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Title: Investigation of Orlistat as an intervention for obesity and cardiovascular risk
factors: A systematic review

Date: November 2010

Originally published as: University of Chester MSc dissertation

Example citation: Wrigley, D. K. (2010). *Investigation of Orlistat as an intervention
for obesity and cardiovascular risk factors: A systematic review*. (Unpublished
master's thesis). University of Chester, United Kingdom.

Version of item: Submitted version

Available at: <http://hdl.handle.net/10034/125056>

**Investigation of Orlistat as an
Intervention for Obesity and
Cardiovascular Risk Factors:
A Systematic Review**

Daniel. K. Wrigley

Acknowledgements

I would like to acknowledge and thank Dr. Stephen Fallows for the support and guidance on how to construct and finalise my research project. Without his support, assistance, and supervision, this review would have been extremely difficult to complete.

I would also like to acknowledge Dr. John Buckley, Mike Morris, and the administration team in the CENS department at the University of Chester, for their support and patience throughout the entirety of my masters degree.

I would like to express my utmost gratitude to my father, Alan Wrigley, my mother, Sandra Kesteven, and grand-parents, Sheila and Kenneth Flintham, for their moral and financial support, without which my continuation into further education and the completion of this review would not have been possible.

I would also like to thank the family of my partner, Paula, Brian, and Lisa Povey, for the continual motivation and support throughout the construction of this review.

Finally, I would like to express special thanks to my partner, Gemma Povey, who over the last two years has supported, encouraged, and been there in every way possible for me in all aspects of life, work, and study. For that I am deeply thankful.

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Word count – 16,097

List of abbreviations (in alphabetical order)

AE – Adverse effect(s).
AF – Atrial Fibrillation.
BED – Binge Eating Disorder.
BMI – Body Mass Index.
CAD – Coronary Artery Disease.
CBT-gsh – Cognitive Behavioural Therapy with Guided Self Help.
CHO – Carbohydrate.
CV – Cardiovascular.
CVD – Cardiovascular Disease.
DBP – Diastolic Blood Pressure.
DM – Diabetes Mellitus.
EU – European Union.
FDA – Food and Drug Administration.
FFA – Free Fatty Acid.
FFM – Fat Free Mass.
GI – Gastrointestinal.
HbA1c – Glycosylated Haemoglobin.
HDL – High Density Lipoprotein.
HR – Heart Rate.
hs-CRP – High Sensitive-C Reactive Protein.
IGT – Impaired Glucose Tolerance.
LDL – Low Density Lipoprotein.
LVEF – Left Ventricular Ejection Fraction.
M1 – Four Member Lactone Ring Hydrolysed.
M3 – M1 with N-Formyl Leucine Moiety Cleaved.
MK-0557 – NPY-Y5 Antagonist.
NHS – National Health Service.
OTC – Over The Counter.
QOL – Quality of Life.
RCT – Randomised Controlled Trial.
SBP – Systolic Blood Pressure.
SD – Standard Deviation.
T2DM – Type 2 Diabetes Mellitus.
t.i.d – Three Times Daily.
VLCD – Very Low Calorie Diet.
VLED – Very Low Energy Diet.
WHO – World Health Organization.

Abstract

Background – Obesity is an ever increasing problem in modern society. Numerous pharmacological interventions have been introduced to combat the detrimental effects of this major health issue, including the lipase inhibitor, orlistat.

Objectives – To investigate, and assess, the pharmacological effect of two differing doses of orlistat (xenical® 120mg; and alli™ 60mg), on weight loss parameters and cardiovascular risk factors.

Search Strategy – Studies were obtained through computerised searches of MEDLIN, PUBMED, CINAHL, EMBASE, The Cochrane Library, Web of Knowledge, and from manual searches in recognised scientific journals.

Selection Criteria – Randomised controlled trials in adult only subjects, of any study duration, comparing orlistat against surgical intervention alternative medical intervention, and placebo, for weight loss and cardiovascular risk factors.

Data Extraction & Synthesis – One reviewer independently assessed relevant studies, risk of bias, and extracted data.

Main Results – Nineteen studies deemed relevant were included for final review. No study included cardiovascular mortality as an outcome. All studies reported significant ($p < 0.05$) weight loss in orlistat treated patients from baseline to end of treatment. Most frequent side effects were mainly gastrointestinal in nature. Onset of diabetes progression was reduced in orlistat patients. Other cardiovascular risk factors were shown to decrease in orlistat patients.

Conclusion – In patients with body mass index $\geq 27\text{kg/m}^2$, orlistat, sibutramine, and metformin reduce body weight to a similar degree. Orlistat reduces waist circumference to the greatest degree. Orlistat induces greater gastrointestinal side effects and a greater attrition rate. Alli™ needs greater investigation of effects.

1.0 Introduction

1.1 Background

1.1.1 The obesity epidemic

“Let me have men around me that are fat”

In the first act of Shakespeare’s *Julius Caesar*, the roman emperor suggests that higher body weight correlates with a well-balanced mental disposition. In Caesar’s time, of course, obesity was not considered a medical risk factor. Since the nineteenth century, however, a high calorie diet together with a sedentary lifestyle has been recognised as a potential risk factor for cardiovascular disease [CVD] (Von Dusch, 1868), cancer, and diabetes mellitus [DM] (Gikas et al. 2004). A variety of factors influence the rate of obesity in any particular geographical region, including age patterns (Bartali et al. 2002), socioeconomic factors (Heitmann, 1999), and a lack of physical activity (Lindstrom, Isaccson & Merla. 2003).

The worldwide prevalence of obesity is now reaching epidemic proportions. According to the World Health Organisation (WHO) regional office for Europe, almost 400 million adults (aged 15 years and older) are estimated to be overweight, with 130 million of these estimated to be obese (WHO, 2006). Approximately 30% of European children are overweight with one quarter of these being obese (Wang & Lobstein, 2008). These figures have been estimated to increase by the end of 2010, with approximately 150 million adults being overweight (WHO, 2006), and increases of 17% and 19% for overweight and obese children respectively from 2006 (Jackson-Leach & Lobstein, 2006).

In the U.S., statistics on obesity are far more concerning. Data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994), showed that the prevalence of obesity had increased by approximately 8% in the U.S

since being relatively stable from 1960-1980 (Kuczmarski, Flegal, Campbell & Johnson. 1994). Since those data were published additional reports from other sources have suggested that trends are continuing (Mokdad, Serdula & Dietz. 1999., Russell, Remington & Rumm. 2000., Mokdad, Bownan, Ford, Vinicor & Rales. 2001). Recent statistics suggest about one in four adult Americans would be classified as obese, based on self reported weight; more than one in three would be classified as obese based on objectively measured weight. These rates have roughly tripled over the past 20 years (Mokdad et al. 2001., Sturm, 2002., Ogden et al, 2006). The prevalence of overweight among children in the U.S. has also been increasing. Between the 1960's and 1988-1994, the prevalence among 6-11 year olds increased from 4% to 11%. During this same period, the prevalence of being overweight among 12-19 year olds increased from 5% to 11%, with the majority of these overweight children becoming overweight adults (Ogden et al, 2006).

1.1.2 Economic burden of obesity

Economic costs represent the monetary burden on society of illness and premature death as foregone alternatives and are measured in terms of direct and indirect costs. Direct costs are the value of resources that could be allocated to other uses in the absence of the disease. Indirect costs are the value of lost output because of cessation or reduction of productivity caused by morbidity or mortality, which represent wages lost through illness and disability, or the value of future earnings lost by people who die prematurely, respectively (Colditz, 1992).

Studies at the end of the last century reported that total U.S. healthcare expenditures attributed to obesity were \$51.6 billion in 1995, which attributes to almost 6% of total healthcare spending in direct costs (Wolf & Colditz, 1998). A

follow up study reported indirect costs to be £47.6 billion (Thompson, Edelsberg, Colditz, Bird & Oster. 1999). Expenditure will continue to rise in the U.S. particularly due to increases in obesity prevalence and in the cost of related health care (Thorpe, Florence, Howard & Joski. 2007).

In 1980, eight per cent of women in England were classified as obese, compared to six per cent of men. By 1998, the prevalence of obesity had nearly trebled to 21 per cent of women, and 17 per cent of men (Joint Health Surveys Unit. 1999), and at present there is no sign that the upward trend is moderating. In 2002, over half of women and approximately two-thirds of men were either overweight or obese. The growth of obesity in England reflects a world-wide trend which is most marked in, though not restricted to, developed countries. Most evidence suggests that the main reason for the rising prevalence is a combination of less active lifestyles and changes in eating patterns (National Audit Office. 2002).

Obesity has a substantial human cost by contributing to the onset of disease and premature mortality. It also has serious financial consequences for the National Health Service (NHS) and for the economy. Though there are inherent uncertainties in quantifying the link between obesity and associated disease, it has been estimated, in the recent past, the cost of obesity alone to industry and the broader economy is £3.7 billion with premature deaths among obese employees costing companies £1.1 billion a year. (National Audit Office, 2006)

It has been estimated that each year approximately €74 billion is spent on treating CVD in the European Union (EU), and about another €106 billion a year are incurred in indirect costs (Liu, Maniadakis, Gray & Raynor, 2006). WHO estimated, in 2001, that between one quarter and one half of CVD was attributable to being

overweight or obese, and as approximately two thirds of death and disability from being overweight or obese are related to CVD, this suggests total costs to European society of between €70 billion and €135 billion in 2001 (Raynor & Raynor, 2003).

Overall, the total cost attributable to obesity and its negative health consequences has been estimated to represent 2% to 7% of national health expenditures worldwide (WHO consultation on obesity, 2000). Reviews of economic evaluations are emerging from pharmacological therapies (O'meara, Riemsma, Shirran, Mather & ter Riet. 2001., Neovius & Narbro. 2008), and are encouraging production of such agents, including orlistat, to combat this economic burden.

1.2 What is orlistat?

Orlistat is a drug designed to treat obesity. The chemical formula of orlistat is $C_{29}H_{53}NO_5$. It is a diastomeric molecule with four chiral centres and a molecular weight of 495.7 (Roche Pharmaceuticals, 1999). Orlistat is a potent, inhibitor of pancreatic and gastric lipases. Also known as tetrahydrolipstatin, it is a chemically synthesized derivative of lipstatin, which is naturally produced by *Streptomyces toxytricini* (Hardvary et al, 1988., Borgstrom, 1988). Orlistat has been produced in two distinct versions. Firstly as prescription only in a 120mg dose called xenical® by Roche Pharmaceuticals, and more recently in a half dosage (60mg) called alli™ by GlaxoSmithKline, which is available over the counter (OTC). With this release of alli™, many issues have been raised, not only for physicians, but also for the worlds health care systems in terms of priorities for drug expenditures, and also for society in general (Lexchin, 2001).

1.3 Clinical pharmacology of orlistat

1.3.1 Mode of action

Olistat exerts its therapeutic activity in the lumen of the gastrointestinal (GI) tract by forming a covalent bond with the active serine residue site of gastric and pancreatic lipase. The inactivated enzymes are unable to hydrolyse dietary fat in the form of triglycerides to absorbable free fatty acids (FFA) and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Orlistat is highly specific for lipase and has no other significant inhibitory effect on other digestive enzymes such as amylase, trypsin, chymotrypsin, and phospholipases (Ballinger & Peikin, 2001).

1.3.2 Pharmacokinetics

Systemic exposure to orlistat is suggested to be minimal. Past research has shown that approximately 1% of orlistat is systemically absorbed with single dose studies showing plasma concentrations of intact orlistat <5mg/ml after a single dose of 800mg, and also after a multiple dose of 400mg for 5-23 days, in plasma samples taken up to 96 hours after dosing (Zhi, Melia & Eggers. 1995). In clinical studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low with no evidence of accumulation (Sjostrom et al. 1998). At therapeutic doses, orlistat is therefore unlikely to produce systemic lipase inhibition. A few cases of hypersensitivity (rash, urticari, and angioedema) have been reported with orlistat treatment (Ballinger. 2000). However, with these few exceptions, side effects of orlistat do not appear to be related to systemic exposure to the drug, or any components of the capsule.

