=445 | TOPAMAX Dosage (mg/day) 50 (n=235) | 100 (n=386) | 200 (n=514) |
|---|---|---|---|---|
| Paresthesia | 6 | 35 | 51 | 49 |
| Fatigue | 11 | 14 | 15 | 19 |
| Nausea | 8 | 9 | 13 | 14 |
| Anorexia | 6 | 9 | 15 | 14 |
| Dizziness | 10 | 8 | 9 | 12 |

*(cont'c*

Table 7: TOPAMAX *(cont'd)*

Incidence (%) of Dose-related Adverse Events From Placebo-controlled Migraine Trials[a]

| Adverse Event | Placebo (n=445 | TOPAMAX Dosage (mg/day) | | |
|---|---|---|---|---|
| | | 50 (n=235) | 100 (n=386) | 200 (n=514) |
| Weight Decrease | 1 | 6 | 9 | 11 |
| Difficulty with Memory NOS | 2 | 7 | 7 | 11 |
| Diarrhea | 4 | 9 | 11 | 11 |
| Difficulty with Concentration/Attention | 2 | 3 | 6 | 10 |
| Somnolence | 5 | 8 | 7 | 10 |
| Hypoesthesia | 2 | 6 | 7 | 8 |
| Anxiety | 3 | 4 | 5 | 6 |
| Depression | 4 | 3 | 4 | 6 |
| Mood Problems | 2 | 3 | 6 | 5 |
| Dry Mouth | 2 | 2 | 3 | 5 |
| Confusion | 2 | 2 | 3 | 4 |
| Involuntary Muscle Contractions | 1 | 2 | 2 | 4 |
| Abnormal Vision | <1 | 1 | 2 | 3 |
| Renal Calculus | 0 | 0 | 1 | 2 |

[a] The incidence rate of the adverse event in the 200 mg/day group was ≥2% than the rate in both the placebo group and the 50 mg/day group.

**Other Adverse Events Observed During Migraine Clinical Trials:** For the prophylactic treatment of migraine headache, topiramate has been administered to 1367 patients in all clinical studies (includes double-blind and open-label extension). During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology.

The following additional adverse events that were not described earlier were reported by greater than 1% of the 1367 topiramate-treated patients in the controlled clinical trials:

**Body as a Whole:** pain, chest pain, allergic reaction.

**Central and Peripheral Nervous System Disorders:** headache, vertigo, tremor, sensory disturbance, migraine aggravated.

**Gastrointestinal System Disorders:** constipation, gastroesophageal reflux, tooth disorder.

**Musculoskeletal System Disorders:** myalgia.

**Platelet, Bleeding and Clotting Disorders:** epistaxis.

**Reproductive Disorders, Female:** intermenstrual bleeding.

**Resistance Mechanism Disorders:** infection, genital moniliasis.

**Respiratory System Disorders:** pneumonia, asthma.

**Skin and Appendages Disorders:** rash, alopecia.

**Vision Disorders:** abnormal accommodation, eye pain.

**Post-market Adverse Drug Reactions:** In addition to the adverse experiences reported during clinical trial testing of TOPAMAX, the following adverse experiences have been reported in patients receiving marketed TOPAMAX from worldwide use since approval. There are insufficient data to support an estimate of their incidence or to establish causation.

The most frequently reported adverse events in spontaneous post-marketing reports on TOPAMAX include:

**Psychiatric:** somnolence or sedation, hallucination(s), depression, anorexia, aggressive reaction, psychosis, thinking abnormal, insomnia, emotional lability, delusion, amnesia, confusion, nervousness, agitation, concentration impaired, personality disorder, anxiety.

**Central and Peripheral Nervous System:** convulsions aggravated, paresthesia, speech disorder, ataxia, dizziness, convulsions, headache, hyperkinesia, convulsions grand mal, hypoaesthesia.

**Metabolic and Nutritional:** weight decrease, metabolic acidosis, hypokalemia, hyperchloremia.

**Vision:** vision abnormal (includes vision decreased, vision blurred, visual disturbance, visual impairment, amblyopia); rarely reported: diplopia, glaucoma, myopia, eye pain.

