COST-EFFECTIVENESS OF SELECTING AN ENANTIOPURE FORMULATION OVER A RACEMIC MIXTURE

MINI-THESIS

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Cost-effectiveness of selecting an enantiopure formulation over a racemic mixture

KEY WORDS

Enantiopure

Chirality

Cost-effectiveness

Efficacy

Racemic

Regulatory

Omeprazole

Esomeprazole

Citalopram

Escitalopram

ABSTRACT

BACKGROUND

The aim of this study is to provide more information in terms of the cost-effectiveness of selecting an enantiopure formulation over a racemic mixture in the context of promoting rational use of medicines. This was done by comparing costs and efficacy of escitalopram versus citalopram and esomeprazole versus omeprazole since they are the most commonly used medicines with both racemate and enantiopure products registered.

METHODS

A search for randomized clinical trials was carried out using PubMed, Cochrane, Medline and other websites and abstracts were reviewed. Efficacy was measured using mean change from baseline in the Montgomery–Åsberg depression rating scale (MADRS) total score for citalopram versus escitalopram and healing percentage rate was used for omeprazole versus esomeprazole. Overall data analysis was done using Forest plots conducted through Microsoft Excel to assess any superiority in efficacy.

RESULTS

The Forest plot results show that esomeprazole 40 mg has better results in treatment of esophagitis due to gastroesophageal reflux disease when compared to omeprazole 20 mg with odds ratio (OR) of 1.10. The results are similar to the head-to-head comparison of citalopram versus escitalopram with OR value of 1.25. Overall results show marginal superiority to enantiopure molecules.

CONCLUSION

The overall results show that improvement in efficacy due to enantiopure medicines is not statistically significant and their tolerability is similar to racemates. However, the costs of the enantiopure are significantly higher since it includes the costs of manufacturing and quality control of the pure racemate. It therefore makes economic sense to continue the use of racemate medicines considering their relatively low prices of acquisition. The health of the patients is not compromised but at the same time access to the medicines is improved.

DECLARATION

I declare that this thesis that I now submit for assessment on the Programme of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for the purpose of a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others save to the extent that such work has been cited and acknowledged within the text of this work. I agree to deposit this thesis in Healthcare-learning's institutional repository and the University of Western Cape's library or allow these institutions to do so on my behalf, subject to the British and South African Copyright Legislation and the University of Western Cape's conditions of use and acknowledgment.

Signed . . . . . **Dated: 27/12.2017**

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1.0 INTRODUCTION

1.1 General Background

Pharmaceuticals are at the core of health care and ensuring their access is very critical. Use of medicine with moderate cost to increase access to effective medication is a top priority for health care. Currently, there is a realization that even though prescription drugs can improve patients' health, there are several issues around their access, efficacy, safety, and cost. Kennedy (2004) wrote about two strategies that could be used to manage pharmaceutical costs involving processes and criteria used to determine which medicines will be covered, pricing policies and negotiations of prices. Some of these processes in most countries include use of information about the comparative clinical and cost-effectiveness of medicines to determine which medicines their health care system can use. The National Institute for Health and Clinical Excellence is responsible for developing evidence based guidance for the UK healthcare system using these methods (Orton *et al*., 2011). The use of research evidence to underpin public health policy has been strongly promoted. However, the amount and quality of research in the public health sector on the effectiveness of newly developed medicines versus the cost and effectiveness of currently used medicines is low. Botswana is a country that believes in evidence based medicine; therefore it relies on clinical studies to develop its own treatment guidelines and essential drugs list. The medicines that are on the treatment guide, essential drugs list and registered are given first priority during procurement unless there are issues of supply. The World Health Organization also has a list of essential medicines which are selected with a lot of consideration focused on the disease prevalence, evidence of efficacy, safety and comparative cost-effectiveness (WHO, 2017). WHO defines cost-effectiveness analysis as a comparison of two or more medicines which are not exactly equivalent in terms of dose or therapeutic effect, but are used to treat the same clinical condition. It requires measuring the cost per defined measurable clinical outcome (effect) for each of the drugs. Medicines which are found to be more efficacious, safe and have a reasonable price are considered to be cost-effective.

In Botswana, there are a fair number of registered enantiopure products which are not included in the essential drug list or treatment guideline. This study focused on finding out if these products are beneficial and if there is need to include them in our formulary. Other countries have done a similar process when new medicines were developed so that they could figure out their role in the health care system. The United States has done the same when deciding which medicines to include in the formulary concerning the so-called specialty drugs which are high tech, high cost and are targeted at a small percentage of patients (Siegfried *et al*., 2013). A value framework was developed which looked at efficacy, risk, cost, and societal benefit. In this framework, each medication would be reviewed against an equivalent medication or alternative therapy and this made deciding on which medication to use a bit simpler. This study will aid the Ministry of Health and Wellness in Botswana when revising the current treatment guide and essential list looking at the results obtained on the chosen medicines. The study was based on one of the treatments for major depression disorder (MDD) which affects several people in Botswana

yearly, mainly because of the scourge of HIV and shortage of employment which has led to some people taking their own lives and other challenges. It also compared proton pump inhibitors which are also among the most commonly prescribed medicines. Proper treatment of this condition is in line with Goal 3 of the 17 Sustainable Development Goals (SDGs) which aims at ensuring healthy lives by prevention and treatment of non-communicable diseases and behavioral disorders.

1.1.1 CHIRAL MOLECULES

Chiral molecules comprise of a carbon atom attached to four different substitutes, making it an asymmetrical molecule (Cameron, Yao and Barnett, 2014). The substitutes can be atoms or groups of atoms, but each must differ from one another. This creates molecules with a chiral center and if there are one or more chiral centers, they can exist in at least two stereoisomeric forms (Hutt and Valentova, 2003). Stereoisomers where the mirror images are not imposable are called enantiomers. The Cahn-Ingold-Prelog rule is used to describe the configuration of these molecules by giving each attached group priority according to its atomic number with the higher priority given to the substitutes with higher atomic numbers and the one with lowest atomic number is then given the last priority number (Aalund and Pincock, 1986). If the path traced from the highest priority is clockwise, the chiral center is assigned (*R*) from Latin meaning *rectus* and if counterclockwise, the chiral center is assigned (*S*) from the Latin *sinister (*Aalund and Pincock, 1986*)*. These molecules also rotate polarized light either clockwise or counterclockwise, but there is no correlation between the two (R can either rotate polarized light to the right or in a clockwise direction where it is said to be the (+) *dextrorotatory isomer* or left or in a counterclockwise direction, the stereoisomer is called the (−) or the *levorotatory isomer* (Böwering N. *et al*, 2001). Even though these molecules have identical physical and chemical properties, their biological actions can be different.

In a journal by Blackmond, 2010 on the origin of biological homochirality, it is shown how the issue of chirality was discovered as early as 1874. It was later found to form the building blocks of living organisms with proteins primarily left-handed and polysaccharides right-handed and this is mainly determined by their chiral characteristics. The chiral biomolecules exist in one of the two possible enantiomers while synthetically made chiral molecules come out as equal amounts of each enantiomer. The macromolecules in the body which drugs interact with pharmacokinetically and pharmacodynamically are chiral in nature. The human body has also been shown to be a stereoselective environment with enantiomers in medicines, food and other compound. These bind selectively to stereoselective receptors resulting in different affinities to the receptors and biological responses. Therefore, different enantiomers may differ in either, or both, their pharmacokinetic and their pharmacological profiles. Metabolism is the most stereoselective among all the pharmacokinetic processes because of the involvement of the enzymes, such as cytochrome P450 enzymes (Shen, Lv and Zeng, 2016). The active or desired enantiomer is known as the eutomer and it is usually more potent than the other which is called the distomer (Nation, 1994). The enantioselectiveness of living organisms has led to this increase

in research on implications of chiral pharmaceutical medicines. There is however limited information comparing effectiveness of these molecules.

1.1.2 Implications in Pharmaceutical drugs

Chiral chemistry has gained much consideration when it comes to therapeutic benefits of using enantiopure molecules. For the past half a century, many pharmaceutical manufacturers have been venturing into this route of pharmaceutical development. Thalidomide has been used as a case that shows the dangers related to use of racemic medicines and promotes use of pure enantiomers. Newly developed technologies have improved the production of enantiopure molecules. Clinical trials have shown that one enantiomer usually has the therapeutic effect while the other one might just have the undesirable effects or no activity at all (Potocka and Dvorack, 2004). The development of enantiopure molecules is mainly done to avoid undesirable side effects of the inactive enantiomer or its hostile properties. However, there are some cases where the active pure enantiomer is more toxic than the racemic an example being labetalol where the enantiopure dilevalol is seen to have more hepatic toxicity (Lennard, 1991). So, a case by case study has to be done so that all switches are justified clinically.

Most currently available medicines are manufactured as racemic mixtures which mean there is a 50:50 mixture of the respective enantiomers. They are produced as racemic due to low costs of production, but the sponsor has to show that there are no obvious effects on the efficacy or toxicity when the two enantiomers coexist (Shen, Lv and Zeng, 2016). In the past 20 years there has been a trend towards chiral switch, which is when a single enantiomer drug is marketed in place of racemic and claimed to bring better clinical benefits compared to their counterpart (Hutt, A. and Valentova, J. 2003). There are medicines that would offer improved clinical outcomes as pure enantiomeric medicines but for some there is a little difference over the racemic. Some of those with clinical benefits are synthetic medicines for example, dopa (-) is found to be active and less toxic while for beta-adrenoreceptors antagonists there are no advantages in using the active enantiomer since most side effects are due the active enantiomer (Lennard, 1991). In general, scientific evidence shows that patients would benefit from the active enantiomer formulation because of lessened side effects. Pharmaceutical companies have used this knowledge to separate enantiomers and only market the therapeutically effective ones. Also, the observation of negative effects from the Thalidomide tragedy, led to stricter regulations. Chiral medicines are now mostly exclusively applied as single enantiomers (Blaser, 2013). Some examples of these medicines include esomeprazole from omeprazole and levocetirizine from cetirizine. This move has many benefits to the pharmaceutical companies including increasing patent life of these products (Peikova, L. *et al* 2014). It is therefore important to look at whether the late movement towards manufacturing single enantiomer medicines is of significant benefit to the patient or just of commercial benefit to the pharmaceutical companies. Current racemic medicines have been efficacious and fairly safe, hence a level of superiority would be needed to move to the single enantiomers.

2.0 Problem Statement/ hypothesis

The aim of the study is to do a cost analysis of racemic drugs versus pure enantiomer drugs. The research was based on a comparison of citalopram versus escitalopram and omeprazole versus Esomeprazole, assessing their efficacy and drug acceptability. For the citalopram versus escitalopram, the primary result of therapy was based on the mean change from baseline of the Montgomery Åsberg Depression Rating Scale (MADRS) total score and for omeprazole versus esomeprazole comparing the healing rates or symptom relief of erosive esophagitis (EE) on patients with gastro-oesophageal reflux symptoms (GERD). The cost analysis was based on the cost per drug of generic brands in Botswana wholesalers. Therefore, the study objectives are:

a) Determine any differences in efficacy and drug acceptability between citalopram versus escitalopram and omeprazole versus esomeprazole.

b) Determine differences in healthcare costs associated with the use of citalopram and escitalopram and omeprazole and esomeprazole.

The hypothesis is that the single enantiomers have better efficacy, are safer and have less adverse events, therefore should be prescribed over the racemic mixture drugs even though the costs might be a limitation in certain cases. The aim of this study is therefore to provide more information in terms of the cost-benefit of selecting an enantiopure formulation over a racemic mixture in the context of promoting rational use of medicines.