After oral dosing, nearly all the administered drug is excreted in the faeces, mostly as intact orlistat. It is likely that the metabolism of orlistat occurs mainly within the GI wall. Two metabolites have been identified in oral [¹⁴C]-orlistat mass balance studies in obese patients. M1 (four member lactone ring hydrolysed) and M3 (M1 with *N*-formyl leucine moiety cleaved), accounted for approximately 42% of the total plasma concentration (Zhi et al. 1996., Zhi, Mulligan & Hauptman. 1999). These studies found that M1 and M3 have extremely weak lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively), and are considered pharmacologically inactive. The cumulative renal excretion of orlistat was less than 2% in these studies. Orlistat and its metabolites also undergo biliary excretion, with complete excretion (faecal and urinary) of radiolabelled orlistat taking 3 to 5 days (Zhi et al. 1996).

1.3.3 Pharmacodynamics

Based on faecal fat measurements, the effect of orlistat 120mg, three times daily, is seen after 2 days of treatment. On dis-continuation of treatment, faecal fat usually returns to baseline within 28-72 hours. The inhibition of dietary fat absorption by orlistat is dose dependent. There is little additional effect on faecal fat excretion at doses greater than 30mg daily and the maximum recommended dose is one 120mg capsule three times a day (Ballinger & Peikin. 2002).

1.4 Recommended intake

There is only one standard dose of orlistat (alli™, xenical®), regardless of age, weight or other medical conditions. However, the dose will differ depending on whether the subject is taking the prescription-only or OTC version [Food and Drug Administration (FDA). 2007]. The recommended dose of prescription-only orlistat (xenical®) for

weight loss in adults and children aged 12 or over, is orlistat 120mg, taken with each meal that contains fat, up to three times daily (t.i.d). The recommended dose of OTC orlistat (alli™), is half the dose of xenical® (60mg), but to be taken at the same frequency throughout the day, taken with each meal that contains fat, t.i.d. However, OTC alli™, is not approved for children, regardless of age. Both xenical® and alli™, are recommended to be taken with each meal, with each version taken up to an hour after a meal if necessary (taking it later than this will make the drug less effective). For both versions of orlistat, if a user skips a meal, or if a meal is consumed without fat, the dose of orlistat should also be missed out. Both versions of orlistat are not meant to be used alone, and should always be taken in conjunction with an appropriate and balanced diet (FDA. 2007).

The daily intake of fat, carbohydrate (CHO) and protein should be distributed as evenly as possible over three main meals. GI side effects may increase when orlistat is consumed with a meal high in fat content (>30% total daily calories from fat). The effect of orlistat on weight loss is diminished in patients consuming less than 30% of calories from fat. No dose adjustment is necessary for the geriatric patient. The safety and efficacy of orlistat has not yet been established in young children (<12 years old). At least one on-going study is attempting to determine the safety, tolerability and efficacy of orlistat in severely obese children and adolescents with obesity-related comorbid conditions. Patients should also be counselled to take a multi-vitamin that contains fat-soluble vitamins to ensure adequate nutrition, because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and β -carotene (Ballinger & Peikin. 2002).

1.5 Adverse effects of orlistat

1.5.1 Side effects

Adverse reactions from orlistat are largely GI in nature and related to the pharmacological effect of the drug on preventing the absorption of ingested fat (Royal Pharmaceutical Society, 2009). GI adverse effects (AE) may increase when orlistat is taken with a diet high in fat (>30% total calories from fat), or if the recommended daily fat intake is not distributed over three meals (Ballinger & Peikin. 2002). Diet related treatment effects include wind (flatulence) with or without oily spotting, sudden bowel motions, soft stools, and fatty oil stools (steatorrhoea). These diet related side effects typically occur about 1-2 days after taking orlistat with a high fat meal and are dependent on GI transit time, which varies between individuals, and is effected by food and drink that has previously been consumed (Royal Pharmaceutical Society. 2009). Other common effects of taking orlistat include anxiety, abdominal pain, liquid stools, faecal incontinence and increased defecation. Diverticulitis, hypersensitivity reactions, skin blistering, hepatitis, cholelithiasis, and mild rectal bleeding has also been reported (Royal Pharmaceutical Society. 2009). Post orlistat treatment has been associated with an increase in hunger and a decrease in fullness measured by visual analogue scales (Feinle, Rades, Otto & Fried. 2001), which may partially offset the benefit of the drug on weight loss. Levels of fat soluble vitamins (A, D, E) and β -carotene have been reportedly lowered by orlistat therapy, with vitamin D the most frequently reported affected (Sjostrom et al. 1998., Hollander et al. 1998., Finer, James, Kopelman, Lean & Williams. 2000., Hauptman, Lucas, Boldrin, Collins & Segal. 2000). In patients with insulin treated type 2 diabetes mellitus (T2DM), episodes of hypoglycemia have been reported. However, these

hypoglycaemic symptoms were mild to moderate, with only small numbers requiring medical intervention due to hypoglycaemia (Kelley et al. 2002).

1.5.2 Drug interactions

Few significant drug interactions have been reported for orlistat (Guercioli. 1997., Sjostrom et al. 1998., Xenical, 2000., Nagale, Peterson, Bonacker & Rodiger. 1999., Oo, Akbari & Lee 1999). However, there have been case reports of decreases in blood concentrations of cyclosporine to sub-therapeutic levels with concomitant use of orlistat, possibly due to a reduction in absorption; this may be associated with potentially dangerous under-immunosuppression (Nagale et al. 1999., Colman & Fossler. 2000). In short term studies, orlistat has not resulted in any change in warfarin pharmacokinetics or pharmacodynamics. However, because of a potential decrease in vitamin k absorption, patients stabilised on warfarin should be closely monitored for changes in coagulation parameters (Ballinger & Peikin. 2002).

1.6 Prevalence of orlistat use

1.6.1 Usage of xenical®

Xenical® was the third most heavily advertised drug in the U.S. throughout 1999; \$76 million were spent on advertising the drug to consumers (Bymark & Waite. 2001). As of 2002, eight drugs had been approved for weight loss. Of these, only xenical® was approved for up to two years of use (American Society of Health System Pharmacists. 2004). Statistics from a past U.S. study (Encinosa, Bernard, Steiner & Chen. 2002) demonstrated that of the 5.1 million patients taking prescription medication, about 4 million had bariatric drug coverage. Of that 4 million, 21,931 used bariatric prescription drugs, with 45% using xenical®. Patients within this study (Encinosa et

al. 2002), spent on average \$356 each for orlistat each year. This annual total payment per person increased with age from \$192 per person for those aged 18 and under, to \$378 dollars for ages 55-64. Although, within the study only 22% of these users were men, men were found to spend more on average on the weight loss drugs than women (\$327 versus \$297), because men used these drugs longer than women (122 days versus 117 days per year) and because a greater proportion of men than women used the most costly drug xenical® (44% versus 36%).

In the U.K the number of men and women using prescription weight loss medication is still rising. According to government figures, around almost 1.5 million weight loss prescriptions were issued for obesity drugs in 2009, which represented a 13% rise on the figure for 2008 and a two thirds increase in prescriptions from the 2005 figures. The most prescribed anti-obesity medication in the U.K in 2009 was xenical®. In all over 900,000 xenical® prescriptions were issued in the U.K alone in 2009 (Viner, Hsia, Neubert & Wong. 2009).

There has also been a dramatic rise in the number of children who are taking anti-obesity drugs. Since 1999, the number of people under the age of 18 on these medications has risen 15 fold across the U.K. A study looking at the rise in anti-obesity drug prescribing for children and adolescents in the U.K, found that, on average each year, a total of 1,334 prescriptions for anti-obesity drugs were issued to children and adolescents between 1999 and 2006, with xenical® making up 78.4% of all prescriptions.

The great majority of prescriptions were issued to female patients (82.3%). The mean age of first prescription was 17.0 years[SD 1.33; range 10-18 years; for females, mean 17.1 years(SD 1.27);for males, mean 16.7 years(SD 1.53)]. From 1999 to 2006 xenical® prescriptions a 28 fold increase. No anti-obesity drugs were

prescribed to children under 10 years old, with prescribing dramatically increasing from the age of 14 onwards (Viner et al. 2009).

1.6.2 Usage of alli™

In 2007 orlistat was approved by the FDA in the U.S for non prescription sales under the brand name alli™, at one half the daily dose of the prescription product xenical®, and at the time of writing, is the only FDA approved weight loss medication available OTC. However, limited research is available looking into the prevalence and usage of alli™, and what little research is available, focuses on the use of alli™ among patients with eating disorders (Steffen et al. 2010).

The majority of U.S adults were classified as obese at the beginning of the 21st century (National Centre for Health Statistics. 2006., Steffan et al. 2010). For these obese individuals, the ability to readily obtain orlistat without a prescription may be of an advantage. However, a substantial percentage of patients with an eating disorder engage in OTC medication and herbal product use to promote weight loss (Cumella, Hahn & Woods. 2007), and often continue using these agents, despite experiencing side effects (Steffan, Roerig, Mitchell & Crosby. 2006). A recent study investigating the frequency of alli™ use among patients with eating disorders, found that the frequency of the use of this drug was higher in those that were categorized as having eating disorders including; full or sub-threshold bulimia nervosa, full or sub-threshold binge eating disorder, and purging disorder (Steffan et al. 2010). The same study also reported that over a quarter of patients with eating disorders reported taking greater than the recommended dose of alli™.

With the release of alli™ onto the U.K market only occurring last year (April 2009), there is currently no official data as to how this drug has been received and

used by the U.K population. However, GlaxoSmithKline, the manufacturers alli™, claim “it was a hugely successful affair, with over £1 million worth of the sales in the first week alone” (GlaxoSmithKline, 2010). The true impact of alli™ on the U.K market, in terms of usage and economic values, remains to be seen.

2.0 Rationale and aim of review

Orlistat was the first of the lipase inhibitors available, as agents such as fenfluramine were withdrawn because of reports of significant adverse events, including aortic valvular regurgitation. Orlistat is capable of causing a caloric deficit, through inhibition of pancreatic and gastric lipases, thus suggesting as having a positive effect on weight control. This focus on weight loss parameters will form the main topic of discussion, with findings of effects of orlistat on cardiovascular (CV) risk factors and events, contributing to a further area of discussion. The purpose of this review is to investigate and analyse the efficacy of both forms of orlistat, OTC alli™ and prescription only xenical®, for use to reduce body weight along with reductions in CV risk factors in obese patients. This has been achieved through a systematic review of particular and relevant studies which were identified in accordance to a strict inclusion and exclusion criteria. One particular feature of this review was the use of a qualitative and quantitative assessment of the methodology of each study using the Jadad, 3-item quality assessment scale for the control bias (Jadad et al. 1996., as cited by Black. 2007). Previous research of existing studies regarding the use of orlistat as an intervention for weight reduction were analysed to determine if they possess relevant information regarding the questions below:

- Does the use of orlistat reduce body weight to desired parameters?
- Does the use of orlistat improve health factors related to obesity?
- Does orlistat have a significant effect on cardiovascular risk factors when taken?
- Are any changes in cardiovascular risk factors with the use of orlistat in conjunction with, or independent of weight reduction?
- Does orlistat dose (alli™ 60mg or xenical® 120mg) influence effect?
- Does gender, body mass/body fat or age influence effect?

3.0 Methodology

This section of the review will be used to explain the methods which were used to categorise and include the papers used for analysis and evaluation, as well as explaining how the papers were searched for and selected. This will ensure that all the relevant studies have been selected for inclusion and quality assessed. The Jadad 3-item quality assessment scale to assess the control of bias (Jadad et al, 1996) was carried out to evaluate the quality of each individual report.

3.1 Search strategy: Key words

The word “orlistat” is an essential text-word to search, as this returns papers which will concentrate on the anti-obesity agent of the chemically synthesized hydrogenated derivative of lipstatin, orlistat. There are two main specific trade names used for orlistat, which are alli™ and xenical®. Xenical® is the most commonly studied form of orlistat as it has been available on the market the longest. However, studies of alli™ are becoming more abundant as the length of time it has been available increases.

Recently, a study conducted looking into optimising search strategies for detecting clinically sound causation studies in MEDLINE (international literature database), found that specificity, defined as the proportion of low quality articles not retrieved, could be achieved using a single term (Wilczynski & Haynes, 2003). However, the same study found that using a combination of terms, (as many as three or more) enhance sensitivity (>93%), defined as proportion of high quality articles for a particular topic retrieved, as well as specificity (>94%), precision (>94%), defined as proportion of retrieved articles of high quality, and accuracy (>94%), defined as the proportion of articles correctly classified (Black. 2007). Wilczynski and Haynes (2003) also recommended using alternative words and terms to broaden the search.