**Gastrointestinal:** nausea, diarrhea, abdominal pain, constipation, vomiting.

**Body as a Whole—General Disorders:** fatigue, fever, dehydration, flushing, hot flushes.

**Urinary System:** renal calculus.

**Skin and Appendages:** rash, alopecia, sweating decreased.

**White Cell and RES Disorders:** leukopenia, thrombocytopenia.

Oligohidrosis (decreased sweating) has been rarely reported with the use of TOPAMAX. The majority of spontaneous post-marketing reports have been in children. Adverse events that may be related to potential cases of oligohidrosis include dehydration, hyperthermia, and heat intolerance. Adequate hydration prior to activities such as exercise or exposure to warm temperatures is recommended (see Warnings and Precautions, Endocrine and Metabolism).

To date, there have been rare spontaneous, post-marketing reports of metabolic acidosis. In some cases, acidosis resolved after dosage reduction or upon discontinuation of topiramate (see Warnings and Precautions, Endocrine and Metabolism).

Rare reports of encephalopathy with or without hyperammonemia have been received for patients treated with TOPAMAX while also taking valproate or other antiepileptic medications (see Drug Interactions).

Reports of increases in liver function tests in patients taking TOPAMAX with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with TOPAMAX.

Very rare reports have also been received for bullous skin and mucosal reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and pemphigus). The majority of these reports have occurred in patients taking other medications that can be associated with bullous skin and mucosal reactions.

There have been rare spontaneous postmarketing reports of suicide attempts and suicide-related adverse events, including fatalities, in patients treated with topiramate alone or in combination with other medications (see Warnings and Precautions, Neurologic, Central Nervous System Effects).

*Drug Interactions:* **Drug-Drug Interactions:** In all of the studies below, except where noted, the maximum TOPAMAX dose administered was 200 mg/day.

**Antiepileptic Drugs:** Potential interactions between TOPAMAX and standard AEDs were measured in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on plasma concentrations are summarized in Table 8.

Table 8: TOPAMAX

Drug Interactions with TOPAMAX Therapy

| AED Co-administered | AED Concentration | Topiramate Concentration |
|---|---|---|
| Phenytoin | ↔[b] | ↓59% |
| Carbamazepine (CBZ) | ↔ | ↓40% |
| CBZ epoxide[a] | ↔ | NS |
| Valproic acid | ↓11% | ↓14% |
| Phenobarbital | ↔ | NS |
| Primidone | ↔ | NS |
| Lamotrigine | ↔ | 15% decrease |
| | at TOPAMAX doses up to 400 mg/day | |

[a] Is not administered but is an active metabolite of carbamazepine.

[b] Plasma concentrations increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

Legend:
↔=no effect on plasma concentration (<15% change).
↓=plasma concentrations decrease in individual patients.
NS=not studied.
AED=antiepileptic drug.

**Effects of TOPAMAX on Other Antiepileptic Drugs:** The addition of TOPAMAX to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TOPAMAX to phenytoin may result in an increase of plasma concentrations of phenytoin.

The effect of TOPAMAX on steady-state pharmacokinetics of phenytoin may be related to the frequency of phenytoin dosing. A slight increase in steady-state phenytoin plasma concentrations was observed, primarily in patients receiving phenytoin in two divided doses. The slight increase may be due to the saturable nature of phenytoin pharmacokinetics and inhibition of phenytoin metabolism ($CYP2C_{meph}$).

The addition of TOPAMAX therapy to phenytoin should be guided by clinical outcome. In general, as evidenced in clinical trials, patients do not require dose adjustments. However, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

**Effects of Other Antiepileptic Drugs on TOPAMAX:** Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX may require adjustment of the dose of TOPAMAX. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate, and therefore, does not warrant dosage adjustment of TOPAMAX.

Rare post-marketing reports of encephalopathy with or without hyperammonemia have been received for patients treated with TOPAMAX, while also taking valproate or other antiepileptic medications. Thus, caution is advised when polytherapy with valproate is necessary (see Adverse Reactions, Post-market Adverse Drug Reactions).