3.0 LITERATURE REVIEW

3.1 CITALOPRAM VERSUS ESCITALOPRAM

The World Health Organization estimates that by 2030, major depression disorder will become the 2nd most common cause of disability and burden of disease (Li *et al*., 2017). Due to this, mental health is one of the greatest concerns for the ministry of Health and Wellness, in Botswana. This is why the importance to get the best of the treatment available cannot be stressed enough. Selective serotonin reuptake inhibitors (SSRIs) are considered a first-line pharmacological treatment for this condition in many countries and these includes citalopram and escitalopram. Citalopram is a racemic mixture of the R- and S-enantiomers in a 1:1 ratio and escitalopram is the S-enantiomer. Nonclinical studies have shown that the S-enantiomer is the active enantiomer, hence the development of the pure enantiomer which was launched in 2002 (Montgomery *et al*., 2008). It is believed the pure enantiomer is more clinically superior to the racemic. This systematic review aims to find out if there is evidence to support this and if there is any, is it worth using them over the racemic looking at the costs attached to them. These medicines are used for generalized anxiety disorder, depression and obsessive-compulsive disorder. Their mode of action is through reduction of neuronal uptake of serotonin increasing its amount in the synaptic cleft (Preskorn, 1997). Most of the antidepressants have been developed as the racemic such as fluoxetine until recently.

Escitalopram has shown a more effective serotonin reuptake inhibition when compared to the R-enantiomer , which showed some antagonistic properties (Höschl and Švestka, 2008). It was first developed by H Lundbeck and Forest Laboratories pharmaceutical companies. Evidence shows that the R-enantiomer competes with the S-enantiomer at a low-affinity site on the serotonin reuptake transporters leading to decreased binding of the S-enantiomer at the high-affinity site. The R- enantiomer competes with the S-enantiomer for the allosteric site which regulates the affinity of the ligand for the active site of serotonin reuptake. The S-enantiomer seems to be more selective to the receptors and in its inhibition of serotonin reuptake by binding to the serotonin transporters. Höschl and Švestka (2008) have also shown that the occupancy times for escitalopram are statistically and significantly higher than that of citalopram. The patient-reported outcomes are used as a secondary endpoint to measure effectiveness of antidepressants and they are the commonly used method. Montgomery–Åsberg Depression Rating Scale (MADRS) is a normally used scale to assess this by looking at different symptoms which affects patients with depression to determine the magnitude of the condition (Fantino and Moore, 2009). MADRS was developed in 1979 and it is defined as a 10-item diagnostic questionnaire with a total score of 60 points used to measure the severity of depressive episodes in patients and it was seen to be sensitive to the changes brought on by antidepressants (Berry, 2012). It is used to evaluate the efficacy of antidepressant treatment, with moderate to severe starting from 18–34 (Carneiro, Fernandes and Moreno, 2015). The other method is the Hamilton Rating Scale for Depression (HAM-D)[5] which is also used to monitor the patient's progress during antidepressants treatment. This scale exists in several versions, ranging from 6 to 31 items with

the 17-item HAM-D-17 frequently used in research studies (Roffman, Silverman and Stern, 2010).

3.2 OMEPRAZOLE VS ESOMEPRAZOLE

3.2.1 INTRODUCTION

Gastric acid reflux is a normal physiological condition which, at prolonged periods can lead to mucosal damage. This is called gastroesophageal reflux disease (GERD), where gastric contents are refluxed into the esophagus and it is a common acid-related disorder (Malfertheiner and Hallerbäck, 2005). It can be exacerbated by different things like food or empty stomach for long periods of time. Some of the symptoms of this condition include heartburn and regurgitation. Omeprazole and esomeprazole are among the common Proton pump inhibitors (PPIs) used for this condition to reduce the excessive production of gastric acid. Esomeprazole is the (S)-enantiomer of omeprazole and it is one of the latest developed PPIs. PPIs are weak bases activated by acid, which act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H+/K+ ATPase) of the gastric parietal cell (Shin and Sachs, 2008). They block the terminal stage in gastric acid secretion responsible for secreting H+ ions into the gastric lumen. Their main target is to maintain the intra-gastric pH above four to treat GERD.

In general, PPIs are the most effective medicines in to treat acid-reflux related conditions, but the pure enantiomer is believed to be superior to the racemic mixture (Asghar, Pittman and Jamali, 2015). Generics for both are registered in Botswana, therefore patients and prescribers have several alternatives to choose from. It is relevant to know their effectiveness in comparison to their cost because this may result in a major pharmacoeconomic impact. This is because acid reflux conditions affect several people at any given point and time. Systematic reviews have been done previously comparing esomeprazole with omeprazole and other PPIs like lansoprazole and pantoprazole. This was done mainly looking at the healing rate of GERD by these medicines, which prove that there is a higher rate of healing by oesomeprazole 40 mg. However, there is no evidence of whether the difference is of statistical clinical significance (Wójcik *et al*., 2015). The economic impact is also not taken into consideration, which is vital in developing countries like Botswana where the economy is still struggling.

3.2.2 PHARMACOLOGICAL DIFFERENCES

PPIs are chiral compounds and their chirality may have an effect on how they are handled by the body including their safety and toxicology. There is a difference in how these molecules are metabolized, however the parietal cell proton pumps are equally susceptible to either of the isomers (Dent, 2003). The main routes of metabolism for the (S)-enantiomer is catalyzed by CYP3A4, which produces omeprazole sulfone and for the (R)-enantiomer is metabolized primarily by CYP2C19, which produces hydroxyomeprazole and a minor metabolite, 5-O-desmethylomeprazole which has shown the difference in oral bioavailability of two enantiomers

(Shen, Lv and Zeng, 2015). Due to the different enzymes used to metabolize the two, it has been realized that esomeprazole has a higher bioavailability than omeprazole (Chen, C. *et al*, 2005).

4.0 METHODOLODY

Botswana has seen an increase in the influx of applications for registration of enantiopure formulations over the last decade. Although enantiopure medicines may be preferable in terms of effectiveness, side effect profile and safety, the increased cost may be a prohibiting factor. Economic evaluation is required to put in consideration both the cost and clinical benefits of these medicines. Plenty of information is required to aid health care practitioners and regulatory bodies to determine if an enantiopure formulation of a compound should be prescribed over the corresponding racemic. An evaluation of the extent of registered enantiopure drugs versus racemic mixtures as well as a cost versus clinical benefit analysis may provide more clarity and promote rational medicine use. The cost benefit analysis for this research was done specifically for omeprazole versus esomeprazole and citalopram versus escitalopram. This was to provide a framework or method that could be used for comparison of racemic vs enantiopure medicines .The benefit versus cost is specific for each active pharmaceutical ingredient (API), hence the need to develop a method that could be used for other API's. The study assessed medicines approved in Botswana over the last 16 years to establish the extent of registration of enantiopure drugs. The analysis was then done for the drug with various products registered as racemic mixtures and enantiopure products to obtain a better understanding of the cost *versus* clinical benefit of utilizing either formulation type.

All registered single and racemic enantiomer drugs between years of 2005 and 2016 were identified using the Blue Book which contains all registered products in Botswana. Application database containing all the products which were ever submitted in Botswana which are either registered or rejected was also searched. This was done to gain an understanding of the quantity or trends of submitted applications. They were systematically searched using the International Nonproprietary Name (INN) prefixes assigned to single enantiomer drugs for example "es "for the dextrorotary and registered racemic mixture. The list of these products was collected and then those with the highest numbers of registered racemic and pure enantiomer containing formulations were used to conduct the research. These products were esomeprazole and Omeprazole, which are both registered from 8 different manufacturers, citalopram versus escitalopram with escitalopram from 4 manufacturers, citalopram from 2 manufacturers. An assessment of available literature on the registered pure enantiomer medicines was then done to compare the safety, toxicology, efficacy and quality of these products. Different aspects were looked at including therapeutic success, symptomatic relief and side effects. This was done by evaluating literature where the single enantiomer was directly compared with the precursor racemic drug and checking for evidence of clinical superiority (Gellad, W.*et al*, 2014).

The approval process was crucial for the research with the current influx of applications of these molecules. This was important to assess the important data required by regulatory agencies

during submission of dossier. A search for the dossiers of the chosen products was performed, evaluation reports were collected and data was analyzed. Aspects such as pharmaceutical development, specifications, stability and all critical information required during registration were evaluated. The emphasis on the single enantiomer products was on the identity, enantiomeric purity of chiral starting materials and chiral reagents, enantioselective test methods used, in-process testing for identity and purity which should be enantioselective and monitoring of enantiomeric purity of the drug substance in the drug product during the stability studies conducted to determine shelf life (Health Canada, 2000). Specifications of the drug substance were assessed for inclusion of an enantioselective test for identity and purity, optical rotation to check if they were carried out. This information was analyzed to assess whether enough information was provided by applicants to make an informed decision and look at the loopholes in the regulatory processes if the products were registered without all the necessary information needed. This is possible since at the moment there is no guideline followed by the regulatory agency in Botswana to register these products. This information will be used to look at the regulatory point of view on what should be carefully looked at when assessing these products and challenges encountered to ensure that single enantiomer products registered are of the required standards. This will also assist in developing a guideline to prevent registration of products without adequate information which could be life threatening since most of them are not registered by other stringent regulatory authorities because their quality, safety and efficacy has not been evaluated by a trusted agency.

Prices for the different brands of citalopram versus escitalopram and omeprazole versus esomeprazole were collected from a pharmaceutical wholesaler. The prices of both innovator products and generic products were collected. Average of costs comparing same pack sizes to identify whether there is a significant price difference between the two groups was done. This would aid in decision making of whether it is worth recommending to Central Medical Stores to source the single enantiomer drugs rather than the racemic medicines.

4.1 CITALOPRAM VERSUS ESCITALOPRAM

4.1.1 Inclusion criteria for review articles

Searches were conducted on PubMed, Cochrane, Medline, the Evidence-Based Medicine Database (EMB), citations from previous meta-analysis and Google Scholar. Searches were performed using keywords ‘escitalopram’ in combination with ‘placebo’ or/and ‘citalopram’, major depression disorder, randomized clinical trials and searches using brand names such as Depramil and Cipralex/Lexapro. Searches were limited to reviews in adults and in English language. The searches were then cross-referenced to avoid duplication. The searches were applied between 2000 and 2016 then a quick review of the abstracts of the papers was done looking at medicines being compared, method of measuring efficacy and similar methodology of the clinical trials.

4.1.2 Inclusion criteria for randomized clinical trials

Unpublished trials were searched through Controlled Trials Database http://www.allerganclinicaltrials.com/ and https://www.clinicaltrials.gov/. Randomized clinical trial studies that compared head-to-head citalopram and escitalopram or with placebo, published in English were considered for the research. No restriction on the formulation type used or gender, either capsules, tablets and any duration of treatment will be considered. Of the retrieved studies, only those with a confirmed primary diagnosis of major depression disorder were selected. There were also no restrictions on duration of illness and method of diagnosis. Regulatory authorities' websites like the United States Food and Administration (FDA) websites were searched for relevant information

Randomized, double-blind studies using adults between 18 and 65 years old, suffering from major depression disorder were included. The study evaluated the efficacy of the targeted medicines using the mean differences on the MADRS hence Patients with MADRS $\geq$ 20 were included. Clinical trials conducted between year 2010 and 2016 were considered.

4.1.3 EXCLUSION CRITERIA

1. **Review Articles**

All duplicate articles, editorial, commentary, animal/ Laboratory studies, patients using multiple SSRIs or allowed to switch, not comparing equivalent doses, not RCT, not in English Language, patients younger than 18 years old will be excluded from the analysis. Additionally, trials in depressive patients with a serious concomitant medical illness, those diagnosed with suffering from other depressive diseases and clinical trials comparing escitalopram and citalopram with other medicines and were excluded.