The first step in this process is to break down the review question to help guide the development of search terms, using a structure such as PICOS (Centre for Reviews and Dissemination. 2009) as detailed below.

Population(s)/Patient(s) – Patients undergoing orlistat treatment

Intervention(s)/Treatment(s) – Orlistat (alli™ & xenical®)

Comparator(s) – placebo, surgery, lifestyle intervention, other medical intervention

Outcome(s) – Weight loss, cardiovascular disease/risk reduction

Study design – Randomized control trials (RCT's)

It is not necessary to include all of the PICOS concepts in the search strategy. It is preferable to search for those concepts that can be clearly defined and translated into search terms. To compile the list of keywords to search, the author's own knowledge of the area of research, the medical subject headings (MeSH) on-line vocabulary, and guidance from University librarians were utilised. The following text words for orlistat, body weight, and cardiovascular disease can be found in table 1.

Table 1 – Orlistat, body weight, and cardiovascular disease: related and associated key-words and text-words

Orlistat	Body-weight	Cardiovascular disease
alli™	body fat	cardiac disease
xenical®	body composition	heart disease
tetrahydrolipstatin	body mass	cardiovascular risk-factors

3.2 Search methodology

Once the concepts of the search had been determined, the next stage was to produce individual search protocols to be used by the author with regards to studies into

orlistat, body weight, and cardiovascular disease, which are described below. The search strategy comprised both indexing terms (from the database thesaurus or controlled vocabulary) and ‘free text’ terms and synonyms (from the database records title and abstracts) to ensure that as many relevant papers were retrieved as possible. For the purpose of this review, if a search retrieved five-hundred articles or more, it was assumed that for this particular database, the specificity of the search term was inadequate. The search protocol was in place to heighten specificity during search progression.

Orlistat and Body Weight search protocol

1. Primary search term: Orlistat AND Body Weight
2. Secondary search term(s): Orlistat AND Body Fat
Orlistat AND Body Composition
Orlistat AND Fat Mass
3. Tertiary search term(s):
Orlistat AND Body Weight AND Body Fat AND Body Composition
AND Fat Mass

Orlistat and Cardiovascular Disease search protocol

1. Primary search term: Orlistat AND Cardiovascular Disease
2. Secondary search term(s): Orlistat AND Cardiac Disease
Orlistat AND Heart Disease
Orlistat AND Cardiovascular Risk-Factors
3. Tertiary search term(s):
Orlistat AND Cardiovascular Disease AND Cardiac Disease AND
Heart Disease AND Cardiovascular Risk-Factors

The above key-words have been combined using Boolean logic (AND, OR, NOT) to create a set of results that should contain articles relating to the topic in question. The AND operator is used to ensure that all the search terms must appear in the record. This is demonstrated above. OR is used to accumulate similar search terms and thus make the search larger. Searching for “alli™ OR xenical® OR orlistat” retrieved all records where either alli™, xenical®, orlistat, or all three were found. NOT is used to exclude records from the search. For example, “lipase inhibitor NOT appetite suppressant” retrieved all records which contained the term ‘lipase inhibitor’, but not

those which also contained the term ‘appetite suppressant’. The final strategy was peer reviewed to check for errors (spelling mistakes, incorrect use of operators, or failure to include relevant MeSH) that could reduce the recall of papers, as advised in earlier research (Sampson & McGowen. 2006)

3.3 Database search

Numerous academic literature specific databases were used for the search terms that have been described previously in this chapter. This phase of the search process firstly uses specified scientific databases that are described below, followed by searches into specified journals.

MEDLINE (www.nlm.nih.gov)

MEDLINE is the U.S. National Library of Medicines® (NLM) premier bibliographical database that contains over 18 million references to journal articles in life sciences with a concentration on biomedicine. A distinctive feature of MEDLINE is that the records are indexed with NLM’s medical subject headings (MeSH).

PUBMED (www.ncbi.nlm.gov)

PUBMED comprises approximately 20 million citations for biomedical literature from MEDLINE, life science journals, and on-line books. PUBMED citations and abstracts include the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and pre-clinical sciences. PUBMED also provides access to additional relevant websites and links to other NCBI molecular biology resources.

PUBMED is a free resource that is developed and maintained by the National Centre for Biotechnology Information (NCBI), located at the National Institute of Health (NIH).

CINAHL (www.edscohost.com)

CINAHL, the Cumulative Index to Nursing and Allied Health Literature, is the most comprehensive resource for nursing and allied health literature. CINAHL provides indexing for nearly 3,000 journals from the fields of nursing and allied health. The database contains more than 2.2 million records dating back to 1981, offering complete coverage of English-language nursing journals and publications from the National League for Nursing and the American Nurses Association. CINAHL covers nursing, biomedicine, health sciences librarianship, alternative/complimentary medicine, consumer health, and 17 allied health disciplines.

EMBASE (www.embase.com)

EMBASE is a biomedical and pharmacological database containing bibliographical records with citations, abstracts and indexing derived from biomedical articles in peer reviewed journals, and is especially strong in its coverage of drug and pharmaceutical research. EMBASE contains over 12 million records from 1974 to present, with over 600,000 citations and abstracts added annually. Each record contains the full bibliographical citation, indexing terms and codes; 80% of all citations in EMBASE include author written abstracts. The EMBASE journal collection is international with approximately 7,000 active peer reviewed journals from 70 countries.

The Cochrane Library (www.thecochranelibrary.com)

The Cochrane Library is a collection of six databases that contain different types of high quality, independent evidence to inform healthcare decision making and a seventh database that provides information about groups in the Cochrane Collaboration. The databases that make up The Cochrane Library are:

- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- Cochrane Methodology Register
- Database of Abstracts of Reviews of Effects
- Health Technology Assessment Database
- NHS Economic Evaluation Database
- About The Cochrane Library

Web of Knowledge (www.wokinfo.com)

Web of Knowledge is a search environment that provides access to objective content and powerful tools to search, track, measure, and collaborate in the sciences, social sciences, art, and humanities. This research platform provides access to powerful citation databases, including powerful cited reference searching, the Analyze Tool, over 100 years of comprehensive back-file, and citation data. Web of Knowledge covers over:

- 23,000 journals
- 23 million patents
- 1110,000 conference proceedings
- 5,500 websites
- 2 million chemical structures
- 40 million source items
- 700 million cited references
- 256 scientific disciplines

3.4 Journal Articles

Searching for specific journal articles using specified search terms can provide published research that is not retrieved in the database searches that use more general

terms. Journal articles that are specific to the topics investigated in this particular review such as drug intervention, obesity, and cardiovascular comorbidities, were searched through individual academic journals which are listed below:

- American Journal of Cardiology
- British Medical Journal (BMJ)
- British Journal of Cardiology
- Circulation
- European Journal of Cardiovascular Prevention and Rehabilitation
- Journal of the American Medical Association (JAMA)
- New England Journal of Medicine (NEJM)
- International Journal of Obesity
- British Journal of Pharmacology

3.5 Selection Criteria

After articles of particular interest have been identified, the next phase of the selection process is to utilise the limit strategies within the database and journal article search.

This allows a more refined search which identifies articles of specific relevance, and limits the articles for review to a more manageable number. Often articles of interest can be gained to allow free online access to full texts through the PUBMED database, or via the electronic resources catalogue through the University of Chester

(www.chester.ac.uk), which subscribes to over 7,000 electronic online journals.

However, if these two options cannot be utilized, an article request can be made through the inter-library loans service, which will provide a copy of a particular article from the British Libraries Supply Centre (Boston Spa, West Yorkshire) (Black. 2007).

Studies were deemed relevant and included for review if:

- Examined orlistat's (either xenical®, alli™, or both) effects on weight loss, weight maintenance, or cardiovascular risk factors, or all three of these outcomes combined.
- Studies were carried out on human subjects.
- Full texts for studies were provided (abstracts not acceptable for review).
- Studies carried out on adults only (age ≥18 years).

- Studies must be written in English language.
- Studies must have been published in last 10 years (August 2000 – August 2010).
- The dose of orlistat must be described.
- Studies were deemed randomized (using the Jadad 3-item scale to control bias).
- Subjects who qualify for orlistat intervention, only to be used.

Only studies which conform to all of the mentioned selection criteria were deemed eligible for review. Any studies which did not conform to all of the mentioned selection criteria were excluded from review, but were used to support analytical debate if information within the article was deemed to be relevant. Duplication of papers was also taken into consideration to ensure that the same article was not reviewed multiple times.

A majority of textbooks define randomized controlled trials as a methodological design that includes random assignment of subjects to two or more subject groups in which the condition or treatment of interest is applied to one of the groups and not to the other (Kane, Wang & Garrard, 2007., as cited by Vasileiadi. 2008). Reports of randomized controlled trials are, at present, the gold standard by which health care professionals and others make decisions about the effectiveness of treatments (Moher, Jones & Lepage. 2001b). The random assignment of subjects is intended to achieve an equalization of subject groups and thereby equally distribute, if not eliminate, extraneous factors that could otherwise influence the outcomes of studies (Kane et al. 2007., as cited by Vasileiadi. 2008). Also, inclusion and exclusion criteria are frequently used to maximise comparability between the intervention and control groups (Kane et al. 2007., as cited by Vasileiadi. 2008).

The randomized controlled trial is one of the simplest, but most powerful tools of research (Stolberg, Norman & Trop. 2004). General use of RCT's has been promoted as an appropriate arena for evaluating interventions ranging from drug

treatment to developments in services (Pringle & Churchill. 1995), and they should and will remain a prominent tool in clinical research (Concato, Shah & Horwitz. 2000). Sibbald and Roland (1998) list numerous important features of RCT's as:

- Random allocation to intervention groups.
- Patients and trialists should remain unaware of which treatment was given until the study is completed, although such double blind studies are not always feasible or appropriate.
- All intervention groups are treated identically except for the experimental treatment.
- Patients are normally analysed within the group to which they were allocated, irrespective of whether they experienced the intended intervention (intention to treat analysis).
- The analysis is focused on estimating the size of the difference in pre-defined outcomes between intervention groups.

Several outcomes were analysed within the above mentioned study and focused on the following: Health outcomes specific to weight loss and more specific variations in morbidity and mortality, changes in body composition including body mass, amount of weight loss, weight maintenance, body shape and morphology, and waist circumference. In addition, cardiovascular outcomes were a novel focal point of this review and included cardiac mortality, modifiable cardiac risk factors, health related quality of life (HRQL), and co-morbidities were also reviewed.

3.6 Quality Assessment

A report of a RCT should convey to the reader in a clear manner why the study was undertaken and how it was conducted and analysed (Moher, Schulz & Altman. 2001). Nothing more clearly indicates the key role of a RCT in modern clinical research than the placement of this specific research method at the top of the list of levels of evidence in evidence-based medicine and intervention of a health-care nature (Sackett, Straus, Richardson, Rosenberg & Haynes, 2000). To

assess the strengths and limitations of RCT's, readers and researchers alike need and deserve to know the quality of their methods (Moher et al. 2001). The assessment of the quality of controlled trials is essential because variations in the quality of trials can effect the conclusions about the existing evidence (Verhagen et al. 1998). The assessment of the validity of the primary studies has been identified as one of the most important steps of the peer-review process and as one of the key components of systematic reviews (Jadad et al. 1996). Khan and colleagues (Khan, ter Riet, Popay, Nixon & Kleijnen.2001) pointed out that some reasons for performing quality assessment include: to determine a minimum quality threshold for the selection of primary studies for a systematic review; to explore differences in quality as an explanation for heterogeneity in study results; to weigh the results in proportion to the quality of meta-analysis; and more importantly, to guide interpretation of findings, help determine the strength of inferences, and guide recommendations for future research and clinical practice.

In a review of trials evaluating primarily medical treatments, Moher and colleagues (Moher, Jadad & Klassen. 1998., Moher, Cook & Jadad. 1999) demonstrated that trials that did not include features such as blinding and allocation concealment tended to report an exaggerated treatment effect compared with trials that did include these features. These factors emphasize the importance of methodological quality assessment in order to provide accurate information on therapeutic effects.