**Other Drug Interactions: Digoxin:** In a single-dose study, serum digoxin AUC decreased 12% due to concomitant TOPAMAX administration (200 mg/day). Multiple-dose studies have not been performed. When TOPAMAX is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

**CNS Depressants:** Concomitant administration of TOPAMAX and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that TOPAMAX not be used concomitantly with alcohol or other CNS depressant drugs.

**Oral Contraceptives:** TOPAMAX (50-200 mg/day) in Healthy Volunteers: In a pharmacokinetic interaction study in healthy volunteers, subjects were stratified into obese versus non-obese (n=12 versus n=12) with both groups concomitantly administered a combination oral contraceptive product containing 1 mg norethindrone plus 35 µg ethinyl estradiol and TOPAMAX (50 to 200 mg/day) given in the absence of other medications. For the ethinyl estradiol component, both obese and non-obese volunteers showed a decrease in mean AUC and $C_{max}$ at 200 mg/day (~10.7% and ~9.4% versus ~15.2% and ~11.3%, respectively) that were not statistically significant. Changes in individual subjects ranged from decreases of approximately 35% to 90% in 5 individuals to increases of approximately 35% to 60% in 3 individuals. At the 50 and 100 mg/day TOPAMAX doses, similar changes in mean $C_{max}$ and AUC were observed for non-obese volunteers. The clinical significance of these changes is unknown. For the norethindrone component, only the non-obese group showed a decrease (~11.8%). In view of the dose-dependent decreases seen in the ethinyl estradiol component in epileptic patients receiving TOPAMAX as adjunctive therapy (below), and the fact that the recommended dose is up to 400 mg/day, there may be greater decreases seen at doses above 200 mg/day as monotherapy.

TOPAMAX as Adjunctive Therapy With Valproic Acid in Epileptic Patients: In a pharmacokinetic interaction study, epileptic patients received TOPAMAX as adjunctive therapy with valproic acid and a combination oral contraceptive product containing norethindrone (1 mg) plus ethinyl estradiol (35 µg). In this study, TOPAMAX did not significantly affect the oral clearance of norethindrone. The serum levels of the estrogenic component decreased by 18%, 21% and 30% at daily doses of 200, 400 and 800 mg of topiramate, respectively. There are minimal clinical data regarding interaction of valproic acid and oral contraceptives.

In view of both of the above study findings, the efficacy of low-dose (e.g. 20 µg) oral contraceptives may be reduced in both the monotherapy and adjunctive therapy situation with topiramate. For topiramate doses up to 200 mg/day, which includes the recommended dose for migraine prophylaxis of 100 mg/day, the mean reduction in norethindrone and ethinyl estradiol exposure from topiramate treatment is not significant, although marked changes in individual patients are possible. In the treatment of epilepsy at doses greater than 200 mg/day, significant dose-dependent decreases in ethinyl estradiol exposure are expected. Patients on topiramate doses greater than 200 mg/day who are taking oral contraceptives should receive a preparation containing not less than 30 µg of estrogen. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

**Hydrochlorothiazide (HCTZ):** A parallel-arm drug-drug interaction study conducted in healthy volunteers (12 males, 11 females) evaluated the steady-state pharmacokinetics of the diuretic HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that mean topiramate $C_{max}$ increased by 27% and mean AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this statistically significant change is unknown. Thus, the concomitant use of topiramate and HCTZ may require a downward adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. In addition, greater decreases in serum potassium were seen with concomitant treatment than with either drug alone, both in terms of percentage of patients with a serum potassium measurements of <3.6 mEq/L at the end of each treatment period [61% (14/23) with concomitant treatment versus 27% (3/11) with topiramate alone versus 25% (3/12) with HCTZ alone] and in mean change from baseline (approximately −0.60 mEq/L for concomitant treatment versus −0.25 mEq/L for topiramate alone versus −0.12 mEq/L for HCTZ alone). One of the subjects who had hypokalemia with concomitant treatment also had an abnormal ECG (non-specific ST-T wave changes), which may have been related to the decrease in plasma potassium levels. See also Warnings and Precautions, Endocrine and Metabolism.