2. **Clinical trial articles**

Participants that were excluded include those below the age of 18 years, pregnant women and breastfeeding, patients who had clinically significant abnormalities on the baseline physical examination, electrocardiogram, or laboratory tests. Volunteers who have taken other antipsychotics, antidepressants, psychoactive herbal remedies in the past 2 weeks, psychiatric disorder or other severe medical conditions such as severe renal or hepatic impairment were also excluded. Also volunteers with observed significant risk of suicide during assessment, patients who are contraindicated or had hypersensitivity to take citalopram or escitalopram and patients with MADRS total score below 18.

4.2 SELECTED TRIALS

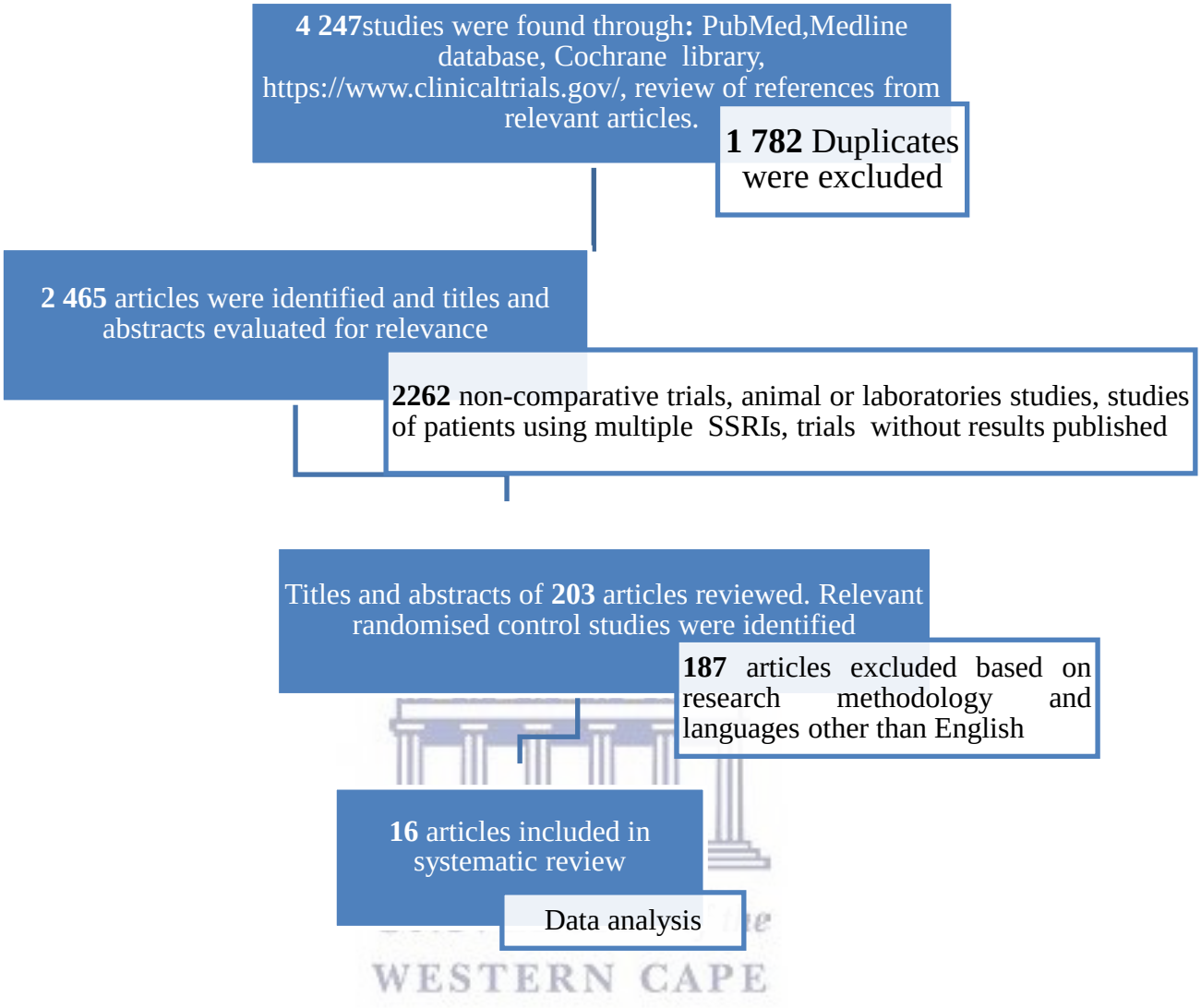

FIG1: FLOW DIAGRAM OF THE SELECTION PROCESS FOR RANDOMISED CONTROLLED TRIALS FOR CITALOPRAM VERSUS ESCITALOPRAM
Search results for clinical trials on citalopram versus escitalopram between 2000 and 2016 of PubMed, Cochrane, Medline and EMBASE databases and screening process.

4.3 DATA EXTRACTION

For each trial report, the following information was extracted: the publication status, publication year, the compared drugs, outcome assessment time, evaluated dosages (fixed or flexible), number of randomized patients, treatment responders, means and standard deviations for depression score at baseline and follow-up, change in depression score from baseline to follow-up, age (mean, range) and sex proportion of subjects.

4.3.1 Outcome measures

The assessment of efficacy was based on short-term treatment of 8-weeks. If 8-week assessment was not reported, then extract outcome data for the closest time point was reported. The outcome

data was reported for the Montgomery-Åsberg depression rating scale (MADRS) and the Hamilton scale. When reports described results from both rating scales, then the MADRS results were used. Efficacy was assessed by the proportion of responders in each treatment group, defined as patients with a decrease in depression score from baseline to follow-up of at least 50%. The numerator would be the number of responders among the "efficacy" subset (i.e., patients who received at least one dose of a drug and had at least one follow-up visit) and, when used, derived by the Last Observation Carried Forward (LOCF). The denominator will be the number of randomly assigned participants. Subjects not included in the efficacy subset and dropouts (when LOCF was not used) will be assumed to be non-responders.

4.3.2 Data analysis tool

Data analysis was done using Forest plots using a Microsoft Excel spreadsheet adapted from Neyeloff, Fuchs and Moreira (2012). Head-to-head trials were used to show any superiority. The calculations were done in steps computed with basic arithmetic operations. Spreadsheet was used to do the analysis of parameters such as the sample size. The raw data is provided in the appendix section appendix C.

4.4 RESULTS

4.4.1 Citalopram vs Escitalopram

A total of 16 trials were included in the study with some from previous meta-analysis publications. The trials were randomized and some of them multicentric, covering different geographical locations. They had a different primary objective, but all analyzed the difference in baseline each treatment made in the participants and most of them assessed the percentage of responders to treatment. In almost all the trials, escitalopram showed superior efficacy results compared to citalopram and placebo. Most trials compared equivalent doses (citalopram 20/40 mg with escitalopram 10/20 mg). However, the study by Colonna, Andersen and Reines, 2005 had double the dose of citalopram compared to escitalopram but the results still showed no significant differences between the two.

4.4.1.1 Assessment of Efficacy

The participants were all adults between the ages of 18 and 65 and outpatients. Most of the trials had a significant number of participants with a few withdrawals along the trials and with more females in all the trials with this data available. They had different study duration from 4 weeks to 24 weeks and their primary objectives were also different. Fixed doses were delivered in 9 studies and 7 had flexible doses where the dose could be doubled along the duration of the trial (Table 1). Their results were then counted in the higher dose group. In all the trials, efficacy was based on intent to treat and depression was quantified on the MADRS scale for 12 trials and 4 on the Hamilton Depression Rating Scale. Patients with MADRS scale of at least 22 were eligible for the trials. Baseline score shows the average baseline MADRS score was approximately 29.

TABLE 1: Characteristics of Selected Randomized Clinical Trials

Trial ID	Age, mean (yr.)	Male, %	Scale used in the analysis	Baseline Depression severity, mean	Setting	Elderly Specific Population	Dosage	Outcome Measurement Delay (weeks)	Funder
citalopram-placebo									
Brown *et al*., 2005	40.4	19.5	HRSD	≥17	Outpatients	No	Fixed	12	Forest Laboratories
escitalopram-placebo									
Wade *et al*. (2002)	NC	NC	MADRS	22-40	Outpatients	No	Fixed	8	NC
Ninan*et al*. (2003)	NC	NC	MADRS	≥22	Outpatients	No	Flexible	8	NC
NCT00668525	41.3	53.2	MADRS	NC	Outpatients	No	Fixed	8	Forest Laboratories
NCT00464711	38.7	47.5	HAMD-17	NC	Outpatients	No	Fixed	12	Massachusetts General Hospital
NCT00384436	42.4	40.1	MADRS	≥30	Outpatient	No	Fixed	12	Forest Laboratories
escitalopram-citalopram									
Yevtushenko *et al*., 2007	35.1	41.6	MADRS	≥35	Outpatients	No	Fixed	6	ARBACOM Russia
Moore,2005	NC	NC	MADRS	≥30	Outpatients	No	Fixed	8	H. Lundbeck
Lalit*et al*., 2004	NC	NC	HAMD	≥18	Outpatients	No	Flexible	4	NC
Colonna, Andersen and Reines, 2005	46	25	MADRS	≥30	Outpatients	No	Fixed	24	H.Lundbeck
Li *et al*, 2006	NC	NC	HAMD	≥18	Outpatients	No	Flexible	6	NC
SCT-MD-02	43	28.2	MADRS	≥22	Outpatients	No	Flexible	8	H. Lundbeck
Lancon*et al*,2006	NC	NC	MADRS	≥30	Outpatients	No	Flexible	8	NC
escitalopram-citalopram-Placebo									
Burke, Gergel and Bose, 2002	40	35.3	MADRS	≥30	Outpatients	No	Fixed	8	H.Lundbeck

Trial ID	Age, mean (yr.)	Male, %	Scale used in the analysis	Baseline Depression severity, mean	Setting	Elderly Specific Population	Dosage	Outcome Measurement Delay (weeks)	Funder
Forest Labs,2005: Anon,2002	NC	NC	MADRS	≥22	Outpatients	No	Flexible	8	NC
Lepola, Loft and Reines, 2003	43	28	MADRS	≥30	Outpatient	No	Flexible	8	H. Lundbeck

MADRS= Montgomery–Åsberg Depression Rating Scale
HAMD= Hamilton Depression Rating Scale
HRSD =Hamilton Rating Scale for Depression significant
NC= unclear

One trial compared citalopram with placebo, 3 compared escitalopram with placebo, 6 compared citalopram with escitalopram and 4 compared citalopram, escitalopram and placebo (Table 2). Results were provided on the % of responders at the end of week 8 and change in MADRS score baseline. Citalopram showed superior results to the placebo, but the results were reported in Hamilton Rating Scale for Depression. The three trials that compared escitalopram with placebo show superiority of escitalopram at all doses to placebo. In the head-to-head trials comparing escitalopram to citalopram, all show superiority of escitalopram to citalopram. Some of the studies such as Yevtushenko *et al*, 2007 and Moore *et al*, 2005 show that this difference was statistically significant. The same applies when the comparison included placebo. From all the trials, escitalopram had consistently showed a greater MADRS reduction at the end of each trial. Patients who were depressed from Lancon *et al* (2006), Moore *et al* (2005) and Yevtushenko *et al* (2007) trials showed a greater change from baseline result for both citalopram and escitalopram. For the Yevtushenko *et al* trial with a baseline of at least 35 and was only 6 weeks, there was substantial change from baseline with escitalopram 20 mg with a change of -28.7 and citalopram 40 mg at -25.2. This showed great improvement from both groups however a minor difference between results achieved from escitalopram was achieved from citalopram in this trial. So, all treated patients showed more improvement when treated with escitalopram 10-20 mg compared to 20-40 mg of citalopram but both treatments were superior to the placebo. This was clear in all efficacy parameters and was confirmed by the summary of all the studies.