Another earlier study by Moher and colleagues (1995) assessed nine checklists and another 25 scales which were designed to measure quality of reports of RCT's. This study concluded that quality gives us an estimate of the likelihood that the results are a valid estimate of the truth. This study assessed all the scales

and checklists that were reviewed, and concluded that all of the checklists and scales that were reviewed, with the exception of the Jadad scale (1996), demonstrated significant weaknesses in a variety of aspects. This five-item scale developed by Jadad and colleagues (1996) is the only known scale developed with standard scale development techniques, as there was a distinct lack of explanation of how each of the other scales and checklists were developed. Jadad himself supports this finding as he and his colleagues suggest that scales have the theoretical advantage over other methods in that they provide quantitative estimates of quality that could be replicated easily and incorporated formally into the peer review process and into systematic reviews (Jadad et al. 1996). Jadad maybe biased towards his own developed scale, however, at present, there is no evidence to suggest more appropriate methods of assessing RCT's. Although the Jadad scale was initially developed and validated to assess the quality of reports on pain relief, it has been used extensively in other clinical areas as it is very efficient to use (Clark et al. 1999). The Jadad scale has also been adopted for use in many health care areas such as medicine, dentistry, psychology, and physical therapy (Olivio et al. 2008).

3.6.1– What is the Jadad Scale

The Jadad scale, sometimes known as Jadad Scoring or the Oxford Quality Scoring System is a procedure to assess, independently, the methodological quality of a clinical trial. It is the most widely used such assessment in the world (Haynes, Sackett, Guyatt & Tugwell. 2005., as cited by Olivio et el. 2008), and as of 2008, its seminal paper has been cited in over 3000 scientific works.

The Jadad scale was developed through a study in 1996 conducted by a Columbian Physician who worked as a research fellow at the Oxford Pain Relief Unit. Jadad and colleagues (1996) carried out this study to develop a scale to measure the quality of RCT's and also to assess the use of this scale on rater blinding on the quality of reports. To develop this scale, Jadad enlisted the help of 14 judges to develop an 11-item instrument for quality assessment, which was used to score 36 research papers and articles (seven previously judged excellent, six as poor, and the remaining 23 were selected randomly). Further to this, Jadad blinded seven of the fourteen raters to the authors' names and affiliation, the names of the journals, the date of publication, the sources of financial support for the study, and the acknowledgements. Finally Jadad had each rater use an 11-item, 6-item (items with adequate frequency of endorsement), and 3-item (directly related to the control of bias) scales to assess all 36 of the reports (Black, 2007).

The study found that although the agreement between the raters using all 3 item scale versions were high, the 3-item scale demonstrated the highest levels of agreement (0.66). The reports that were that were reviewed that were previously suggested as having an excellent scoring, demonstrated significantly higher ($p < 0.001$) scores than those that were randomly selected or previously deemed to be poor study reports. This demonstrates that the construct validity was of good quality. This good quality of the construct validity was further supported as randomly selected reports also scored significantly higher ($p < 0.001$) higher than those studies that were previously as being of poor quality. Jadad et al. (1996) also found that blinded raters scored the reports significantly ($p < 0.001$ and $p < 0.01$) lower when using the 6-item and 3-item scales respectively, when compared with those of the open raters (Black, 2007). The consequence of this is non-randomized

trials or RCT's that do not adapt to the double-blind design are more likely to show advantage of an innovation over a standard treatment (Jadad et al. 1996). As a result the 3-item instrument was the final version chosen by Jadad et al (1996) for assessment of quality.

The items on the Jadad scale are presented as question to elicit a “yes” or “no” answer (Jadad et al. 1996). Jadad et al (1996) constructed the following instructions to report a paper:

“It should take no longer than ten minutes to score a single paper and there are no right or wrong answers. Each question is to be answered with either a “yes” or “no” answer. Each “yes” answer will score a single point, each “no” answer will score zero point. There are to be no fractional points. Please read the article and try to answer the following questions” (Jadad et al. 1996., as cited by Vasileidi, 2008):

- Was the study described as randomized (this includes the use of words such as random, randomly, and randomized)?
- Was the study described as double blind?
- Was there a description of withdrawals and dropouts?
- Was the randomization described as appropriate?
- Was the blindness described as appropriate?

Give one additional point if:

“For question one, the method to generate the sequence of randomization was described and it was appropriate” (table of random numbers, computer generated etc.) (Jadad et al. 1996., as cited by Vasileidi, 2008).

And/or

“For question two, the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy etc.)” (Jadad et al, 1996., as cited by Vasileidi, 2008).

Deduct one point if:

“For question one, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, according to their date of birth, hospital number etc.)” (Jadad et al. 1996., as cited by Vasileidi, 2008).

And/or

“For question two, the study was described as double blind the method of blinding was inappropriate” (e.g comparison of tablets v injection with no double dummy) (Jadad et al. 1996., as cited by Vasileidi, 2008)

3.6.2 – Guidelines for Assessment

Clinical trials are conducted for the purpose of collecting data on the efficacy of medical treatments (Chow & Liu, 2004). The treatment might be, for example, a new drug, a medical device, a surgical procedure, or a preventative regime (Chow & Liu, 2004). Clinical treatment protocols vary considerably depending on the nature of the treatment that is under investigation (Everitt & Pickles, 2004), but typically in a controlled trial researchers gather a group of volunteers and subject some to the test treatment, while giving the others no treatment (known as a placebo), or an established treatment for comparison. However, trials can greatly vary in quality. Methodological errors such as poor blinding or poor randomization allow factors such as the placebo effects or selection bias to adversely affect the results of a trial (Colditz, Miller & Mosteller, 1989).

Randomization

Randomization is a process to remove distortion of statistical results, arising from the manner in which the trial is conducted, in particular in the selection of participants. Studies have indicated, for example, that non-randomized trials are more likely to show a positive result for new treatment than for an established one (Colditz et al. 1989). In accordance, a method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next (Jadad et al. 1996).

Blinding

The importance of scientific controls to limit factors under test is well established. However it is also important that none of those involved in a clinical trial, whether it be the researcher, the subject patient, or any other involved parties, should allow their own prior expectations to effect the reporting of results (Day & Altman, 2000). The placebo effect is known to be a confounding factor in trials, affecting the ability of both patients and researchers to report accurately on the clinical outcome. Experimental blinding is a process to prevent bias, both conscious and sub-conscious, skewing the results (Day & Altman, 2000).

Jadad et al. (1996) indicated that double blinding is a strong factor in controlling bias. Double blinding may eliminate any such psychological effects from the study. The method of a study will be regarded as appropriate if neither the person doing the assessments nor the study participant could identify the intervention being assessed, or in the absence of such a statement, the use of active placebos, identical placebos or dummies is mentioned (Jadad et al. 1996)

Withdrawals and Dropouts

Withdrawals and dropouts are those patients and subjects who fail to complete a course of treatment, or fail to report back on its outcomes to the researchers. The reasons for doing so might be varied: the individuals may have moved away, abandoned the course of treatment, or died. Whatever the reason, the attrition rate can skew results of a study, particularly if those subjects ceased treatment due to

perceived inefficacy. In smoking cessation studies, for example, it is routine to consider all dropouts as failures (Lancaster & Stead, 1999).

For this review the guidelines of Jadad et al. (1996) were heeded. The first states ‘participants who were included in the study but that did not complete the observation period, or who were not included in the analysis must be described (Jadad et al. 1996). The second state the number and the reasons for withdrawal in each group must be stated, and if there were no withdrawals, it should be stated in the article (Jadad et al. 1996). The third states if there is no statement on withdrawals, this particular article must be given zero points for withdrawals and dropouts (Jadad et al. 1996).

With the Jadad scale (Jadad et al. 1996) the maximum number of points one particular study can receive for the reporting of the controlling of bias is five points, with the minimum number of points one particular study can receive is zero points, for not reporting factors that are related to the controlling of bias. The scale contains a total of five questions; two concerning randomization, two concerning blinding, and a further question assessing the reported withdrawals and dropouts (Jadad et al. 1996). It is important to note that for the questions regarding randomization and blinding, if the question is not answered, no points are given. However, for the final question, concerning withdrawals and dropouts, if the answer is negative, then one point is deducted from the overall score. A fairly straight-forward and simple calculation is then carried out to reach a total mark for that particular study. Scores of three or above, out of five, are usually accepted as indicative of a high quality RCT (Jadad et al. 1996). This guideline was used to include studies for analysis in this review. When using the Jadad scale it may be important to ensure that good agreement is achieved prior to using the scale (Clark et al. 1999), since a major disadvantage of the

instrument described above, is that the assessment of the quality of a RCT depends on the information available in the reports (Jadad et al. 1996., as cited by Vasileidi, 2008). Figure 1, below, demonstrates how the Jadad scale (Jadad et al.1996) works, and to where points are allocated:

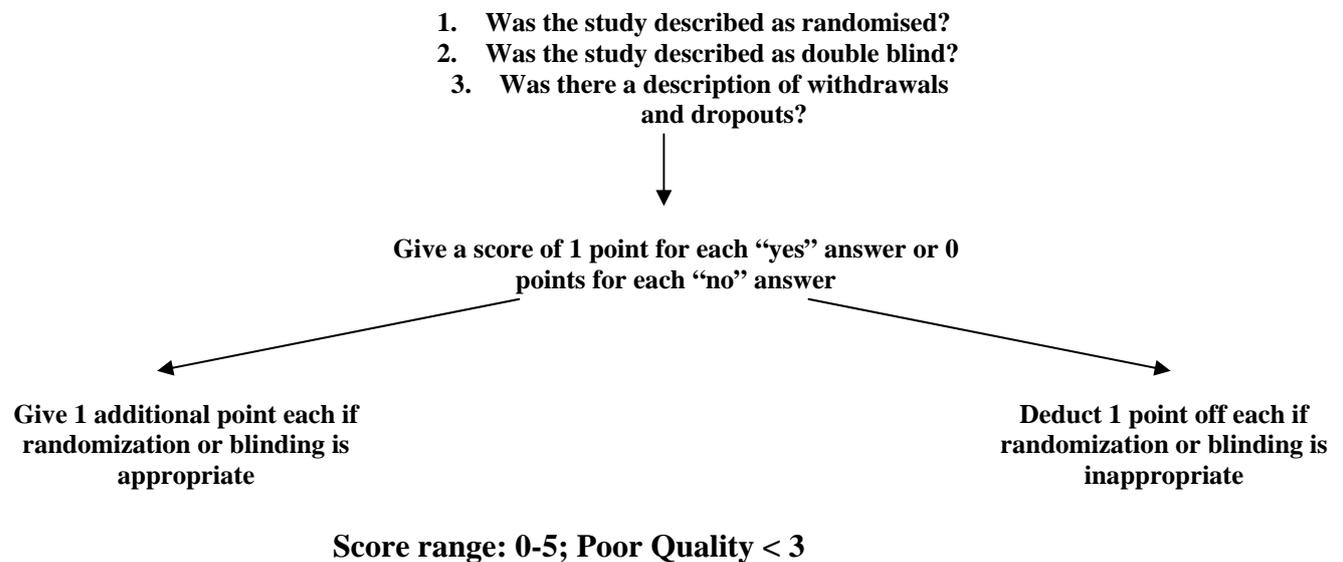


Figure 3.1 – Guidance on the use of the Jadad 3-item scale instruction (adapted from Jadad et al. (1996): Assessing the quality of reports on randomized controlled trials: Is blinding necessary? *Controlled Clinical Trials*, 17: 1-12)

A worked example of this instrument is implemented to demonstrate the application of quality assessment in the relation of the control of bias in Table 2:

Table 2 – Demonstration of Jadad et al. (1996) 3 –item Quality Assessment of Studies on the use of orlistat intervention for obesity and cardiovascular risk factors in the controlling of bias (Adapted from Black (2008): A comprehensive review into the efficacy of chromium supplementation on enhancement of body composition and physical performance.

Principal Author(s)	Date	Jadad 3-item Quality Assessment Scale					
		Randomization		Double-blinding		Withdrawals <i>Statement?</i>	Total score (Out of 5)
		Yes/No	Appropriate	Yes /No	Appropriate		
Grilo & Masheb	2007	1	1	1	1	1	5/5
Ozcelik	2005	1	0	0	0	0	1/5

The two studies selected for the purposes of this demonstration of the quality assessment process of the Jadad 3-item scale will both be reviewed in full in the results section of this review. The two papers selected demonstrate both ends (poor quality and good quality) of the Jadad 3-item quality assessment scale.