**Metformin:** A drug-drug interaction study conducted in 18 healthy volunteers, ages 18-37, evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin (500 mg b.i.d.) was given alone and when metformin and topiramate (50, 75 and 100 mg) were given simultaneously for 6 consecutive days. The results of this study indicated that metformin mean $C_{max}$ and mean $AUC_{0-12h}$ increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with TOPAMAX (up-titrated to 100 mg b.i.d.). TOPAMAX did not affect metformin $t_{max}$. The effects of higher doses of topiramate (>100 mg b.i.d.) on metformin are unknown. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When TOPAMAX is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

**Pioglitazone:** A drug-drug interaction study conducted in healthy volunteers (26 males, 26 females) evaluated the steady-state pharmacokinetics of topiramate and the antidiabetic agent, pioglitazone, when administered alone and concomitantly. The pharmacokinetic parameters of topiramate were not affected; mean pioglitazone AUC decreased by 15%, mean $C_{max}$ increased non-significantly by 10%, but with individual subjects showing large increases, and 3 of the 4 highest values were recorded by males. In addition, each of the active hydroxy-metabolite and the active keto-metabolite showed mean decreases in $C_{max}$ and AUC (approximately 15% for the hydroxy-metabolite and 60% for the keto-metabolite). The clinical significance of these findings is not known. When TOPAMAX is added to pioglitazone therapy or pioglitazone is added to TOPAMAX therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

**Risperidone:** There was an approximate 25% decrease in each of $C_{max}$ and AUC of the atypical anti-psychotic risperidone (2 mg single dose) in 12 healthy volunteers (6 males, 6 females) receiving 200 mg/day of topiramate. Therefore, patients receiving risperidone in combination with topiramate should be closely monitored for clinical response to risperidone.

**Haloperidol:** The pharmacokinetics of a single dose of the antipsychotic haloperidol (5 mg) were not affected following multiple dosing of topiramate (200 mg/day) in 13 healthy adults (6 males, 7 females).

**Amitriptyline:** There was a 12% increase in both AUC and $C_{max}$ for the tricylic antidepressant amitriptyline (25 mg/day) in 18 normal subjects (9 males, 9 females) receiving 200 mg/day of topiramate. Individual subjects experienced large changes in amitriptyline concentration, either up or down, in the presence of topiramate; any adjustments in amitriptyline dose should be made according to patients clinical response and not on the basis of plasma levels.

**Pizotifen:** Multiple dosing of topiramate (200 mg/day) in 19 healthy volunteers (12 males, 7 females) had little effect on the pharmacokinetics of the antihistamine pizotifen following daily 1.5 mg doses. There was a mean 12% and 15% decrease respectively in topiramate $C_{max}$ and AUC in the volunteers (12 males and 7 females) receiving 200 mg/day topiramate and 1.5 mg/day pizotifen. This is not considered to be clinically significant.

**Dihydroergotamine:** Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 males, 12 females) had little effect on the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine and a 1 mg subcutaneous dose of dihydroergotamine similarly had little effect on the pharmacokinetics of a 200 mg/day dose of topiramate.

**Sumatriptan:** Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (14 males, 10 females) had little effect on the pharmacokinetics of single doses of the anti-migraine medication sumatriptan, either orally (100 mg) or subcutaneously (6 mg).

**Propranolol:** Multiple dosing of topiramate (100, then 200, mg/day) in 34 healthy volunteers (17 males, 17 females) had little effect on the pharmacokinetics of propranolol following daily 160 mg doses. There was a 17% increase in $C_{max}$ of the metabolite 4-OH propranolol at 100 mg/day topiramate. Propranolol doses of 80, then 160, mg/day in 39 volunteers (27 males, 12 females) had a dose-dependent effect on exposure to topiramate (200 mg/day), reaching approximately 16% increases for each of $C_{max}$ and AUC at 160 mg/day propranolol.

**Other Carbonic Anhydrase Inhibitors:** Concomitant use of TOPAMAX, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g. acetazolamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided if possible.