TABLE 2: INTERVENSIONS OF THE DIFFERENT TRIALS AND RESULTS INCLUSIVE IF CHANGE FROM MADRS SCORE BASELINE CHANGE

PUBLICATION STATUS	PUBLICATION YEAR	INTERVENSION	DURATION OF STUDY (Weeks)	#PATIENTS	Completed	Results (Response=MADRS≤50%	%Responders or change at week 8	Baseline MADRS score± SD	MADRS SCORE CHANGE
Citalopram-placebo									
Published	Brown *et al*., 2005	citalopram 20 mg/day or placebo	12	90	82	t_{185} =0 .29, p = 0.78)	54 49	24.0 and 23.4	20.5points 18.8points
escitalopram-placebo									
Published	Wade *et al*. (2002)	escitalopram 10 mg Placebo	8	380		escitalopram>placebo onset in 1-2 weeks	55 47	29.2±4.2 28.7±3.7	-17.4 -14.7
Published	Ninan*et al*. (2003)	escitalopram 10-20 Placebo	8	247		escitalopram=placebo	-13.3±0.9 -10±0.9	30.4±4.0 30.5±4.1	-14.7 -10.7
Unpublished	NCT00668525(2010)	escitalopram 10-20 mg (248 and 239) Placebo (167)	8	824	654				-12.8±0.6 -14.4±0.6 -10.1±0.7
escitalopram-citalopram									

PUBLICATION STATUS	PUBLICATION YEAR	INTERVENSION	DURATION OF STUDY (Weeks)	#PATIENTS	Completed	Results (Response=MADRS≤50%	%Responders or change at week 8	Baseline MADRS score± SD	MADRS SCORE CHANGE
Published	Yevtushenko *et al*., 2007	escitalopram 20 mg/day Citalopram 20 and 40 mg/day	6	330	322		95.4 83.3	34.8±3.5 35.4±3.3 35.7±3.8	-28.7 -25.2
Published	Moore at al ,2005	escitalopram 20 mg/day (138) citalopram 40 mg/day (142)	8	280	265		76.1 61.3	36.3±4.8 35.7±4.4	-22.4±12.9 -20.3±127
Published	Lalit*et al*., 2004	escitalopram 10-20 mg (69) citalopram 20-40 mg (74)	4	143	136		90 86	26±6 25±5	-23.2 -20.0
Published	Colonna, Andersen and Reines, 2005	escitalopram 10 mg/day (175) citalopram 40 mg/day (182)	24	357	279	Results at 8weeks	63 55	29.5±4.3 30.2±4.7	-16.8 -15.7
Published	Li *et al*, 2006	escitalopram 10-20 mg citalopram 20-40 mg	6	56	56			23.7±4.3 23.8 ±3.6	
Published	Lancon *et al*,2006	escitalopram 5-20 mg/ day (67) citalopram 10-40 mg/day (60)	8	127	127		79.4 44 (p<0.001)	≥30	-23.5 -17.5 (p<0.001)

PUBLICATION STATUS	PUBLICATION YEAR	INTERVENSION	DURATION OF STUDY (Weeks)	#PATIENTS	Completed	Results (Response=MADRS≤50%	%Responders or change at week 8	Baseline MADRS score± SD	MADRS SCORE CHANGE
escitalopram-citalopram-Placebo									
Published	Lepola *et al* (2003)	escitalopram 10-20 mg (155) citalopram 20-40 mg (160) Placebo (154)	8	469		escitalopram=citalopram>placebo onset in 1 week	64	29.0±4.3 29.2±4.2 28.7±4.0	-15.9 -14.6 -13.5
Published	SCT-MD-02	escitalopram10-20 mg/day (129) citalopram 20-40 mg Placebo (128)	8	257				28.7±4.3 28.3±5.0 28.8±5.0	
Published	Burke, Gergel and Bose, 2002	escitalopram 10 mg escitalopram 20 mg citalopram 40 mg Placebo	8	369	366		59 53 41	28.0±4.9 28.9±4.6 29.2±4.5 29.5±5.0	-15.0 -13.5 -10.0
Published	Forest Labs,2005: Anon,2002	escitalopram 10-20 mg citalopram 20-40 mg Placebo	8	248	243			28.7±4.3 28.3±5.0 28.8±.0	

HEAD-TO-HEAD FOREST PLOT

Only 8 trials were used in the forest plot since they had head-to-head comparison of citalopram and escitalopram. Forest plot results showed favorable results for escitalopram over citalopram. In all the trials the horizontal lines cross the vertical line, which indicates the results achieved by each trial are similar and statistically insignificant. The I^2 showing heterogeneity of the trials was more than 50% indicating the dissimilarity of the results of the trials involved. All the raw calculation data is provided in appendix C. The heterogeneity could be due to differences in study methods like participant demographics, such as severity of disease, the settings in which the research was conducted, the unfixed doses and how outcomes were measured across studies. The overall results show that escitalopram is better than citalopram but the difference between the two treatments are statistically insignificant since the diamond indicating summary of the results is on both sides of the vertical line. This is consistent with the summary results in table 2.

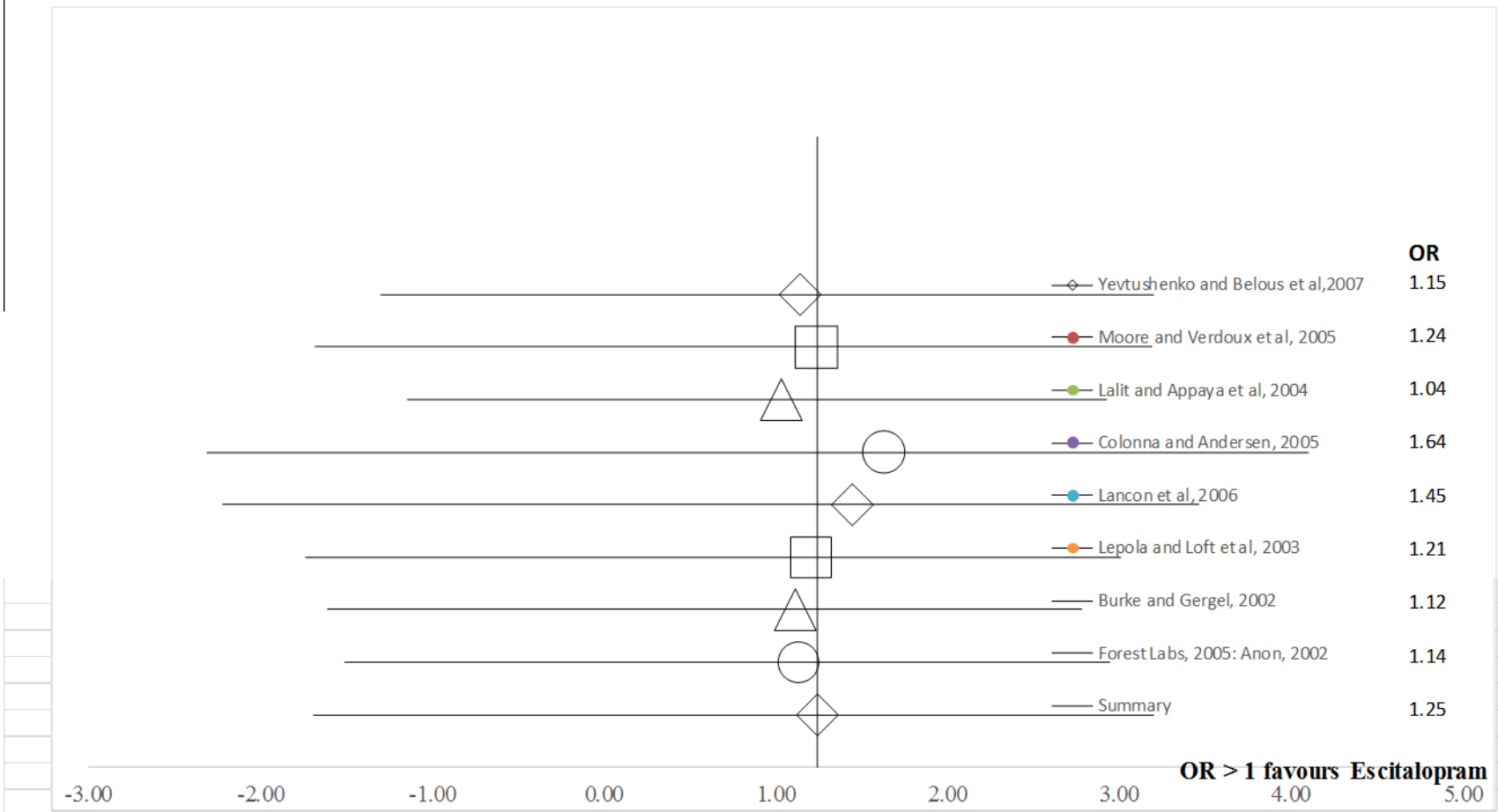

FIG 2: HEAD-TO-HEAD FOREST PLOT OF ESCITALOPRAM VERSUS CITALOPRAM

4.5 DISCUSSION

Depression is one of the most disabling chronic conditions that can intensively affect one's quality of life. This means the medications used should be of high quality, efficacy and safety to normalize the situation for the patients. Due to the increasing prevalence of those affected by this condition, pharmacoeconomics assessments are important to evaluate the relative cost-benefit advantage of these antidepressants. Citalopram and escitalopram are both second generation antidepressants used in major depressive disorder. There are some meta-analyses that have been conducted showing evidence that escitalopram is superior to other antidepressants such as paroxetine (Montgomery *et al*, 2008). However there is mixed evidence of superiority of escitalopram to citalopram. MDD is a chronic or recurrent illness which can lead to someone being on treatment for long periods of time. It is usually untreated or under-treated leading to a negative poor quality of life to the affected and even leading to other medical conditions (Wu *et al*., 2008). Because of this, MDD has a substantial indirect cost to the health system. So, a decision based only on cost of the medicine may lead to use of a less cost-effective treatment. Citalopram has been manufactured for a while and has a greater number of affordable generics to use compared to escitalopram. In Botswana we have more escitalopram brands including the innovator brand and two generics registered while for Citalopram. We have one innovator brand and one generic product registered. However, from the research, the innovator product of escitalopram is the one that is readily available. The study mainly looked at the studies that measured efficacy using the MADRS score. The higher MADRS score indicates more severe depression with MADRS score of >34 indicating severe depression (Müller, 2003).