The first study selected for this demonstration is by Grilo and Masheb (2007) titled: Rapid response predicts binge eating and weight loss in binge eating disorder: Findings from a controlled trial of orlistat with guided self-help cognitive behavioural therapy. This report received a maximum of points out of five for the control of bias, which represents a detailed approach to the method of controlling bias. The points for randomization were awarded as the authors thoroughly explained that the subjects were randomly assigned to either an orlistat intervention group or placebo group, without any restriction, by a recognised computer generated table. The authors also explained that the study was carried in a double-blind fashion as the participants received either orlistat (xenical 120mg three times a day) or an identical pill placebo (3 times a day), during the 12 week treatment period. The authors also detailed withdrawals of subjects by explaining that of the 50 randomized patients, 78% (N=39)

completed treatments without a significant differential dropout between orlistat or placebo groups, which allowed maximum points scored for the controlling of bias for this study.

The second study selected for demonstration purposes is an investigation by Ozcelik, Ozkan, Karatas and Kelestimur (2005) into exercise training as an adjunct to orlistat therapy to reduce oxidative stress in obese subjects. This study received one point out of a maximum of five available for the control of bias. There was one point awarded for randomization as the authors state that the subjects were randomly divided into two groups. However, Ozcelik et al. (2005) fail to indicate what method of randomization was used, therefore a second point cannot be allocated for randomization. As this between groups study compares exercise against medical intervention, blinding is not possible, so zero points were allocated for blinding. A total of 24 obese subjects participated in this study (Ozcelik et al. 2005), however, there is no statement with regards to participant withdrawals or dropouts, therefore a point cannot be given for this particular area.

Although the Jadad scale (Jadad et al. 1996) has the most merit since it uses a simple and easy to understand approach that incorporates the most important individual components of methodological quality, it must be acknowledged that the Jadad Score is not a completely perfect instrument. For example, it places greater emphasis on the quality of reporting as opposed to the actual methodological quality of a trial. In addition, it does not assess allocation concealment. However, despite these limitations, the Jadad scale is the only instrument that has been constructed according to psychometric principles (Juni, Altman & Egger. 2001). In support of the use of the Jadad scale (Jadad et al. 1996) for this review, it is not often that we will

read a published RCT that is a true masterpiece of methodological perfection and rigor in all the various aspects of trial reporting and conduct (Towheed. 2006).

There are numerous scales available for the assessment of bias and control of quality, such as Downs and Black. (1998), or the CONSORT scale which incorporate a 25-item checklist to assess the methodological quality of RCT,s (Schulz, Altman & Moher. 2010). However, after assessing the scales and checklist available for the control of bias and quality assessment of RCT,s, the Jadad scale (Jadad et al. 1996) was the most appropriate to use for the purpose of this investigation, as it is quick and simple to use. This is vital in the timeframe available to carry out this review.

4.0 – Data Collection and Analysis

As studies that have been incorporated into a systematic review will differ in their aims and objectives, outcomes, analysis and overall conclusions, each methodology will have a different protocol. Therefore, it is of vital importance that a universal, self-explanatory method of data extraction and subsequent presentation is used to allow effective comparison between studies (Black, 2007). To ensure that adequate data presentation is achieved, the following data points were extracted from the research studies included in the review (adapted from Black, 2007):

1. Author and date.
2. Number of subjects.
3. Orlistat dosage.
4. Duration of treatment (including follow up-period).
5. Low Calorie Diet (if any).
6. Compliance monitored.
7. Measurement technique.
8. Outcomes.

Clarification of points 5-8 below:

1. (5) – In conjunction with orlistat intervention, a low calorie diet may have been prescribed, in which case is often controlled and recorded with a subject diet diary and regular contact with researchers.
2. (6) – “Compliance can be monitored in a number of ways such as: capsule or tablet counting, determining number of capsules remaining following the completion of a study, or by an interview or questionnaire” (Black, 2007)
3. (7) – Weight loss and CV risk factors are measured using a variety of methods. Weight loss can be measured in varying ways including: waist circumference measurements, underwater densitometry, skin-fold measurements, and weighted scales.
4. (8) – “This refers to the outcome findings that are deemed statistically significant ($p > 0.05$), therefore 95% of the results are real and are not due to chance” (Black, 2007).

4.1 – Selection of studies

One reviewer (myself) performed an electronic search, where all initial results were then screened, and limits performed to restrict findings to relevant articles. Any papers that did not meet the strict inclusion criteria were then rejected as did not

contain sufficient material. Only one reviewer (myself) independently assessed all of the potentially relevant studies for inclusion in the review. The reviewer was not blinded to the database, journal, author, institution, or funding of publication.

4.2 – Data extraction and management

Only a single reviewer (myself) extracted the data from included studies, and then recorded it. Any data that was not printed in written form was extracted from graphs of tables, where necessary. If there were inadequate data or information for a given outcome, that particular published article was deemed inappropriate for analysis and was therefore excluded from the review.

5.0 – Limitations

One of the major limitations of a systematic review comparing recently approved medical interventions is a lack of previously published research into this particular area (Black, 2007)

Alli™ was only released onto the European market in 2007. As a result, there are insufficient data available on the treatment effects of all™ in comparison to xenical®, which has been available, as a prescription drug, for a far greater period of time. After extensive searching, there were insufficient data available on the effects of all™ as an intervention to combat the effects of obesity and CV risk factors. Any research that was found on the effects of all™ were mainly of a psychological nature, with outcomes focusing on binge eating disorder (BED). Other reviews discussed the implications that all™ may cause in the future. These articles and reviews were insufficient for the systematic review at hand, thus leaving the analysis of all™, as an intervention for obesity and CVD, out of this particular review.

A number of trials were funded by, or implemented in the laboratories of the pharmaceutical companies that produce orlistat, which may increase the potential for positive bias results (Lexchin, 2003). Finally, the very limited number and specified type (RCT's only) of studies that were included in this review may limit the overall interpretation of the findings and outcomes.

6.0 Results

6.1 Literature search results

From the search through the previously described databases and journal titles, there was a yield of a potential 2,506 articles for review. After limiting the search to incorporate only those that were applicable to the review, and then identified those that met the inclusion criteria, along with disregarding duplicate articles, a total of 38 papers were deemed sufficient enough for inclusion. These papers were then subjected to the Jadad scale (Jadad et al. 1996), to put together a final list of articles for review. After this, reference tracking was then carried out to find any other potential papers that were missed during the initial search. In total, 19 papers, that were carried out to assess the various effects of orlistat, were included for analysis. This was only after the selection process, previously described, was completed.

Studies that were not included for review were excluded for a number of reasons including: Inappropriate subjects (i.e. age grouping), low Jadad score, non-availability of full-text, and inappropriate use of intervention. Of the 19 papers that were included for review, all met the strict inclusion criteria, and met with a score of at least three points out of a maximum of five, when subjected to the Jadad 3-item quality assessment of bias scale (Jadad et al. 1996). Figure 4.1 demonstrates the overall results of the literature search and identifies where papers were excluded and included for final review.

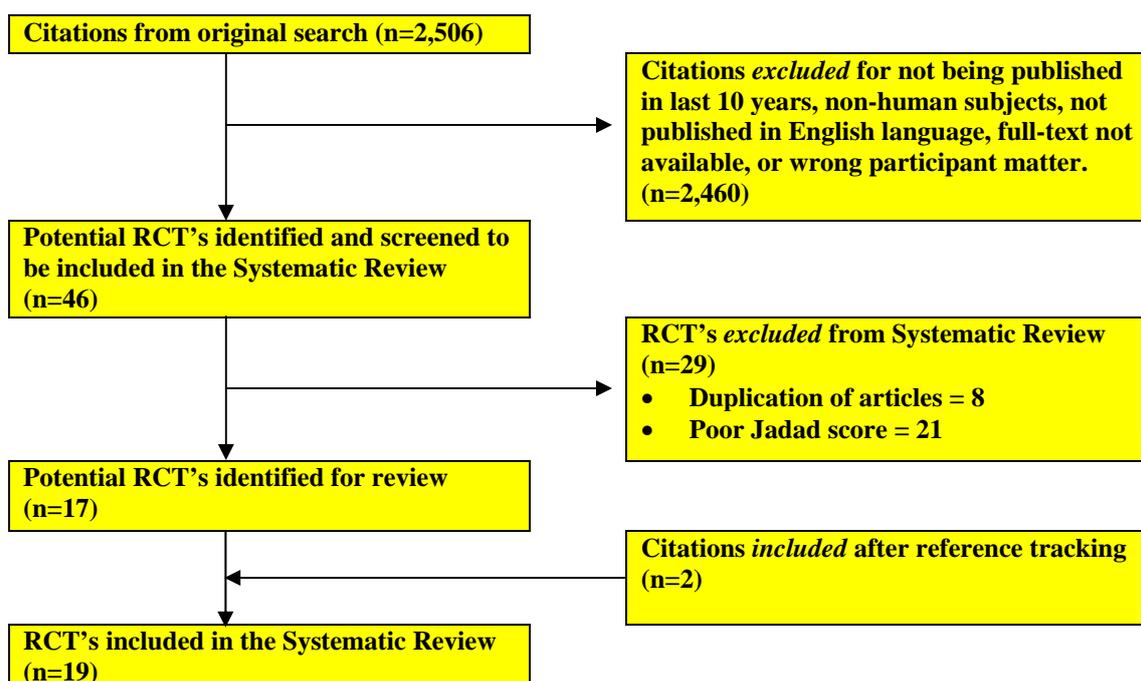


Figure 4.1: Results of overall literature search for relevant articles for inclusion in the Systematic Review.

6.2 Characteristics of included articles

As previously stated only papers that were published in the last 10 years were included for review. Of the papers included for review, a majority of them (13 in total) have been published within the last five years. In accordance with the inclusion criteria, all of the studies reviewed were written in English. Of the 19 studies included for review, the main objective of these articles was to assess the effects of orlistat on obesity, and co-morbidities of CVD, including metabolic profiles, waist circumference, markers of diabetes, mortality, and morbidity. Two of the studies assessed psychological markers in relation to BED. Another study looked at the effects of orlistat on mineral balances within the body. A further study assessed ovulation rates of anovulatory women after orlistat treatment. The study durations ranged from 21 days to 4 years.

One of the objectives of this study was to review the effects of alli™, the recently released OTC version of orlistat given at half the dosage (60mg) of prescription only orlistat, xenical®. However, after a thorough search for relevant articles to be included for review, there was a distinct lack of the papers needed to analyse the effects of alli™ on obesity and CVD. Given this, there is no analysis of alli™ within this review, which will be discussed further in the limitations section of this document.

6.3 – Characteristics of review population

Of the studies included for review, the majority were carried out that included populations from Europe (12 out of 19 studies) and from North America (five studies), with the remaining two studies coming from Australia. There was a wide range of sample sizes, which varied between 13 subjects from one RCT, to 19,619 subjects which were included in a previous systematic review that was included for analysis. Over half of the studies (10 out of 19 articles) had a sample size of less than 100, with the remaining studies demonstrating a wide range of participant numbers. All of the studies incorporated subjects of 18 years of age or older, to comply with the inclusion criteria of the review, and included subjects up to the age of 70 years old. Three studies comprised only female populations, with only one study having an all male study sample. Of the 19 studies reviewed, 17 included only participants with a body mass index (BMI) $\geq 27\text{kg/m}^2$. One further study included only hypertensive participants regardless of BMI, with the final study including only subjects with T2DM upon commencement of intervention regardless of BMI. Of the studies that included only participants with a BMI $\geq 27\text{kg/m}^2$, one included only participants of Caucasian ethnicity. The remaining 18 studies had unrecorded ethnicity of subjects. In total the studies included for analysis reviewed 32,063 subjects which were randomised to either orlistat monotherapy intervention group, placebo, usual care,

alternative medical intervention (sibutramine, metformin, cetilistat), surgery, or orlistat + MK-0557.