**Drug-Food Interactions:** There was no clinically significant effect of food on the bioavailability of topiramate.

**Drug-Herb Interactions:** Interactions with herbal products have not been established.

**Drug-Laboratory Interactions:** There are no known interactions of TOPAMAX with commonly used laboratory tests.

**Dosage and Administration: Dosing Considerations:**

- Patients with renal impairment
- Patients undergoing hemodialysis
- Patients with hepatic disease

**Recommended Dose and Dosage Adjustment:** TOPAMAX (topiramate) Tablets or Sprinkle Capsules can be taken without regard to meals.

**Epilepsy: Monotherapy: Adults and Children (Age 6 years and older):** The recommended initial target dose for topiramate monotherapy in adults and children 6 years of age and older is 100 mg/day and the maximum recommended dose is 400 mg/day, administered in two divided doses, as needed and tolerated.

The recommended titration rate for topiramate monotherapy to 100 mg/day is:

| | Week 1 | Weeks 2-3 | Weeks 3-4 |
|---|---|---|---|
| Morning Dose | None | 25 mg | 50 mg |
| Evening Dose | 25 mg | 25 mg | 50 mg |

If doses above 100 mg/day are required, the dose may be increased at weekly intervals in increments of 50 mg/day to a maximum of 400 mg/day. Dose and titration rate should be guided by clinical outcome. Some patients may benefit from a slower titration schedule. Daily doses above 400 mg have not been adequately studied. Only 14 pediatric patients have received 500 mg/day topiramate in controlled clinical trials (see Adverse Reactions, Epilepsy, Clinical Trial Adverse Drug Reactions, Table 2).

**Adjunctive Therapy: Adults (Age 17 years and older):** It is recommended that TOPAMAX as adjunctive therapy be initiated at 50 mg/day, followed by titration as needed and tolerated to an effective dose. At weekly intervals, the dose may be increased by 50 mg/day and taken in two divided doses. Some patients may benefit from lower initial doses, e.g. 25 mg and/or a slower titration schedule. Some patients may achieve efficacy with once-a-day dosing.

The recommended total daily maintenance dose is 200-400 mg/day in two divided doses. Doses above 400 mg/day have not been shown to improve responses and have been associated with a greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above 1600 mg have not been studied.

**Children (Ages 2-16 years):** It is recommended that TOPAMAX as adjunctive therapy be initiated at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week followed by titration as needed and tolerated to an effective dose. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Some patients may benefit from lower initial doses and/or a slower titration schedule.

The recommended total daily maintenance dose is approximately 5 to 9 mg/kg/day in two divided doses.

**Migraine: Adults:** The usual total daily dose of TOPAMAX as treatment for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used. No extra benefit has been demonstrated from the administration of doses higher than 100 mg/day and the incidence of some adverse events increases with increasing dose (see Adverse Reactions, Migraine, Table 7).

The recommended titration rate for topiramate for migraine prophylaxis to 100 mg/day is:

| | Morning Dose | Evening Dose |
|---|---|---|
| Week 1 | None | 25 mg |
| Week 2 | 25 mg | 25 mg |
| Week 3 | 25 mg | 50 mg |
| Week 4 | 50 mg | 50 mg |

**Pediatrics:** Safety and efficacy of topiramate in the management or prevention of migraine in pediatrics have not been established.

**Patients With Renal Impairment:** In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73 $m^2$), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

**Patients Undergoing Hemodialysis:** Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an antiseizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of TOPAMAX may be required. The actual adjustment should take into account 1) the duration of dialysis, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

**Patients With Hepatic Disease:** In hepatically impaired patients, topiramate plasma concentrations are increased approximately 30%. This moderate increase is not considered to warrant adjustment of the TOPAMAX dosing regimen. Initiate topiramate therapy with the same dose and regimen as for patients with normal hepatic function. The dose titration in these patients should be guided by clinical outcome, i.e. seizure control, and avoidance of adverse effects. Such patients will require a longer time to reach steady-state at each dose.

**Geriatrics:** See Warnings and Precautions.

**Missed Dose:** The missed dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next scheduled dose should be taken. Doses should not be doubled.