To assess if there is any clinical advantage of using escitalopram instead of citalopram, a systematic analysis was done to analyze all trials done comparing these two molecules. The main findings from the analyzed data is that escitalopram consistently demonstrated greater efficacy compared citalopram and the placebo showed by changes in the scores from baseline results. Treatment with escitalopram was superior to that of citalopram, which was in turn better than the placebo. The forest plot also favors escitalopram when compared with citalopram. The results indicate that escitalopram has marginal superior efficacy when used in the treatment of MDD in patients with both moderate and severe disorder. The superiority results achieved from 10-20 mg/day escitalopram compared to citalopram 20-40 mg/day doses support the R-enantiomer inhibits the effects of the S-enantiomer by allosteric interaction with the serotonin transporter (Sanchez *et al*., 2004). Then the issue becomes clinical relevance of the difference. The percentage of responder's analysis used in the forest plot is important in addressing this question with clinical relevance shown by 50% difference between two groups (Montgomery and Möller, 2009). This is also used by the European Medicines Agency (EMA) to check if statistical difference is equivalent to clinical difference (Ema.europa.eu, 2013). Statistical significance indicates the likelihood that a research results is true and not due to chance which is determined by the p-value where $p < 0.05$ whereas the clinical significance is the practical importance of the

treatment effect, which tells us about the effect of this difference or how meaningful it is for patients (Fethney, 2010). This research shows a higher percentage of responders in those given escitalopram however the overall difference was statistically insignificant. Some individual trials did have significant differences between citalopram and Escitalopram. For example, in the trial by Lancon *et al* (2006) and Yevtushenko *et al* (2007) even though the overall results from the studies do not show significant clinical difference between the two. Another supportive study was conducted by Höschl, C. and Švestka, J. (2008) on response rate and it found that response rate was at 59% for escitalopram while citalopram at 53% and placebo at 41%. These results show minor differences between escitalopram and citalopram. In conclusion, the study shows that there is evidence that escitalopram is superior to citalopram when used for short-term of 4 to 24 weeks however the difference between the two groups is minor. This study did not look at the depression relapse percentage depending on which medication a patient was taking. This is important since relapse cases can add more to the cost of health care. This requires another systematic analysis to look at the cost that maybe due to relapse but not just immediate cost of the medicines.

4.5.1 ADVERSE EVENTS

The study did not carry out a separate analysis of the adverse events experienced by those taking the racemic compared to those on the enantiopure drug. Data was assessed from existing literature of the differently conducted trials. There seemed to be minor differences in adverse events experienced by those taking citalopram and escitalopram. They are documented to be both well tolerated with similar adverse events profile. A systematic review conducted by Trkulja, V. (2010), showed that there was an insignificant difference of p=0.521 of experienced adverse events. In another systematic review done by Lepola, Wade and Andersen (2004) where they analyzed two trials which compared escitalopram with citalopram and placebo, headache was found in 16% of those taking escitalopram and 19% in those taking citalopram and for nausea 16% for those taking escitalopram and 18% of those on citalopram. In conclusion, their tolerability was found to be more or less the same because the differences between the two groups were not significant. Even when the treatments were given for longer periods of time (for example in the 24 weeks trial conducted by Colonna, Andersen and Reines (2005)), 20 mg per day of citalopram had similar overall adverse events as the 10 mg/day escitalopram.

4.5.2 LIMITATIONS OF THE STUDY

A limitation of this meta-analysis was that most of the clinical trials were old and limited number randomized clinical trials were conducted to compare the molecules of concern. The study did not analyze side effects experienced due to racemic versus the pure enantiomer molecule which is critical to assess tolerability of the molecules. Some of the studies used the lowest recommended doses, which could be the reason for the low percentage of responders hence generalization of achieved results may not be possible. Also in some of the trials the doses were flexible which made it hard to know which doses were responsible for the effect. The studies

used focused mainly on the short-term efficacy effects and not long-term which could be crucial since usually patients take these medications for 6 months or more. Most of the clinical trials were sponsored by the manufacturer which could lead to biased results however the results are consistent with those trials done by different sponsors.

4.6 CONCLUSION

The efficacy of escitalopram was shown to be marginally superior to Escitalopram. However, the differences in price are significant with escitalopram being more than twice the price of citalopram (Table 5). With the limited resources given annually to the Ministry of Health in the still growing country's economy, it only makes sense to use the racemic medicine to reduce costs and improve access of medicines. The study has shown that the effectiveness of the two medicines are similar, hence a patient would benefit from either medicine they are given.

5.0 OMEPRAZOLE VERSUS ESOMEPRAZOLE

A structured electronic search of Medline, Chochrane library https://www.clinicaltrials.gov/ for unpublished trials and Embase for all the relevant clinical trials. Searches were performed using keywords 'esomeprazole' in combination with 'placebo' or/and 'omeprazole', gastro-oesophageal reflux symptoms, randomized clinical trials and also searches using brand names such as Nexium and Prilosec. The abstracts were reviewed to check if the trials met the inclusion criteria, in English-language, and randomized clinical trials. The searches were applied between 2000 and 2016 then a quick review of the abstracts of the papers was done reviewing medicines being compared, method of measuring efficacy and similar methodology of the clinical trials. The study evaluates efficacy of the targeted medicines using measures including percentage of healing rates. Trials with confirmed cases of esophagitis and treatment were given for 4 weeks or more were being considered. The measure of efficacy was percentage of healing rate confirmed endoscopically. These were seen as the best methods to measure the effectiveness of a treatment. In addition, the short-term treatment had a different efficacy measure which was mean percentage of 24-hour period with intra-gastric pH › 4.0; therefore, it was difficult to combine the two types of trials.

5.1 INCLUSION CRITERIA

All randomized controlled trials (RCTs) comparing esomeprazole with placebo or omeprazole were included regardless of duration of study. RCT conducted in the adult population between the age of 18 and 65 years with participants with Esophagitis (EE) or gastroesophageal reflux disease (GERD) were eligible for inclusion, regardless of their *Helicobacter pylori* status. All formulations with approved doses were considered for the study.

5.2 EXCLUSION CRITERIA

5.2.1 Review Articles

All duplicates editorial, commentary, animal/ Laboratory studies, patients using multiple PPIs or allowed to switch, not RCT, not in English language, patients younger than 18 years of age were excluded from the analysis. Trials in depressive patients with a serious concomitant medical illness or those diagnosed with esophageal cancer were also excluded.

5.2.2 Clinical trial articles

Participants excluded are those below the age of 18 years, pregnant women and breastfeeding, those with hypersensitivity esomeprazole or omeprazole, patients who had clinically significant abnormalities on the baseline physical examination, bleeding disorders or signs of gastrointestinal (GI) bleeding, a history of gastric or esophageal surgery. If they had used a PPI within 28 days before the baseline visit or an H_2-receptor antagonist daily during the 2 weeks before the baseline check. Studies that are observational cohort, case reports and experimental studies.

5.2.3 SELECTED CLINICAL TRIALS

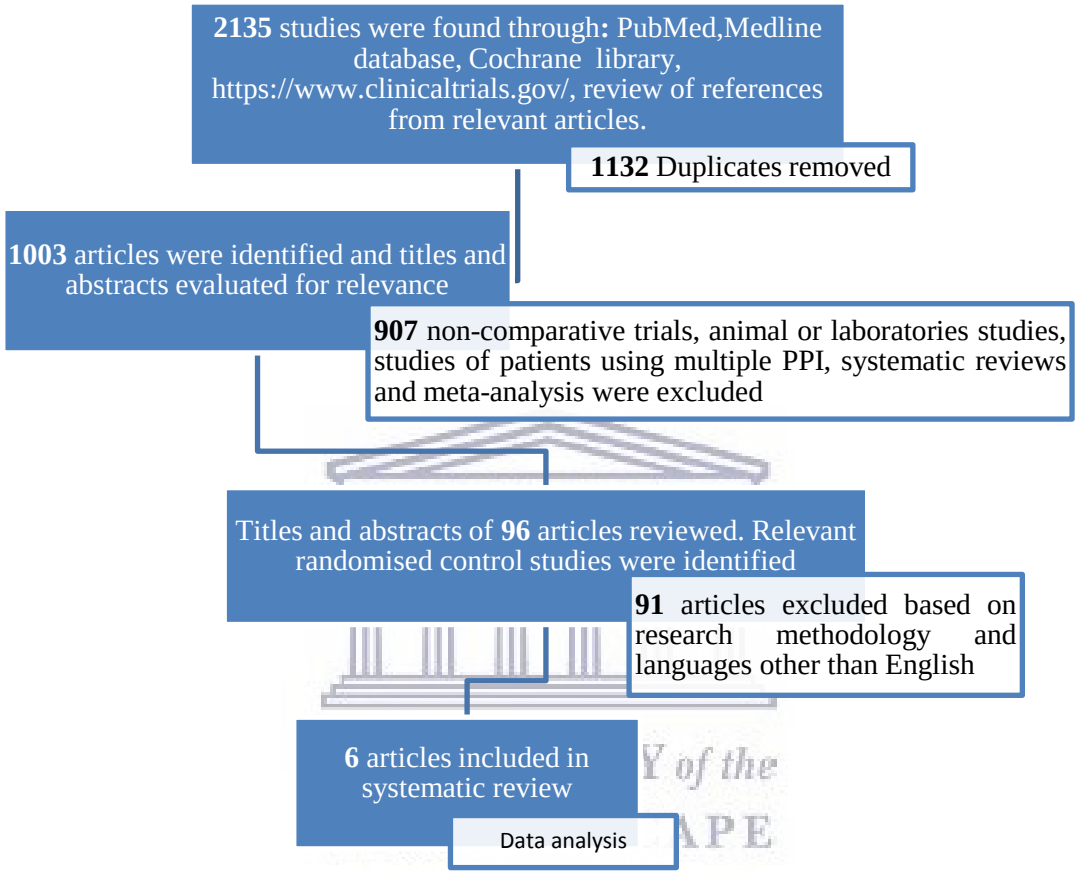

FIG 3: FLOW DIAGRAM OF THE SELECTION PROCESS FOR RANDOMISED CONTROLLED TRIALS REPORTING OMEPRAZOLE VS ESOMEPRAZOLE

Search results for clinical trials on omeprazole versus esomeprazole between 2000 and 2016 of PubMed, Cochrane, Medline and EMBASE databases and screening process.

5.3 DATA EXTRACTION

For each trial report, the following information was extracted; the publication status, publication year, the compared medicines and their doses, outcome assessment in percentage, evaluated dosages (fixed or flexible), number of randomized patients and age (mean, range) and sex proportion of subjects.

5.3.1Outcome measures: Assessment of long-term treatment that is between 4 and 8 weeks. The outcome data was reported in percentage of those healed by the end of the trial.

5.3.2 Data analysis tool

Data analysis was also done using Forest plots through a Microsoft excel spreadsheet adapted from Neyeloff, Fuchs and Moreira (2012). Head-to-head trials were used to show any superiority between the enantiopure drug and the racemic. The calculations were done in steps calculated with basic arithmetic operations. Spreadsheet was used to do the analysis of parameters such as the effect of sample size. The raw data comparing omeprazole and esomeprazole was provided in the appendix section E.

5.4 RESULTS

5.4.1 omeprazole vs esomeprazole

6 trials were included in the studies which were carried out between 4 weeks and 8 weeks. They included outpatients who were diagnosed with GERD and both *H. pylori* positive and negative patients were included. In all the trials esomeprazole shows an improved healing rate compared to omeprazole however the difference is not statistically significant. Most of the trials compared a higher dose of esomeprazole (40 mg) with a lower dose of omeprazole (20 mg) which are not comparative doses while the standard adult dose for omeprazole and esomeprazole are both from 20- 40 mg for treatment of GERD. Mostly, studies that focused on *Helicobacter pylori (H. pylori)* eradication used comparative doses while those assessing the healing rate of GERD used mostly a higher dose of esomeprazole.

5.4.1.1 Assessment of Efficacy

Trials were conducted in outpatients between the age of 18 and 65 years. Of the six trials only one was conducted for 4 weeks and the rest for 8 weeks and all had fixed dose rules. Two of the trials included *H. pylori* positive patients and they were of significant numbers. The trial by Kahrilas *et al*. (2000) and Lightdale *et al*. (2006) did not include participants who had *H. pylori*, however the subjects who were discovered to be positive along the trial were included in the analysis. The Funder for the trials is the manufacturer of both esomeprazole and omeprazole.