Table 3 - Basic characteristics of included studies within systematic review

<u>Authors</u>	<u>Subjects</u>	<u>Dosage</u>	<u>Duration</u>	<u>Jadad Score</u>	<u>Orlistat Effects</u>
Kopelmann et al. (2009)	612 (mixed gender) mean BMI 28.45kg/m ²	120mg t.i.d	12 weeks	4/5	Decrease in body weight. More AE
Torgeson et al. (2004)	3,305 (mixed gender) BMI ≥30kg/m ²	120mg t.i.d	4 years	5/5	Decrease in diabetes Incidence. Decrease in body weight
Svendson et al. (2008)	306 (mixed gender) mean BMI 37.5 kg/m ²	120mg t.i.d	3 years	4/5	Increase in dietary Restraint. Decrease in binge eating. Decrease in body weight
Richelson et al. (2007)	309 (mixed gender) BMI 30 – 45kg/m ²	120mg t.i.d	3 years	5/5	Decrease in new cases diabetes. Decrease in waist circumference
Pace et al. (2000)	28 males. BMI ≥30kg/m ²	120mg t.i.d	21 days	4/5	Decrease in fat absorption
O'Brien et al. (2006)	801 (mixed gender)	120mg t.i.d	2 years	3/5	Lesser effects than surgery group
Metwally et al. (2009)	40 anovulatory women. BMI ≥30kg/m ²	120mg twice daily	12 weeks	3/5	Decrease in BMI, testosterone, and androstendin
Madsen et al. (2008)	93 (mixed gender) BMI 30 – 45kg/m ²	120mg t.i.d	3 years	4/5	Less weight regain after 3 years
Haugaard et al. (2009)	13 (mixed gender) mean BMI 35.7kg/m ²	120mg t.i.d	24 weeks	3/5	Decrease in body weight. Better glycemic control. Increase in SMPL
Grilo & Masheb. (2007)	50 (mixed gender) BMI ≥30kg/m ²	120mg t.i.d	12 weeks	5/5	If rapid response occurred, improvement was sustained
Erondu et al. (2007)	497 (mixed gender) BMI 30 – 43kg/m ²	120mg t.i.d with meals	24 weeks	4/5	Decrease in body weight
Erdmann et al. (2004)	384 (mixed gender) mean BMI 28.4kg/m ²	120mg t.i.d	24 weeks	4/5	Reduction in body weight, LDL cholesterol, and CV risk-factors
Dixon et al.	55 (mixed				Less fat free mass

(2007)	gender) BMI 30-35kg/m ²	120mg Before each meal	24 months	3/5	and skeletal muscle loss. Increase in body protein
Bergholm et al. (2003)	57 females. Mean BMI 28.35kg/m ²	120mg t.i.d	6 months	4/5	Decrease in LDL cholesterol increase in ACH response
Aydin et al. (2004)	86 (mixed gender) mean BMI 36.1kg/m ²	120mg t.i.d	12 weeks	3/5	Strongest BMI and waist circumference association
Sibenhofer et al. (2009)	3,132 (mixed gender) hyper- tensive patients	Review used various doses	Mean Treatment Period of 4 months	3/5	Higher GI side effects. Decrease in body Weight. Decrease in SBP and DBP
Padwal et al. (2009)	19,619 (mixed gender) BMI ≥27kg/m ²	Review used various doses	Minimum follow up of 1 year	3/5	Reduction in body- weight, diabetes incidence and LDL- cholesterol
Norris et al. (2009)	3,376 (mixed gender) type 2 diabetes patients	Review used various doses	Studies of any dura- tion and follow up	3/5	Reduction in body weight. Higher GI side effects
Jayagopal et al. (2005)	21 caucasian women. Mean BMI 36.7mg/m ²	120mg t.i.d	12 weeks	3/5	Reduction in total cholesterol and body weight

The articles included for review have been separated into three different sub-categories, to help present the findings of the review in a clear and concise manner. The sub-categories, the articles have been divided into within this review are: 6.4 – Orlistat vs. Alternative medical interventions; 6.5 – Orlistat vs. Surgical interventions; and 6.6 – Orlistat vs. Placebo. Studies which include multiple comparison groups will be reported under each section in order to report all of the findings.

6.4 – Orlistat vs. Alternative medical interventions

This section of the review will focus on the results obtained from studies which compared the effects of orlistat with those of other medical interventions. Other comparative medical interventions included within this review are: Sibutramine, metfarmin, cetilistat, and orlistat in conjunction with MK-0557.

6.4.1 – Orlistat vs. Sibutramine

Two studies comparing orlistat treatment against sibutramine therapy, included a total of 583 patients, aged between 18-70 years, and BMI between 30 and 45kg/m² (Aydin et al. 2004., Erondü et al. 2007). The population of these studies were of a mixed gender. Sibutramine is a centrally-acting serotonin-norepinephrine reuptake inhibitor, prescribed as an adjunct in the treatment of exogenous obesity. At this point it should also be noted that sibutramine has been withdrawn from the European markets due to an increased risk of stroke and heart attack.

The first of these studies (Aydin et al. 2004), BMI decrease was significantly differing between groups ($p=0.001$), being highest in the combination therapy group (sibutramine 10mg once daily + orlistat 120mg t.i.d), followed by sibutramine monotherapy group, orlistat monotherapy, and finally diet therapy. Even though orlistat monotherapy was less effective on BMI, it proved to reduce waist circumference as effectively as sibutramine monotherapy ($-14.04 \pm 5.88\text{cm}$ vs $-13.54 \pm 4.83\text{cm}$, $p=0.806$). The orlistat monotherapy group revealed a decrease of 3.4cm in waist circumference per unit decrease in BMI. In the combination therapy group, each unit change in BMI accounted for 2.6cm decrease in waist circumference, with sibutramine monotherapy group demonstrating a decrease of 1.8cm in waist circumference per unit decrease in BMI.

Erondü et al. (2007) support the changes in waist circumference of Aydin et al. (2004), as the changes in waist circumference with treatment of orlistat monotherapy, sibutramine monotherapy and placebo groups are parallel across body weight measurements. However, within this study (Erondü et al. 2007) there were no significant differences between sibutramine and orlistat were observed in the per-protocol population or in the 5% and 10% responder analyses. Erondü et al. (2007) showed that both orlistat and sibutramine induced statistically significant changes in body weight ($p<0.001$ for both compounds vs placebo). Erondü et al. (2007) reported findings of low density lipoprotein (LDL)-cholesterol, where in the study by

Aydin et al. (2004) there were no reports of LDL cholesterol, high density lipoprotein (HDL)-cholesterol, or total cholesterol. Erondu et al. (2007) reported LDL cholesterol increased from baseline in both sibutramine and orlistat groups. However the smallest increase of LDL cholesterol was observed in the orlistat group (0.5%). Levels of HDL cholesterol also increased in both groups, with the largest effect observed in the sibutramine group (3.5%). In this study (Erondu et al. 2007) triglyceride levels decreased in both groups, with sibutramine showing the greatest reduction (-9.0%) compared with orlistat (-2.2%). Erondu et al. (2007) showed that orlistat treatment was accompanied by a small reduction in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (-1.4 and -1.2mmHg respectively), whereas sibutramine treatment was accompanied by a 2.1mmHg elevation in SBP. Erondu et al. (2007) also reported the highest patients with drug related adverse experiences were in the orlistat monotherapy group (40.4%), with sibutramine monotherapy patients reporting significantly fewer AE (28.0%). Orlistat monotherapy patients also showed the greatest discontinuation as a result of drug related AE, with 4% dropouts compared to 1% in the sibutramine monotherapy group. This was further supported with the orlistat monotherapy group demonstrating a total of 31% dropouts due to varying AE.

Both studies involving orlistat vs sibutramine therapies (Aydin et al. 2004., Erondu et al. 2007) did not report total mortality, diabetes or CV mortality as outcomes, with only Erondu et al. (2007) reporting outcomes of triglycerides, SBP and DBP.

6.4.2 – Orlistat vs Metformin

Two studies compared the effects of therapy against metformin treatment, included a total of 61 female patients, aged between 18 and 40 years, with a BMI $\geq 30\text{kg/m}^2$ (Jayagopal, Kilpatrick, Holding, Jennings & Atkin. 2005., Metwally, Amer, Li & Ledger. 2009). The population of these two studies were female only. One study recruited only women with Polycystic Ovarian

Syndrome (PCOS) (Jayagopal et al. 2005), with one other study recruiting only obese anovulatory women (Metwally et al. 2009). It should be noted that the primary action of metformin is as an oral anti-diabetic drug in the biguanide class, but is mainly used for diabetes patients who are overweight or obese with normal kidney function.

Both studies demonstrated a reduction in weight markers for patients treated with orlistat. However, in one of the studies (Metwally et al. 2009), both of the study arms (orlistat and metformin) showed a significant decrease in their mean BMI ($p < 0.001$) and waist circumference ($p < 0.0001$). There was no influence for the prescribed medication on this effect ($p < 0.05$, Bonferroni adjustment). For the between groups analysis, Metwally et al. (2009) demonstrated there was no significant difference in the mean BMI or waist circumference between the orlistat and metformin arms at the start of the study, or at any time during the follow up visits. In the earlier study (Jaygopal et al. 2005) the eight week run-in period of dietary stabilisation did not produce a significant change in weight in either the metformin group or the orlistat group. However, treatment with orlistat for 12 weeks resulted in a 4.69% reduction in weight when compared with baseline, which was more significant than the reduction in weight seen in the metformin treated group.

Both studies (Jayagopal et al. 2005., Metwally et al. 2009) demonstrated a significant reduction in testosterone levels from baseline to 12 weeks treatment, in both metformin and orlistat groups. In both studies there was no significant differences in the mean serum testosterone levels between the orlistat and metformin arms at the start of the study or at any time during the follow up visits.

Jayagopal et al. (2005) reported no significant improvement in any of the lipid parameters studied in either treatment group. In addition there was no difference in the comparison between treatment groups in any of the lipid parameters. Metwally et al. (2009) did not report outcomes of lipid parameters.

Jayagopal et al. (2005) reported no significant reduction in fasting insulin from baseline in either metformin or orlistat study arms. Similarly, there was no statistical difference in comparison between the two treatments for change in fasting insulin. Metwally et al. (2009) did not report the outcomes of fasting insulin.

Metwally et al. (2009) reported that orlistat was better tolerated than metformin. No patients experienced any significant AE in the orlistat group, and there were no drop-outs due to drug related AE. In the metformin group, two patients dropped out due to intolerable GI disturbances that were not corrected by a temporary reduction in the dose. Jayagopal et al. (2005) reported drug related AE for both treatment arms. Four subjects were treated with metformin reported to have mild nausea (4), heartburn (2), and abdominal pain (1), with two subjects treated with orlistat reporting mild to moderate flatulence and oily stools intermittently during the study period.

Of the two studies investigating the effects of orlistat vs metformin intervention, none reported total mortality, CV mortality, or quality of life (QOL).

6.4.3 – Orlistat vs Cetilistat

Cetilistat works in the same way as orlistat by inhibiting pancreatic lipase. However, at the time of writing this review cetilistat is still in its clinical trial phase and not yet approved for the open market. One study comparing the effect of orlistat treatment against varying doses of cetilistat, included a total of 612 patients (50.4% male and 49.6% female) with a mean age of 53.4 years, all with T2DM. All subjects had a BMI between 28 and 45kg/m² (Kopelman et al. 2009).

Kopelman et al. (2009) reported a 15% patient dropout. The primary reasons for discontinuation were AEs (31/612; 5.1%, 2, 6, 3, 13, and 7 patients in the 40, 80, and 120mg cetilistat, 120mg orlistat, and placebo groups, respectively). The weight loss in the group receiving orlistat 120mg t.i.d was similar to that with cetilistat at 80 and 120mg t.i.d, and was a statistically greater weight loss than the group receiving cetilistat 40mg t.i.d. The patients who achieved $\geq 5\%$ weight loss was greater in the 80mg and 120mg cetilistat groups, and in the orlistat group, than in cetilistat 40mg t.i.d. Significant reductions relative to placebo were seen for waist circumference in the cetilistat 80mg and 120mg t.i.d dose groups, and in the orlistat group. The reduction in waist circumference in the cetilistat 40mg t.i.d group was similar to that in the placebo group. Levels of glycosylated haemoglobin (HbA_{1c}) in the orlistat treatment group was significant compared to placebo ($p=0.04$), and was similar to that seen in the cetilistat 80mg and 120mg groups. No consistent changes in lipid profile from baseline, which were all within the normal range, were seen in any of the treatment groups. The proportion of patients in the orlistat group reporting AE (93%) was similar to that in the cetilistat groups ($p=0.3251$ compared to 120mg cetilistat). However, the patients in the orlistat group reported more severe events (55; $p=0.0546$ compared to 120mg cetilistat group), and more GI AE (431; $p=0.0184$ compared to 120mg cetilistat group). The number of reported GI AE in the orlistat treated patients classified as severe (54) was substantially higher than in the cetilistat groups (17-28). No deaths were reported for any group. No clinically significant changes in routine laboratory parameters (heart rate [HR], SBP, DBP), vital signs, or electrocardiogram (ECG) readings were observed during treatment, in any group. The active treatment groups for both cetilistat and orlistat had significantly reduced, but comparable, vitamin E values compared to the placebo group. However, none of the changes in level was reported as an AE. Kopelman et al. (2009) did not report any data on total or CV mortality.