**Administration:** Tablets should not be broken. TOPAMAX Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use. The sprinkle formulation is provided for those patients who cannot swallow tablets, e.g. pediatric and the elderly.

**Overdosage:**

For management of a suspected drug overdose, CPhA recommends that you contact your **regional Poison Control Centre.** See the *CPS* Directory section for a list of Poison Control Centres.

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases but deaths have been reported after polydrug overdoses involving topiramate.

Topiramate overdose can result in severe metabolic acidosis (see Warnings and Precautions, Endocrine and Metabolism, Metabolic Acidosis).

A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

In acute topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate in vitro. Treatment should be appropriately supportive. Hemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

**Action and Clinical Pharmacology: Pharmacodynamics:** TOPAMAX (topiramate) is a novel agent classified as a sulfamate substituted monosaccharide. Three pharmacological properties of topiramate are believed to contribute to its anticonvulsant activity. First, topiramate reduces the frequency at which action potentials are generated when neurons are subjected to a sustained depolarization indicative of a state-dependent blockade of voltage-sensitive sodium channels. Second, topiramate markedly enhances the activity of GABA at some types of GABA receptors. Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor. Third, topiramate antagonizes the ability of kainate to activate the kainate/AMPA subtype of excitatory amino acid (glutamate) receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of topiramate's antiepileptic activity.

***Pharmacokinetics:*** Topiramate exhibits low intersubject variability in plasma concentrations and therefore has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 100 to 400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. The mean $C_{max}$ following multiple twice-a-day oral doses of 100 mg to healthy subjects was 6.76 µg/mL. The mean plasma elimination half-lives from multiple 50 mg and 100 mg q12h doses of topiramate were approximately 21 hours. The elimination half-life did not significantly change when switching from single dose to multiple dose.

In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations and its clinical efficacy. It is not necessary to monitor topiramate plasma concentrations to optimize therapy with TOPAMAX.

No evidence of tolerance requiring increased dosage has been demonstrated in patients during 5 years of use.

Concomitant multiple-dose administration of TOPAMAX, 100 to 400 mg q12h, with phenytoin or carbamazepine shows dose-proportional increases in plasma concentrations of topiramate.

**Absorption:** Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration ($C_{max}$) of 1.5 µg/mL was achieved within 2 to 3 hours ($T_{max}$). The mean extent of absorption from a 100 mg oral dose of $^{14}C$-topiramate was at least 81% based on the recovery of radioactivity from the urine.

There was no clinically significant effect of food on the bioavailability of topiramate.

**Distribution:** Approximately 13% to 17% of topiramate is bound to plasma proteins. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/mL has been observed.

The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 L/kg for a single-dose range of 100 to 1200 mg.

**Metabolism:** Topiramate is not extensively metabolized (≈20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and feces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of $^{14}C$-topiramate.

Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no pharmacological activity.

**Excretion:** In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of $^{14}C$-topiramate was excreted unchanged in the urine within 4 days. The mean renal clearance for 50 mg and 100 mg of topiramate, following q12h dosing, was approximately 18 mL/min and 17 mL/min, respectively. Evidence exists for renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid, and a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

**Special Populations and Conditions: Pediatrics:** Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. As in adults, topiramate pharmacokinetics were linear with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Compared with adult epileptic patients, mean topiramate clearance is approximately 50% higher in pediatric patients. Steady-state plasma topiramate concentrations for the same mg/kg dose are expected to be approximately 33% lower in children compared to adults. As with adults, hepatic enzyme-inducing antiepileptic drugs (AEDs) decrease the plasma concentration of topiramate.

**Geriatrics:** Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

**Race, Gender and Age:** Although direct comparison studies of pharmacokinetics have not been conducted, analysis of plasma concentration data from clinical efficacy trials have shown that race, gender and age appear to have no effect on the plasma clearance of topiramate. In addition, based on pooled analyses, race and gender appear to have no effect on the efficacy of TOPAMAX.