TABLE 3: Characteristics of Selected Randomized Clinical Trials

Trial ID	Age, mean (yr.)	Male, %	%H-pylori positive	Setting	Elderly Specific Population	Dosage	Outcome Measurement (Weeks)	Funder
(Zheng, 2009)	57.5	49	74	Outpatients	No	Fixed	8 weeks	NC
Armstrong *et al*., 2004	48	43.1	38	Outpatients	No	Fixed	4 weeks	AstraZeneca
Kahrilas*et al*., 2000	45.4	60	0	Outpatients	No	Fixed	8weeks	AstraZeneca
Lightdale*et al*., 2006	45	63.5	0	Outpatients	No	Fixed	8weeks	AstraZeneca
Schmitt *et al*., 2006	46.5	59	NC	Outpatients	No	Fixed	8weeks	NC
Chen *et al*, 2005	54.1	79	NC	Outpatients	No	Fixed	8weeks	NC

NC= unclear

All of the trials included were head-to-head trials comparing omeprazole with esomeprazole. Five trials compared 40 mg esomeprazole with 20 mg omeprazole and two trials compared esomeprazole 20 mg and 20 mg omeprazole. In all the trials, there was a higher healing rate in patients treated with esomeprazole compared to those given omeprazole. Only in the trial conducted by Chen *et al* (2005) a huge difference between the two treatment groups was noticed and only a few participants were enrolled when compared to the other trials.

TABLE 4: INTERVENSIONS FOR THE TRIALS AND HEALING RATES

PUBLICATION YEAR	REFERENCE	INTERVENSION	MEAN AGE	MALE %	DURATION OF STUDY	#PATIENTS	HEALING RATE%
2004	Armstrong *et al*., 2004	Eso 40 mg vsOme 20 od	48	43.1	4 weeks	1282	73.5 72.8
2000	Kahrilas*et al*., 2000	Eso 40 mg vsEso 20 vsOme 20 od	45.4	60	8weeks	1960	94.1 89.9 86.9
2006	Lightdale*et al*., 2006	Eso 20 mg Ome 20 mg	45	63.5	8weeks	1176	90.6 88.3
2006	Schmitt *et al*., 2006	Eso 40 mg Ome 20 mg	46.5	59	8weeks	1148	87.0 85.5
2009	Zheng, 2009	Esome 40 mg Ome 20 mg	57.5	49	8weeks	136	91.1 87.7
2005	Chen *et al*, 2005	Esomeprazole 40 mg Omeprazole 20 mg	54.1	79	8weeks	48	72.2 50.0

HEAD-TO-HEAD FOREST PLOT

The 6 trials were used in the forest plot since they were all had head-to-head comparison of omeprazole and esomeprazole. The comparison was done between 20 mg omeprazole and 40 mg esomeprazole results. Five of the trials had statistically meaningful results while one was not statistically significant crossing the horizontal line. The Forest plot results shows that esomeprazole 40 mg has better results in treatment of esophagitis due to gastroesophageal reflux disease when compared to omeprazole 20 mg. However, since the triangle showing the overall results touches the horizontal line and its confidence interval is on both sides, it indicates that the difference is not statistically significant, which shows that the difference in efficacy is minor. Overall, the trials had similar results which were consistent with the forest plot.

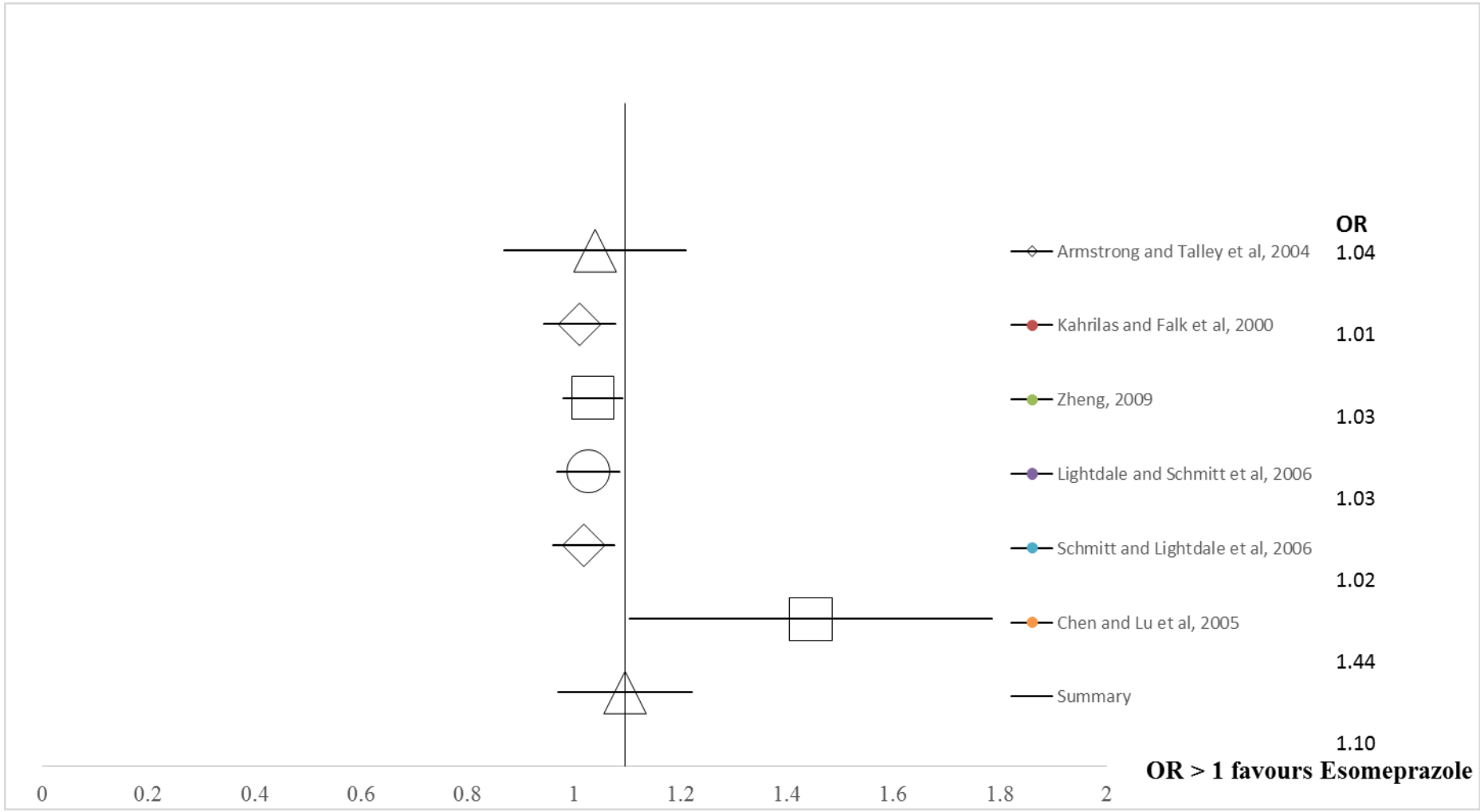

FIG 4: HEAD-TO-HEAD FOREST PLOT OF OMEPRAZOLE VERSUS ESOMEPRAZOLE

5.5 DISCUSSION

Both omeprazole and esomeprazole have been used for over a decade for the treatment of GERD. The controversy has always been there on which one has better efficacy than the other. Long-term clinical trials from 4 weeks to 8 weeks, which assessed the healing rates of omeprazole versus esomeprazole were used for the study to assess if there is proof of superiority when esomeprazole is compared to omeprazole. From the study, there were no major differences between 20 mg omeprazole and 40 mg esomeprazole with respect to therapeutic evidence. Although a higher dose of esomeprazole was used and expected to yield way better results compared to omeprazole because of increased bioavailability. Also in trials conducted by Kahrilas *et al* (2000) and Lightdale *et al* (2006), which compared same doses of omeprazole 20 mg and esomeprazole 20 mg, they found that there was still no significant statistical difference in healing rates of the two with the value of 0.09 for the Kahrilas trial. In another trial where they increased the dose of omeprazole from 20 mg to 40 mg, healing rates for oesophagitis did not show much improvement with results increasing from 74% to 75% (Andersson, 2004).

The results achieved by acute treatment trials were also consistent with the long-term treatment results. Acute treatment trials measured intra-gastric pH since it is a common method used to demonstrate the acid inhibitory effect over a short period of time. The pH of 4 was defined as the threshold and anything lower than that has been recognized to be related to acid reflux conditions (Armstrong, 2004). It was used as a surrogate parameter for healing of GERD while above 3 is a surrogate marker for peptic ulcer (Kirchheiner *et al*., 2008). So, when a medicine manages to control the pH to higher than 4, it was seen as a good measure of effectiveness since there is evidence of correlation between acid suppression and clinical benefit. A study conducted by Sahara (2013) showed that for an effective treatment of GERD, pH must be maintained >4 for longer than 2-4 hrs. Both omeprazole and esomeprazole were able to achieve these results. There was also no statistical difference when median pH was measured in 24 hrs between esomeprazole and omeprazole (Sahara, 2013). In another study conducted by Asghar, Pittman and Jamali (2015) where they assessed the differences in pH control of the two, they also found no significant differences between esomeprazole and omeprazole.

To reduce inter individual variations; studies with a crossover design were preferred so that response can be seen in the same individuals. Literature also shows that genotypes for cytochrome P450 2C19 (CYP2C19) and *Helicobacter pylori* infection have an effect on how PPIs work with better results seen in poor metabolizers of PPIs, and *H. pylori* positives are known to show an increase intra-gastric pH reading (Celebi *et al*., 2016). Some of the studies had positive *Helicobacter pylori* status patients while others used healthy volunteers. This was to prevent any false positive results that could be due to this, hence; the combination could give broad results. PPIs with an influence on CYP2C19 are seen to be more effective; hence, esomeprazole is expected to perform better than omeprazole. Genetic polymorphisms of CYP2C19 have been documented to affect the metabolism of the PPIs since they go through extensive hepatic metabolism. The variations in acid inhibition by CYP2C19 are not accounted

for in most of the included studies. However, due to esomeprazole being less hepatically metabolized, it is expected not to have much effect on the results. In addition, S-omeprazole is mostly metabolized by CYP3A4. A study done by Kent (2013) showed that 20 mg and 40 mg of esomeprazole had more than 180% and 500% plasma concentration compared to 20 mg omeprazole, hence the higher bioavailability. This effect of metabolism on the bioavailability was studied by Sahara (2013) and it indicates that the intermediate to rapid metabolizers may need to be dosed twice daily to get sufficient acid suppression.

One of the limitations to the trials is the monitoring of medication compliance since the participants were outpatients and treatment was taken for 4 to 8 weeks with routine checks only done weekly. Most of the trials did not provide data for compliance of the participants which could have an effect on the results achieved. The trial conducted by Kahrila s*et al* (2000) reported that compliance was around 90% for all the treatment groups, however this was not accounted for when the results were finalized. The study did not consider the effect of *H. pylori* positive participants which could have an effect in the overall results achieved. This is also one of the limitations of the study. Some studies conducted between esomeprazole and pantoprazole shows that it has better remission maintenance rates when compared to lansoprazole (Kazantzakis and Björnsson, 2007). The study did not compare remission rates between esomeprazole and omeprazole which could lead to higher costs due to reoccurrence of the condition. This is also a limitation to the study.