6.4.4 – Orlistat vs Orlistat + MK-0557

One study comparing orlistat monotherapy treatment against orlistat + NPY-Y5 receptor antagonist (MK-0557), included a total of 497 obese patients, between the ages of 18 and 65 years, with a BMI between 30 and 43kg/m² (Erondu et al. 2007). The population of this study was of mixed gender.

Erondu et al. (2007) demonstrated that after 24 weeks of treatment, MK-0557 did not induce significant weight loss when co-administered with orlistat compared with orlistat alone (p=0.250). For pre-specified adverse experiences of general and GI events, there was no significant differences in rates between MK-0557 plus orlistat and orlistat alone. Erondu et al. (2009) did not report outcomes of diabetes, total mortality, or CV risk factors, when comparing and analysing orlistat monotherapy vs orlistat plus MK-0557.

6.5 – Orlistat vs Surgical Interventions

This section of the review will focus on the results obtained from studies which compared the effects of orlistat treatment with those of surgical interventions. The surgical intervention that was part of the studies included within this review is a laproscopic gastric band surgery.

6.5.1 – Orlistat vs Laproscopic Gastic Band Surgery

Two studies comparing orlistat treatment against laproscopic gastric band surgery included a total of 135 patients aged between 20 and 50 years, with a BMI between 30-35kg/m² (O'Brien et al. 2006., Dixon, Strauss, Laurie & O'Brien. 2007). The population of these studies were of mixed gender.

The first of these two studies (O'Brien et al. 2006) demonstrates that both groups had an identical weight loss at 6 months, with 13.8% of initial weight lost. The surgical group continued to lose weight at each study point during the follow up period with means of 21.6% (95% CI,

19.3% to 23.9%) of initial weight lost and 87.2% (CI, 77.7% to 96.6%) of excess weight lost at two years. The orlistat group showed progressive weight regain after the six month point with means of 5.5% (CI, 3.2% to 7.9%) initial weight lost and 21.8% (CI, 11.9% to 31.6%) of excess weight lost at two years. 85% of surgical patients compared to 26% of non-surgical patients lost more than 50% of excess of excess weight at two years. All of the surgical patients compared to 35% of the non-surgical patients achieved satisfactory weight loss (>25% of excess weight lost).

Dixon et al. (2007) report similar results, with both the surgical group and the orlistat treatment group being well matched for all measured characteristics at baseline, and weight loss and change in basic anthropometric measures at six months after randomisation were very similar. Changes in weight, waist circumference, and waist to hip ratio were all significant and similar for groups at six months treatment. Weight loss was associated with significant decreases in fat mass and fat free mass (FFM) in both groups. Similar weight loss was associated with similar loss of fat mass, but the surgical group lost more FFM and had a higher proportion of FFM to fat mass loss at six months. At two years, Dixon et al. (2007) showed that the surgical group had significantly greater decreases in both total body fat and FFM, but the ratio of the change in FFM to fat mass was very similar. At two years there was a greater decrease in skeletal muscle mass in the surgical group, but a similar ratio of skeletal muscle mass loss to fat mass loss ratio in both groups.

O'Brien et al. (2006) reported that the resolution of the metabolic syndrome statistically significantly differed between the surgical group and the orlistat group. The surgical group had a statistically significantly greater improvement at two years for DBP, fasting plasma glucose level, insulin sensitivity index, and HDL cholesterol level. The reduction in the proportion of patients with the metabolic syndrome during the study period was significant for the surgical group ($p < 0.001$) but not for the orlistat group ($p = 0.22$). Dixon et al. (2007) did not report on outcomes of metabolic syndrome.

For quality of life, O'Brien et al. (2006) report that at two years, the non-surgical group had statistically significant improvements in three domain scores: physical function, vitality, and mental health. The surgical group had statistically significant improvements in all eight domain scores. Dixon et al. (2007) did not report on outcomes of QOL.

O'Brien et al. (2006) reported in the surgical group, one patient developed an infection of a 5mm port site, four patients developed prolapse of the posterior gastric wall through the band at 4, 10, 12, and 24 months after placement. One patient developed acute cholecystitis at 23 months and had an elective uncomplicated laproscopic cholectectomy. In the non-surgical group, eight patients could not tolerate orlistat, and three others chose not to take orlistat. Dixon et al. (2007) did not report on AE of surgical or orlistat interventions. There were no data reported on total or CV mortality, or diabetes within these studies.

6.6 – Orlistat vs Placebo

This section of the review will focus on studies which compared the effects of orlistat therapy against a placebo. The majority of studies (14 out of 19 studies) within this review compared orlistat treatment against a placebo group (Pace, Blotner & Guerciolini. 2000., Bergolm et al. 2003., Erdmann, Lippl, Klose & Schusdziarra. 2004., Torgeson, Hauptman, Baldrin & Sjostrom. 2004., Erondy et al. 2007., Grilo & Mashed. 2007., Richelson et al. 2007., Madsen et al. 2008., Svendson et al. 2008., Haugaard, Vaag, Mu & Madsbad. 2009., Kopelman et al. 2009., Norris et al. 2009., Padwal, Rucker, LI, Curioni, & Lau. 2009., Siebenhofer et al. 2009) with a number of these having multiple comparison groups.

6.6.1 – Effect of orlistat vs. Placebo on weight loss

Eight studies included weight loss as a measurable outcome (Erdmann et al. 2004., Torgeson et al. 2004., Richelson et al. 2007., Haugaard et al. 2009., Kopelman et al. 2009., Norrise et al. 2009., Padwal et al. 2009., Siebenhofer et al. 2009.). Erdmann et al. (2004) reported that the total decrease in body weight of 7.4kg in the orlistat group was significantly greater compared with 4.9kg with placebo ($p=0.01$), with the first statistically significant difference in body weight between the two study arms observed at week four. Torgeson et al. (2004) demonstrated with their result that mean weight loss was significantly greater with orlistat than placebo at one year (10.6 vs. 6.2kg; $p<0.001$) and remained significantly greater at the end of the four year study (5.8 vs. 3.0kg; $p<0.01$). Richelson et al. (2007) reported the weight loss after eight week very low energy diet (VLED) was 14.3 ± 2.0 kg in those who were randomised to orlistat and 14.5 ± 2.1 kg in those who were randomised to placebo. From before VLED to month 36, the mean weight loss was 9.4kg (8.3%) after orlistat treatment which was significantly greater ($p<0.05$) when compared with 7.2kg (6.4%) weight loss after placebo. Haugaard et al. (2009) showed that among the nine subjects who fulfilled this study, five subjects received orlistat 120mg t.i.d. The changes in body weight among the orlistat study arm lost more weight (-3.9kg vs. +2.2kg; $p<0.05$). Kopelmann et al. (2009) showed that weight loss in the group receiving orlistat 120mg t.i.d. was significantly greater than in the placebo group and was statistically significant ($p=0.0075$). Three previous systematic reviews were included in this investigation. The first of these reviews (Norris et al. 2009) reported modest reductions in weight for orlistat of 2.0kg (95% CI, 1.3-2.8) at 12 to 57 weeks follow up. The second of these reviews (Padwal et al. 2009) showed reductions in weight of 2.9kg (95% CI, 2.5-3.2kg) when compared to placebo. The third of these reviews (Siebenhofer et al. 2009) reported orlistat was found to lower body weight significantly more effectively than placebo in all studies. The meta-analysis of orlistat studies obtained a weighted mean difference (WMD) of -3.7kg (95%, -4.7 to +3.8kg)

6.6.2 – Effect of orlistat vs. Placebo on diabetes

Five studies concerning the effect of orlistat against placebo had outcome measurements of T2DM, a major risk factor for CVD. Three studies included a populations with existing T2DM, or risk factors for T2DM (Richelson et al. 2007., Kopelman et al. 2009., Norris et al. 2009). Richelson et al. (2007) included subjects with T2DM risk factors, but who had not yet developed T2DM. This study reported that significantly more patients in the placebo group developed T2DM (17 subjects [10.9%]) compared with the orlistat group (8 subjects [5.2%]) during the three year study ($p=0.041$). Kopelman et al. (2009) performed included subjects with existing T2DM, and found there were small, but not clinically significant, reductions in mean levels of insulin, fasting blood glucose, and fructosamine in all study arms. Norris et al. (2009) performed a review of patients with existing T2DM, and found that HbA_{1c} was modestly and significantly reduced in the orlistat group.

Two studies reported progression to T2DM as an outcome (Torgeson et al. 2004., Padwal et al. 2009). Torgeson et al. (2004) reported that during the four years of treatment orlistat plus lifestyle changes significantly decreased the progression to T2DM compared with placebo plus lifestyle changes (log rank, $p=0.0032$). Cumulative incidence rates after four years were 6.2 vs. 9.0% for orlistat and placebo groups respectively. A previous review by Padwal et al. (2009) reported that orlistat reduced the incidence of T2DM from 9.0% to 6.2% (hazard ratio 0.63, 95% CI 0.46 to 0.86%). This reduction was primarily observed inpatients with impaired glucose tolerance (IGT) at baseline.

6.6.3 – Effect of orlistat vs. placebo on cholesterol

Four studies were included in the review that reported cholesterol (LDL, HDL, and/or total) as outcome measurements (Bergholm et al. 2003., Erdmann et al. 2004., Erondu et al. 2007., Haugaard et al. 2009.)

Bergholm et al. (2003) reported that serum LDL cholesterol decreased significantly in the orlistat group (by 11% or -0.48 ± 0.15 mmol/l, $p < 0.01$) but not in the placebo group (-0.17 ± 0.09 mmol/l, NS). Erdmann et al. (2004) reported that after randomisation, orlistat treated patients showed a significantly greater decrease of total, LDL, and HDL cholesterol compared with the placebo treated group, where total and LDL cholesterol remained constant after the initial four weeks of the study period, while HDL cholesterol rose more rapidly and to greater extents. Erondu et al. (2007) reported LDL cholesterol increased from baseline levels in placebo and orlistat groups, with the largest relative increase observed in the placebo groups (7.8%: 95% CI, -3.5%, 4.5%). The change in LDL cholesterol for the orlistat group was significantly different from the change in placebo ($p = 0.010$). Haugaard et al. (2009) reported both orlistat and placebo groups showed the same reversal of plasma cholesterol levels towards pre very low calorie diet (VLCD) levels.

6.6.4 – Effect of orlistat vs. Placebo on triglycerides

Two studies directly reported triglyceride measurements as outcomes (Erondu et al. 2007., Haugaard et al. 2009).

Erondu et al. (2007) reported that triglyceride levels increased in the placebo group (3.3%; 95% CI, -5.8%, 12.4%) but decreased in the orlistat group (-2.2%, 95% CI, -9.6%, 5.3%). Haugaard et al. (2009) reported that both orlistat and placebo groups showed the same reversal of plasma triglycerides towards pre-VLCD levels.

6.6.5 – Effect of orlistat vs. Placebo on other cardiovascular risk factors or cardiovascular events

Three studies reported CV risk factors as a whole, or differing CV risk factors than those previously reported within this review. (Erondu et al. 2007., Padwal et al. 2009., Siebenhofer et al. 2009).

Erondu et al. (2007) reported systolic and diastolic blood pressures were almost unchanged over 24 weeks in the placebo group. Orlistat treatment was accompanied by a small reduction in both systolic and diastolic blood pressure (-1.4 and -1.2mmHg, respectively). Padwal et al. (2009) reported that orlistat resulted in placebo-subtracted SBP reductions of 1.5mmHg (95% CI, 0.9 to 2.2mmHg) DBP reductions of 1.4mmHg (95% CI, 0.7 to 2.0mmHg). One study within the review of Padwal et al. (2009) evaluated the effect of orlistat on the change in the Framingham CV risk score and found nearly identical changes to that of placebo with no significant difference between the study arms. Siebenhofer et al. (2009) presented data on CV morbidity. In Bakris et al. (2002), two patients in the orlistat group suffered from a myocardial infarction (MI), two had chest pain, and one had an episode of atrial fibrillation (AF). In the placebo group, one had a MI, one had a worsening of atherosclerotic coronary artery disease (CAD), and two had an episode of chest pain. Cocco et al. (2005) reported inpatients with resting left ventricular ejection fraction (LVEF) below 50% at baseline that LVEF did not change with placebo (0.6%), but was increased by 4.3% in the orlistat group.