**Hepatic Insufficiency:** The plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.

**Renal Insufficiency:** The plasma and renal clearance of topiramate are decreased in patients with impaired renal function ($CL_{CR}$ <70 mL/min/1.73 m²), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renally impaired patients as compared to those with normal renal function.

**Hemodialysis:** Topiramate is effectively removed from plasma by hemodialysis (see Dosage and Administration).

**Storage and Stability:** TOPAMAX Tablets or Sprinkle Capsules should be stored in tightly closed containers at controlled room temperature (15 to 30°C). Protect from moisture.

**Information for the Patient:** Published in e-CPS, available by subscription at www.e-cps.ca.

**Dosage Forms, Composition and Packaging: Tablets: 25 mg:** Each white, embossed, round, coated tablet, marked "TOP" on one side, "25" on the other, contains: topiramate 25 mg. Nonmedicinal ingredients: carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, pregelatinized starch, microcrystalline cellulose, polyethylene glycol, polysorbate 80, purified water, sodium starch glycolate, titanium dioxide, and may contain synthetic iron oxide. Bottles of 100 with desiccant.

**100 mg:** Each yellow, embossed, round, coated tablet, marked "TOP" on one side, "100" on the other, contains: topiramate 100 mg. Nonmedicinal ingredients: carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, pregelatinized starch, microcrystalline cellulose, polyethylene glycol, polysorbate 80, purified water, sodium starch glycolate, titanium dioxide, and may contain synthetic iron oxide. Bottles of 60 with desiccant.

**200 mg:** Each salmon, embossed, round, coated tablet, marked "TOP" on one side, "200" on the other, contains: topiramate 200 mg. Nonmedicinal ingredients: carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, pregelatinized starch, microcrystalline cellulose, polyethylene glycol, polysorbate 80, purified water, sodium starch glycolate, titanium dioxide, and may contain synthetic iron oxide. Bottles of 60 with desiccant.

**Sprinkle Capsules: 15 mg:** Each white and clear gelatin capsule, containing small white to off-white spheres, marked "TOP" and "15 mg" on the side, contains: topiramate-coated beads 15 mg. Nonmedicinal ingredients: black pharmaceutical ink, cellulose acetate, gelatin, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres (sucrose and starch) and titanium dioxide. Bottles of 60 without desiccant.

**25 mg:** Each white and clear gelatin capsule, containing small white to off-white spheres, marked "TOP" and "25 mg" on the side, contains: topiramate-coated beads 25 mg. Nonmedicinal ingredients: black pharmaceutical ink, cellulose acetate, gelatin, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres (sucrose and starch) and titanium dioxide. Bottles of 60 without desiccant.

*(Shown in Product Identification Section)*

## Topicort® Preparations ℞

***Desoximetasone***

**Topical Corticosteroid**

Dermik

**Pharmacology:** Topicort preparations are primarily effective because of their anti-inflammatory, antipruritic and vasoconstrictive actions.

**Indications:** For the relief of acute or chronic corticosteroid-responsive dermatoses.

**Contraindications:** Topical corticosteroids are contraindicated in untreated bacterial, tubercular, fungal and most viral lesions of the skin (including herpes simplex, vaccinia and varicella) and in those patients with a history of hypersensitivity to any of the components of the preparation.

Topicort preparations are not for ophthalmic use.

**Warnings:** Systemic side effects may occur with topical corticosteroid preparations, particularly when these preparations are used over large areas or for an extended period of time or with occlusive dressings. A patient who has been on prolonged therapy, especially occlusive therapy, may develop adrenal suppression due to sufficient absorption of the steroid.

*Pregnancy:* The safety of topical corticosteroid preparations during pregnancy and lactation has not been established. The potential benefit should be weighed in these conditions against possible hazard to the fetus or the nursing infant. When indicated, they should not be used extensively, in large amounts or for prolonged periods of time in pregnant patients or nursing mothers.

*Lactation:* See Pregnancy.

**Precautions:** General: Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see Children).

If local infection exists, suitable concomitant antimicrobial or antifungal therapy should be administered as primary therapy. If it is considered necessary, the topical corticosteroid may be used as an adjunct to control inflammation, erythema and itching. If a favorable response does not occur promptly, application of the corticosteroid should be discontinued until the infection is adequately controlled.