5.5.1 ADVERSE EVENTS

The adverse events experienced by patients on the different regimens were not analyzed; however, available data from different trials was considered. In the study conducted by Chen, C. *et al* (2005) where they compared adverse events between esomeprazole and Omeprazole, it revealed no significant differences in the participants who experienced adverse events such as constipation, dry skin, diarrhea, headache, somnolence, cellulitis and bronchitis. Also in a trial conducted by Kahrilas *et al* (2000) where they recorded the number of participants who discontinued therapy due to adverse events, they were found to be 2.0% for esomeprazole 40 mg, 2.6% for esomeprazole 20 mg and 2.0% for omeprazole 20 mg. In conclusion the adverse events experienced by patients on either medicine were found to be comparable and within the same range.

5.5.2CONCLUSION

In the study, efficacy of esomeprazole was compared with omeprazole. The healing rates were higher for those given esomeprazole compared to those taking omeprazole but the differences were not statistically significant. The slight difference in results achieved between esomeprazole and omeprazole is accounted to esomeprazole having less extensive first pass metabolism than the racemic Omeprazole, hence the ability to maintain a higher blood concentration for longer periods of time (Armstrong, 2004). The other reason for the slight difference in the healing rates is most likely due to the higher dose of esomeprazole compared to omeprazole. The other difference is that Esomeprazole has been found to act faster because of its rapid onset of anti-secretory activity than Omeprazole, so better efficacy is found in the first two days but at the end of the trials there is no significant difference (Zheng, R, 2009).

From the study results, there is no difference between efficacy of esomeprazole and omeprazole. They are equally effective even when esomeprazole is given at a higher dose. From the prices acquired from wholesalers on table 6, esomeprazole is more than twice the price of omeprazole. From this, it only makes sense for the ministry of health to continue using omeprazole over the notion given that the pure enantiomer drug offers better results. This would help in the economical use of funds without compromising the patients since evidence shows that patients would equally benefit from either treatment.

6.0 COST COMPARISON

WHOLESALES PRICES IN BOTSWANA

An average cost of the different brands of both generics and innovator products were calculated from 2 wholesalers in Botswana.

TABLE 5: CITALOPRAM VERSUS ESCITALOPRAM

CITALOPRAM	PACK SIZE	PRICE	ESCITALOPRAM	PACK SIZE	PRICE
DEPRAMIL 20 mg	30	P61.08	CIPRALEX 5MG (**Innovator**)	28	P151.72
DEPRAMIL 40 mg	30	P87.19	CIPRALEX 10 mg	28	P191.43
RAN-CITALOPRAM 10 mg	30	P50.50	CIPRALEX 20 mg	28	P359.49
RAN-CITALOPRAM 20 mg	30	P65.20	EPRA LIFE 10 mg	OS	OS
RAN-CITALOPRAM 40 mg	30	P93.20	ISOLIFT 10 mg ISOLIF 20 mg	OS	OS

OS-OUT OF STOCK

TABLE 6: OMEPRAZOLE VERSUS ESOMEPRAZOLE

OMEPRAZOLE	PACK SIZE	PRICE	ESOMEPRAZOLE	PACK SIZE	PRICE IN PULA
LOSEC MUPS 20(Innovator)	28	430.13	NEXIUM 10 mg (**Innovator**)	28	257.66
ALTOSEC 10 mg	28	150.92	NEXIUM 20 mg	28	270.04
ALTOSEC 20 mg	28	151.20	NEXIUM 40 mg	28	416.46
OMIZAC 20 mg	30	33.3	NEXPRO 20 mg	50	148.00

OMEPRAZOLE	PACK SIZE	PRICE	ESOMEPRAZOLE	PACK SIZE	PRICE IN PULA
LOMEP 20MG	30	44.4	NEXPRO 40 mg	50	239.50
ZOMACID 40 mg	OS	OS	NEXMEZOL 20 mg	28	213.36
ZOMACID 20 mg	OS	OS	NEXMEZOL 40 mg	28	329.28

OS-OUT OF STOCK

All medicines that had the molecules being compared that are registered and available at the wholesalers were included in the price comparison. It was observed that even though generics maybe registered by the regulatory body, some of them were not available in the country. Innovator prices were included for escitalopram, and they were the only ones available in the wholesales and the registered generics have not been there for more than a year. Even though Innovator products are always more expensive than generics and may lead to biased conclusions, it is the current situation which is worth noting. From the tables above, it is clear that enantiopure medicines are more expensive the racemic medicines. Escitalopram being more than twice the cost of citalopram and esomeprazole cost significantly higher than omeprazole.

There are many other factors that can affect prices of medications such as demand and supply, which are part of the limitations of the study since they were not considered. Further in a study conducted by VanMourik *et al*. (2010), it was shown that the retail prices of originator medicines in developing countries were often double those in European countries, and there is a huge variability of prices between the African countries. This shows that there are several discrepancies in the pricing of medicines in general. Prices of medicines can also be affected by negotiations that happen between the buyer and the seller. The negotiated price discounts can sometimes not give a true normal value of the product.

7.0 REGULATORY PERSPECTIVE

Nation (1994) wrote on how undertaking the development and seeking regulatory approval for an enantiomeric pure drug over the racemic is not a new concept, but has been lagging behind due to lack of appreciation of the clinical impact of these and the technical difficulties in manufacturing commercial scale pure enantiomers. But with increasing knowledge and technologies, several pure enantiomers have been developed in the last few decades. Regulatory agencies developed regulations for these medicines to ensure that they are of the required standard in their quality, efficacy and safety. The US Food and Drug Administration (FDA) developed their guidelines in 1992, followed by the European Medicines Agency in 1993 on the development of guidance on Investigation of chiral Active Substances. Japan and Canada also followed in developing these guidelines to guide their regulatory agencies. What is common among all these guidelines is that the sponsor has to support the development of the pure enantiomer on the basis of efficacy and safety data (Srinivas, Barbhaiya and Midha, 2001). The European Medicines Agency (EMA) requires the development of a single enantiopure form of racemic to be sufficiently supported. Pharmacodynamics, pharmacokinetics and bridging toxicology studies should be done and compared to the racemic compound. Even when a racemic mixture medicine is developed, it is important that minimal data on pharmacology, toxicity and safety of each enantiomer is collected.

TABLE 5: SOME OF THE CRITICAL PARAMETERS TO BE MONITORED FOR ENANTIOPURE MOLECULES INCLUDE:

Test	Analytical Procedure	Acceptance Criteria
Identification and Test	Stereo chemically specific method for example Chiral HPLC, Optical Rotatory Dispersion (ORD) (Shen, Lv and Zeng, 2016)	Determined by manufacturer from the reference standard
Impurities		
By Enantiomeric purity	The retention time of the major peak in the chromatogram of the sample solution corresponds to that of the standard solution as obtained in the test of Enantiomeric purity	Determined by manufacturer from the reference standard
Enantiomeric Purity	PhEur	Determined by manufacturer from the reference standard
Specific optical rotation	Pharmacopeial or in-house	-º To -º

One of the critical aspects to be looked at during assessments of these products dossiers is highlighted by the USFDA on how analytical methods for enantiomers should be stereo chemically specific to identify and assay the molecules. It is critical that test methods used are sensitive and selective to the enantiomers to ascertain dosage form used in development studies, toxicology and clinical trials (Srinivas, Barbhaiya and Midha, 2001). Enantiospecific methods are important to prevent misleading data especially the plasma-drug concentration profile. These should be included in the specifications of both the active pharmaceutical ingredient (API) and Finished Pharmaceutical Product (FPP). This should also be in place during stability studies in case there is stereochemical conversion to the other enantiomer. These analytical methods have to be extensively validated with the key parameters such linearity, accuracy, specificity, precision, Limit of Quantification (LOQ) and Limit of Detection (LOD) being monitored. Some of the commonly used and acceptable enantioselective analytical methods include chiral high-performance liquid chromatography (HPLC), chiral gas chromatography (GC), supercritical fluid chromatography (SFC), capillary electrophoresis (CE), nuclear magnetic resonance (NMR), optical rotation and immunoassay (Shen, Lv and Zeng, 2016).

Another critical issue is the labeling. Labeling should include a name with the appropriate stereochemical description. This is to prevent dispensing errors since the doses of racemic medicines and pure enantiomers are different. Most prescribers and even national formulary such as the British National Formulary do not pay attention to drug chirality and are not aware that most of the medicines are racemic. This was one of the regulatory issues when these products were registered since the prescribers and dispensers could think they are interchangeable. Since for example, escitalopram 10 mg is equivalent to 20 mg of the racemic citalopram, a conditional registration was given to the applicants of these pure enantiomer medicines by the Drug Regulatory Unit in Botswana. Their products would only be allowed in the country if some training or workshops are carried out to sensitize the health care officers, both the prescribers and the dispensers on the differences in these products.

7.1 COMMON EVALUATION DEFFICIENCIES

One of the most common deficiencies in the dossiers assessed were that in the sections of Controls of Critical Steps and Intermediates, no information was provided into how the critical step of the pure enantiomer intermediate is separated from the mixture. This raises a query sent to the applicants being to provide information on how this critical manufacturing step is controlled to get the desired isomers. This is followed by the issue on Reference Standards, or Materials since they are required to provide details on how a particular batch is further purified or show how a particular API batch is selected to be the reference standard. The details (working standard certificates of analysis and comparative IR spectra) of the reference standards used by the FPP manufacturer to test for compliance of the API with the FPP manufacturer's API specifications should always be provided which most of the time is not.

8.0 CONCLUSION AND RECOMMENDATIONS

The aim of the Ministry of Health is to improve the physical, mental, and social well-being of every Motswana so that everyone can contribute to the development of Botswana through a healthy nation. One of the ways of achieving this is providing access to affordable, high efficacy, safe and high-quality medicines. With advances in science and technologies, new and improved medicines are introduced now and then which come at a significantly higher price. Some are worth changing treatment guidelines to include them regardless of price since their benefits outweigh their cost while some may not make any difference when compared to existing ones. One of the recent notions in medicine is that switching from racemic to pure enantiomer products is better and safer. However, from the systematic review of the two molecules, the use of pure enantiomer is not always justified since in these cases, there is no indication of significant differences in their effectiveness and tolerability .The study results demonstrate that there are no significant differences between omeprazole and esomeprazole with respect to therapeutic evidence in treatment of Esophagitis. The findings on the omeprazole and esomeprazole are also supported by a systematic review done by Asghar et al (2015) where they were used as part of triple therapy for the treatment of *H. pylori,* where they compared comparable doses. The study also resulted in no significant difference in the therapeutic success. Also, minor differences are seen between escitalopram and citalopram. However, the costs are significantly different with the pure enantiomer costing twice or more of the price of racemic mixture. Contrary to the findings of this study, there is some evidence that some of the racemic mixture such as ofloxacin need to be switched to levofloxacin since they have shown significant difference in terms of their antimicrobial activity compared to their counterpart (Maestri *et al*., 2006). In a study done by Healy et al (2004) on topical administration of levofloxacin 0.5% and ofloxacin 0.3% solution in patients with stromal scar or dystrophy, keratoconus, Levofloxacin had greater penetration into human corneal stromal than ofloxacin 0.3% . This had potential of better clinical effects. A case by case may need to be assessed.

From this study, recommendation to the Ministry of Health is that Botswana is to keep the use of racemic medicines analyzed in the systematic review. This is because the results showed that there is no significant difference therapeutically between the racemic and the pure enantiomer medicines that were assessed. The health of the patients will not be compromised by the use of these racemic medicines since the adverse events experienced are even comparable. Switching would not only be costly to the ministry but would also impede on the access of these medicines to everyone who needs it. However, since only two groups of racemic and enantiopure medicines were compared, studies comparing racemic versus pure enantiomer formulations of other active pharmaceutical ingredients are required to assess rational medicine use. A case by case cost efficacy analysis may therefore be required to assess tolerability and superiority in efficacy for upcoming pure enantiomeric molecules.