6.6.6 – Effect of orlistat vs. Placebo on other outcomes

Two studies reported outcomes of BED (Grilo & Masheb. 2007., Svendsen et al. 2008.). Grilo and Masheb. (2007) reported that of the 50 patients that were randomised to treatment, 21 (42%) showed a rapid response, defined as 70% or greater reduction in binge eating by the fourth treatment week. However, rapid response rates did not differ significantly in patient receiving cognitive behavioural therapy delivered by guided self help (CBTgsh) + orlistat, versus CBTgsh

+ placebo (N=13 of 25 [52%]) versus 8 of 25 (32%). Svendsen et al. (2008) studied eating behaviour and reported that scores for hunger were reduced more in the orlistat group at month 33 and this was statistically significant in men (between group difference -1.1 [95% CI, -1.2, 0.0] $p=0.0493$). This tendency was similar in women in numerical terms but did not achieve significance (between group difference -1.0 [95% CI, -2.2, 0.3] $p=0.1395$).

Pace et al. (2000) reported the short term effect of orlistat treatment in mineral balance. This study reported no significance difference between the placebo and orlistat groups in the observed-to-expected radiopaque marker ratios seen during the balance period (0.92 and 0.95, respectively).

Madsen et al. (2008) reported secondary outcomes of adiponectin, high sensitive-C reactive protein (hs-CRP), and fibrinogen. This study reported that changes in adiponectin, hs-CRP, and fibrinogen did not differ significantly between the orlistat and placebo groups during period I (baseline to after VLED) period II (from after VLED to 3 years), nor in period III (from baseline to 3 years) analysed through a mixed linear model.

6.6.7 – Effects of orlistat vs. Placebo on adverse effects

Pace et al. (2000) reported the incidence of AE was similar in both orlistat and placebo groups for most body systems. However, a higher proportion of patients in the orlistat group had AE in the GI system. AE were of a mild to moderate intensity and resolved without any patient discontinuing treatment.

Berghom et al. (2003) reported the orlistat group had significantly more GI but not other AE compared with the placebo group (total 93 vs. 60%, $p<0.01$; fatty stools 81 vs. 17%, $p<0.005$; soft stools 37 vs. 17%, $p<0.001$).

Torgeson et al. (2003) reported during the first year of treatment, the proportion of patients experiencing at least one GI event with orlistat or placebo was 91 vs 65% respectively. This compares with 36 vs. 23% for orlistat or placebo, respectively, during the fourth year.

Erondu et al. (2007) reported the highest proportion of patients with drug related AE were in the orlistat group (40.4% for orlistat monotherapy vs. 17.8% for placebo). GI AE were most common in the orlistat group.

Richelson et al. (2007) reported increase in GI complications in the orlistat group compared to placebo group. These included fatty/oily stools (23 vs. 2.5%), oily spotting (17.5 vs. 0%), abdominal pain (21.5 vs. 16%), and faecal urgency (8.5 vs. 5%) in the orlistat and placebo groups respectively.

Kopelman et al. (2009) showed that the patients in the orlistat group reported more events than the placebo group (541 in total). One serious AE was reported in the orlistat group, but was not considered to be related to the medication.

Norris et al reported only minor GI AE, with most being mild to moderate in transient, within the orlistat group.

Padwal et al. (2009) reported GI events were the predominant AE associated with orlistat. The categorization of outcomes and detail of reported GI AE varied between trials. Over 80% of orlistat treated patients experienced at least one GI AE, with an absolute frequency that was 24% (95% CI, 20 to 29%) higher than patients treated with placebo.

In the review by Siebenhofer et al. (2009) the four studies comparing orlistat treatment against placebo all showed significantly higher AE for orlistat treated patients compared to the placebo group.

7.0 – Discussion

Orlistat, and its direct and indirect therapeutical effects on weight loss, CVD, CV risk factors, have been investigated through varying RCT,s and systematic reviews of RCT,s. However, the studies included within this review provide no definitive information as to the effects, positive and negative, of orlistat therapy, for the reduction of body weight and CV risk factors, in overweight and obese subjects. To evaluate the efficacy and effect of orlistat, the reported findings of previously published RCT,s and relevant systematic reviews have been described and evaluated within the following discussion.

7.1 – Summary of main results

The systematic review at hand was carried out to assess and determine the effects of weight loss and maintenance, and CV risk factors, through pharmacological intervention of orlistat, in two marketed forms (alli™ and xenical®), on numerous outcomes including weight loss parameters, metabolic markers, morbidity, and diabetes, in clinically overweight or obese patients, but found at present there are no RCT,s, or previous reviews, that can measure this comparison in full. The search at hand revealed only relevant data on 120mg dose orlistat (xenical®) that was relevant to the review area. Published papers on 60mg orlistat (alli™) reviewed only psychological measures as effects of alli™, as opposed to statistical data on treatment effects. The remainder of this discussion will refer to 120mg xenical® as orlistat, unless otherwise stated. The search identified 19 papers that were relevant to the research topic. The studies included, were individual RCT,s, or previous systematic reviews of RCT,s. Comparison groups were alternative medical interventions, surgical interventions, or placebos.

The systematic review at hand showed that patients who were randomised to orlistat therapy, reduced their body weight statistically significantly greater than those patients randomised to a placebo group. While these results support the notion that orlistat may be a beneficial option in the reduction of body weight in obese subjects, there are still some important questions that need to be answered. Most importantly, the subjects who were randomised to orlistat treatment, demonstrated statistically significantly greater amounts and intensity of AE. The majority of these AE experienced in the orlistat treatment groups were in the GI system. This might limit the effectiveness of orlistat medication in settings outside of scientific clinical studies (Siebenhofer et. 2009). Furthermore, improvements in other aspects of health, which will be discussed further on, that are related to a decrease in body weight, may be reversed, as some of the studies revealed that weight was put back on once the orlistat treatment period was ceased. This area remains unclear, and needs further investigation.

In two studies comparing sibutramine (10mg once daily), an appetite suppressant, against orlistat (120mg t.i.d), the results were similar, with both drugs demonstrating statistically significant decreases in body weight from baseline. One study (Aydin et al. 2004) demonstrated sibutramine monotherapy produced a slightly greater reduction in BMI. However, even though orlistat monotherapy had a lesser effect on BMI (still significant improvement from baseline), it proved to be as effective as sibutramine in reducing waist circumference. This suggests that both drugs have a significant effect in reducing abdominal adiposity, which is a significant predictor of insulin sensitivity into old age (Rocette, Evans, Weiss, Hagberg & Holloszy. 2006), and of T2DM (Wang, Rimm, & Stampfer. 2005). Sibutramine was found to increase LDL cholesterol to the highest levels, with orlistat showing smaller

increases (0.5%). This suggests that although sibutramine induces a greater reduction in body weight, it may increase the likelihood of another CV risk factor, atherosclerosis, when compared to orlistat. However, the findings of triglycerides within this review are contrasting compared to findings of LDL cholesterol, for both orlistat and sibutramine. The findings of the review suggest that sibutramine induces the greatest decrease in levels of triglycerides. This suggests that sibutramine has a greater therapeutical effect on triglycerides than orlistat. The results of the review suggest that sibutramine induces far less AE than orlistat, with fewer participants discontinuing as a result of sibutramine side effects. As there are safety and ethical considerations in obese and overweight subjects, this could prove to be a key factor when prescribing for the obese patient. However, sibutramine treatment was accompanied by an increase in SBP, whereas orlistat induced a decrease in both SBP and DBP, which is of vital importance when considering medication for the hypertensive patient. This major AE is one of the main reasons that sibutramine has now been withdrawn. However in light of this review, is it conceivable that orlistat may also be withdrawn due to AE?

Two studies investigated the effects of metformin in comparison to orlistat. As the studies that included metformin therapy were of female populations only, it is extremely difficult to interpret findings that influence the effect of metformin on men. Subjects under metformin therapy reduced their body weight significantly from baseline, but were not statistically significantly different from reductions observed in the orlistat therapy group in the study by Metwally et al. (2009). However there was a significantly greater decrease in body weight for orlistat subjects than metformin observed in the other metformin study (Jaygopal et al. 2005). Significant reductions in testosterone levels were reported in both metformin and orlistat groups, but were not

significantly different from each other. Each study had differing doses of metformin. (Jayagopal et al. 2005, constant 1500mg each day; Metawally et al. 2009, incremental titrated from 500mg daily up to 2000mg daily after 4 weeks). As Metwally et al. (2009) reported no significant differences in weight loss parameters between the two groups after treatment, compared to Jayagopal et al. (2005) who reported greater reductions in BMI for orlistat group, this would indicate that a higher dose of metformin is needed to match the therapeutical effects of orlistat. This higher dose of metformin could influence AE, as Metwally et al. (2009) reported that orlistat was better tolerated than metformin.

Weight reduction finding for cetilistat and orlistat, suggest that at similar doses, each drug induces similar results in parameters of weight loss. This is reported by Kopelman et al. (2009) who report that orlistat 120mg t.i.d reduces weight not significantly different to cetilistat 80mg and 120mg t.i.d, but is significantly greater than cetilistat 40mg t.i.d and placebo groups, and is a significant reduction from baseline. However, the subjects in the orlistat group reported more severe AE than any of the cetilistat or placebo groups, which were mainly GI in nature.

One study reported that orlistat + MK-0557 did not induce significant weight loss parameter compared with orlistat monotherapy, suggesting MK-0557 inhibits the effect of orlistat on treatment of obesity. More evidence is required.

Surgical interventions show a greater weight reduction and maintenance of weight over longer term periods. After six months (from surgical treatment, and of continual orlistat treatment), both surgery and orlistat treatment arms had significantly reduced their weight, and shown improvements in other anthropometric measurements. At two years, the surgical patients had more positive measurements for domain scores when referring to quality of life, proportion of patients with

metabolic syndrome, DBP, and insulin sensitivity. The surgical groups continued to lose weight after six months, with the orlistat groups showing progressive weight regain from six months onward. This suggests that bariatric surgery may be more beneficial on weight parameters over a longer period of time. However there are major health and economic problems associated with surgery.

When comparing orlistat to placebo, orlistat induced significantly greater reductions in weight loss parameters, including BMI, and waist circumference, over both short-term and long-term periods. AE were a predominant finding amongst orlistat patients, with a majority of studies reporting the main reason for attrition due to AE that were GI in nature.

7.2 – Areas for concern

The increase in SBP observed with sibutramine therapy, is of potential concern, particularly in the overweight and obese population, where even mild increases in blood pressure can be expected to result in an increase in CV events in a population already at risk. This is one of the major reasons why this agent has now been withdrawn from the European market. A small rise in blood pressure may have a detrimental effect on patients with pre-existing CVD (Padwal et al. 2009). As orlistat produced a small reduction in SBP and DBP, this would indicate that this drug has a positive effect on subjects with existing CVD or CV risk factors. However, studies examining mortality and CV morbidity are needed to provide further extensive information.

If we assume the results observed from orlistat treatment, within this review are fully valid and are capable of being reproduced to an accurate and sufficient

extent, outside of a clinical setting or field, we need to know if the observed positive effects on weight loss parameters, or CV risk factors, are of a benefit to the obese or overweight population. Weight reduction of approximately 5% - 10% of initial body weight is associated with improvements in blood pressure, lipids, and glucose parameters (Blackburn. 1995., Goldstein. 1992., as cited by Padwal et al. 2009), but RCT data examining the impact of weight reduction, and the direct influence of orlistat, on CV events, CV risk factors, and CV mortality, are short in number, and more investigation is needed into this area. However, results of RCT,s involved within this review of orlistat, have been shown to reduce diabetes incidence and progression to T2DM in subjects who were overweight or obese.

Although the majority of studies within this review are not comparable due to various aspects of design including; population type and number, medication dose and titration, and intervention type, the weight loss for subjects undertaking orlistat medication was significantly reduced when compared to baseline measurements and placebo study groups. Some studies reporting on CV risk factors suggest that orlistat directly, or in-directly, has a positive influence. However, further investigation is needed over both short term and long-term time frames.