If local irritation or sensitization develops, desoximetasone creams, gel and ointment should be discontinued and appropriate therapy instituted.

The use of occlusive dressings increases the percutaneous absorption of corticosteroids; their extensive use increases the possibility of systemic effects and is therefore not advisable. For patients with extensive lesions it may be preferable to use a sequential approach, treating one portion of the body at a time. The patient should be kept under close observation if treated with large amounts of topical corticosteroid or with the occlusive technique over a prolonged period of time.

Occlusive dressings should not be applied if there is an elevation of body temperature.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Topical corticosteroids should be used with caution on lesions close to the eyes.

Prolonged use of topical corticosteroid products may produce atrophy of skin and s.c. tissues, particularly on flexor surfaces and on the face. If this is noted, discontinue the use of this product.

The product should be used with caution in patients with stasis dermatitis and other skin diseases associated with impaired circulation.

Children: **Pediatric patients may demonstrate greater susceptibility to topical corticosteroid induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.**

Hypothalamic-pituitary-adrenal [HPA] axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

**Adverse Effects:** Topicort preparations are well tolerated. Side effects have been rare. Similar to other topical corticosteroid preparations, they may cause: burning sensation, dryness, itching, erythema, change in skin pigmentation, folliculitis, pyoderma, striae, telangiectasia and skin atrophy. The following reactions are reported when corticosteroid preparations are used extensively on intertriginous areas or under occlusive dressings: maceration of the skin, secondary infection, striae, miliaria, hypertrichosis and localized skin atrophy.

Adrenal suppression has been shown to occur with prolonged use of large doses of topical corticosteroids, particularly under occlusion, due to increased percutaneous absorption.

Posterior subcapsular cataracts have been reported following systemic use of corticosteroids.

**Overdose:**

For management of a suspected drug overdose, CPhA recommends that you contact your **regional Poison Control Centre**. See the *CPS* Directory section for a list of Poison Control Centres.

**Symptoms:** Toxic effects due to prolonged percutaneous absorption of large amounts of corticosteroids may include: reversible suppression of adrenal function, skin striae, ecchymoses, discoloration or atrophy, acneiform eruptions, hirsutism, infection. Prolonged systemic corticosteroid action may cause hypertension, peptic ulceration, hypokalemia, muscle weakness and wastage and subcapsular cataracts.

**Treatment:** Treatment should include symptomatic therapy and discontinuation of corticosteroid administration. In chronically affected patients, a gradual discontinuation may prevent the development of steroid withdrawal symptoms.

**Dosage:** Apply a thin film to the affected skin areas twice daily. Rub in gently.

**Supplied: Topicort Cream:** Each tube contains: desoximetasone, 0.25%. Nonmedicinal ingredients: isopropyl myristate, methylparaben, propylparaben, wool alcohols and wool alcohols ointment. Tubes of 20 and 60 g.

**Topicort Mild Cream:** Each tube contains: desoximetasone, 0.05%. Nonmedicinal ingredients: edetate disodium, isopropyl myristate, lactic acid, methylparaben, propylparaben, wool alcohols and wool alcohols ointment. Tubes of 20 and 60 g.

**Topicort Gel:** Each tube contains: desoximetasone, 0.05%. Nonmedicinal ingredients: alcohol, carbopol 940 (carboxypolymethylene), docusate sodium, edetate disodium, isopropyl myristate, trolamine and water. Extended-tip tubes of 20 and 60 g.

**Topicort Ointment:** Each tube contains: desoximetasone, 0.25%. Nonmedicinal ingredients: aluminum stearate, beeswax, butylated hydroxyanisole, citric acid, fatty acid pentaerythritol ester, fatty alcohol citrate, propylene glycol, sorbitan sesquioleate and white petrolatum. Tubes of 20 and 60 g.

Store between 15 and 30°.

**The safety of immunization programs is in part maximized through monitoring vaccine-associated adverse events. To report a vaccine-associated adverse event, complete the Report of Vaccine-associated Adverse Event form found in the APPENDICES.**