This research would help in decision making of Central Medical Stores that procures medicines for all government health care facilities and in the decision process of recommending medicines

to be included in the treatment guidelines for Botswana. Since the safety, quality, efficacy and costs related to these products were assessed, the research will assist in making informed decisions based on evidence based knowledge. It will also play an important role in the assessment process by harmonizing information an assessor would need to critically assess to ensure that pure enantiomer products of high quality, safety and efficacy are registered in the country. Scrutiny needs to be done when evaluating these products dossiers and reference made to the already available guidance from other regulatory agencies such as the FDA and EMA.

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APPENDICES

APPENDIX A

NUMBER OF APPLICATIONS RECEIVED OF RACEMIC MIXTURE MEDICINES VS PURE ENANTIOMERS FROM 2005-2016

Racemic mixture	NO	Single-enantiomer	NO
Amlodipine	16	S-amlodipine	6
Cetirizine	9	Levocetirizine	5
Citalopram	5	Escitalopram	5
Ofloxacin	3	Levofloxacin	10
Omeprazole	10	Esomeprazole	13

NUMBER OF REGISTERED RACEMICE MIXTURE MEDICINES VS PURE ENANTIOMERS

Racemic mixture	NO	Single-enantiomer	NO
Amlodipine	12	S-amlodipine	0
Cetirizine	6	Levocetirizine	3
Citalopram	2	Escitalopram	4
Ofloxacin	2	Levofloxacin	10
Omeprazole	8	Esomeprazole	6

APPENDIX B: TRIALS AND REFERENCES FOR COMPARISON OF CITALOPRAM AND ESCITALOPRAM

TRIAL ID	REFERENCE	PUPLICATION STATUS
CITALOPRAM-PLACEBO		
	Brown *et al*., 2005	Published
NCT00692445		Unpublished
ESCITALOPRAM-PLACEBO		
	Kirino, 2012	Published
Wade *et al*. (2002)	Höschl, C. and Švestka, J. 2008	Published
Ninan*et al*. (2003)	Höschl, C. and Švestka, J. 2008	Published
NCT01814098		Unpublished
NCT00668525		Unpublished
NCT02480400		
NCT00464711		
NCT00785434		
NCT01814085		
NCT00108979		
NCT03122158		

NCT00384436		
CITALOPRAM-ESCITALOPRAM		
	Ou*et al*., 2010	Published
	Yevtushenko *et al*., 2007	Published
	Moore ,2005	Published
	Lalit*et al*., 2004	Published
	Colonna, Andersen and Reines, 2005	Published
Li *et al*, 2006	Montgomery, Hansen and Kasper, 2010	Published
SCT-MD-02	Ciprian*et al*,2012	
Lancon*et al*,2006	Montgomery, Hansen and Kasper, 2010	Published
CITALOPRAM-ESCITALOPRAM-PLACEBO		
	Burke, Gergel and Bose, 2002	Published
Forest Labs,2005:Anon,2002	Montgomery, Hansen and Kasper, 2010	Published
	Lepola, Loft and Reines, 2003	Published

APPENDIX C: HEAD-TO-HEADDATA FOR THE FOREST PLOT OF CITALOPRAM VERSUS ECITALOPRAM

Head to Head Trials (Esci vs Cita)

Study	Events (**Esci**)	Sample Size	Outcome (es)	SE	Var	w	w*es	w*(es^2)	w^2	w_v	w_v*es	w_v*(es^2)	w_v^2
Yevtushenko and Belous et al,2007	103	108	0.9537037	0.093971218	0.00883059	113.242718	108	103	12823.9133	45.1911461	43.0989634	41.1036411	2042.23969
Moore and Verdoux et al, 2005	105	138	0.76086957	0.074253266	0.00551355	181.371429	138	105	32895.5951	53.1598591	40.4477189	30.7754383	2825.97062
Lalit and Appaya et al, 2004	122	136	0.89705882	0.08121589	0.00659602	151.606557	136	122	22984.5482	50.267273	45.0927008	40.4508051	2526.79874
Colonna and Andersen, 2005	62	69	0.89855072	0.114116056	0.01302247	76.7903226	69	62	5896.75364	37.9937582	34.139319	30.6759098	1443.52566
Lancon et al, 2006	110	175	0.62857143	0.059931934	0.00359184	278.409091	175	110	77511.6219	59.2084708	37.2167531	23.3933876	3505.64302
Lepola and Loft et al, 2003	93	146	0.6369863	0.066052402	0.00436292	229.204301	146	93	52534.6116	56.6233513	36.0682991	22.9750125	3206.20392
Burke and Gergel, 2002	56	95	0.58947368	0.078771734	0.00620499	161.160714	95	56	25972.7758	51.2751498	30.2253515	17.8170493	2629.14099
Forest Labs, 2005: Anon, 2002	90	124	0.72580645	0.076506718	0.00585328	170.844444	124	90	29187.8242	52.2168226	37.8993067	27.5075613	2726.59656
k	8				Sums:	1191.78513	867	651	230619.82	353.719008	266.289106	207.191244	18179.5226
df	7												
										v	0.01329764		
Q	20.27473			Q_v	6.72170099								
I^2	65.47426			I^2_v	-4.14030636								
es (fixed)	0.72748			es (random)	0.75282668								
SEes (fixed)	0.028967			SEes (random)	0.05317051								
CI (fixed)	0.670705	0.78425512		CI (random)	0.64861248	0.85704087							

Study	Events (**Cita**)	Sample Size	Outcome (es)	SE	Var	w	w*es	w*(es^2)	w^2	w_v	w_v*es	w_v*(es^2)	w_v^2
Yevtushenko and Belous et al,2007	178	214	0.8317757	0.062344225	0.0038868	257.280899	214	178	66193.4609	58.1921757	48.4028378	40.2603043	3386.32932
Moore and Verdoux et al, 2005	87	142	0.61267606	0.065685768	0.00431462	231.770115	142	87	53717.3862	56.7786349	34.7869101	21.3131069	3223.81338
Lalit and Appaya et al, 2004	64	74	0.86486486	0.108108108	0.01168736	85.5625	74	64	7320.94141	40.024012	34.6153617	29.9376101	1601.92154
Colonna and Andersen, 2005	100	182	0.54945055	0.054945055	0.00301896	331.24	182	100	109719.938	61.2872872	33.6743336	18.5023811	3756.13158
Lancon et al, 2006	26	60	0.43333333	0.084983659	0.00722222	138.461538	60	26	19171.5976	48.7332743	21.1177522	9.15102595	2374.93202
Lepola and Loft et al, 2003	80	152	0.52631579	0.058843894	0.0034626	288.8	152	80	83405.44	59.6650083	31.402636	16.5277031	3559.91322
Burke and Gergel, 2002	49	93	0.52688172	0.075268817	0.00566539	176.510204	93	49	31155.8521	52.7341793	27.7846751	14.6392374	2780.89367
Forest Labs, 2005: Anon, 2002	76	119	0.63865546	0.073258806	0.00536685	186.328947	119	76	34718.4766	53.577673	34.2176735	21.8533041	2870.56704
k	8				Sums:	1509.62526	917	584	370684.616	377.414572	231.784507	150.331369	20683.9347
df	7												
										v	0.01580728		
Q	26.98163			Q_v	7.98377173								
I^2	74.05642			I^2_v	12.3221426								
es (fixed)	0.607436			es (random)	0.61413767								
SEes (fixed)	0.025737			SEes (random)	0.05147433								
CI (fixed)	0.55699	0.65788091		CI (random)	0.51324799	0.71502735							

Study	Outcome (Esci)	Outcome (Cita)	OR	SE (Esci)	SE (Cita)	SE (OR)	CI lower	CI upper		Rate	CI lower	CI upper			
Yevtushenko and Belous et al,2007	0.9537	0.83178	1.146588	0.093971218	0.062344225	1.146587599	-1.29360799	3.201015397	9	114.6588	244.0196	205.4428			
Moore and Verdoux et al, 2005	0.76087	0.61268	1.241879	0.074253266	0.065685768	1.24187906	-1.673213393	3.194952524	8	76.08696	243.4083	243.4083			
Lalit and Appaya et al, 2004	0.89706	0.86486	1.037224	0.08121589	0.108108108	1.037224265	-1.135900735	2.930018382	7	89.70588	203.296	203.296			
Colonna and Andersen, 2005	0.89855	0.54945	1.635362	0.114116056	0.054945055	1.635362319	-2.30675942	4.10386087	6	89.85507	320.531	320.531			
Lancon et al, 2006	0.62857	0.43333	1.450549	0.059931934	0.084983659	1.450549451	-2.214505495	3.471648352	5	62.85714	284.3077	284.3077			
Lepola and Loft et al, 2003	0.63699	0.52632	1.210274	0.066052402	0.058843894	1.210273973	-1.735150685	3.009123288	4	63.69863	237.2137	237.2137			
Burke and Gergel, 2002	0.58947	0.52688	1.118797	0.078771734	0.075268817	1.118796992	-1.603368421	2.782315789	3	58.94737	219.2842	219.2842			
Forest Labs, 2005: Anon, 2002	0.72581	0.63866	1.13646	0.076506718	0.073258806	1.136460102	-1.501655348	2.953268251	2	72.58065	222.7462	222.7462			
Summary	0.76138	0.62299	1.247142	0.080602402	0.072929791	1.24714172	-1.683020186	3.205775357	1	78.54881	246.8508	242.0287	142.0287	7612.852	

APPENDIX D: HEAD-TO-HEAD DATA FOR THE FOREST PLOT OF OMEPRAZOLE VERSUS ESOMEPRAZOLE

Metanalysis Study: Esomeprazole vs Osomeprazole.

Study (**Eso**)	Sample Size	Outcome (es)	SE	Var	w	w*es	w*(es^2)	w^2	w_v	w_v*es	w_v*(es^2)	w_v^2
Zheng, 2009	68	0.911	0.115745664	0.013397059	74.64324918	68	61.948	5571.615	59.03430611	53.78025287	48.99381	3485.0493
Armstrong and Talley et al, 2(	425	0.735	0.041586197	0.001729412	578.2312925	425	312.375	334351.4	189.6937142	139.4248799	102.47729	35983.7052
Kahrilas and Falk et al, 2000	654	0.899	0.037075838	0.001374618	727.4749722	654	587.946	529219.8	203.381753	182.8401959	164.37334	41364.1374
Lightdale and Schmitt et al, 2	588	0.906	0.039253233	0.001540816	649.0066225	588	532.728	421209.6	196.7318695	178.2390737	161.4846	38703.4285
Schmitt and Lightdale et al, 2	576	0.87	0.038864079	0.001510417	662.0689655	576	501.12	438335.3	197.9155194	172.1865019	149.80226	39170.5528
Chen and Lu et al, 2005	25	0.722	0.169941166	0.02888	34.62603878	25	18.05	1198.963	30.84302227	22.26866208	16.077974	951.292023
k	6			Sums:	2726.051141	2336	2014.167	1729887	877.6001844	748.7395664	643.20926	159658.165
df	5									v	0.0035422	
Q	12.408516			Q_v	4.409332491							
I^2	59.705091			I^2_v	-13.39584869							
es (fixed)	0.8569172			es (random)	0.853167057							
SEes (fixed)	0.0191528			SEes (random)	0.033756052							
CI (fixed)	0.8193776	0.89445671		CI (random)	0.787005195	0.919329						

Study (**Ome**)	Sample Size	Outcome (es)	SE	Var	w	w*es	w*(es^2)	w^2	w_v	w_v*es	w_v*(es^2)	w_v^2
Zheng, 2009	68	0.877	0.113565218	0.012897059	77.53705815	68	59.636	6011.995	60.8298295	53.34776047	46.785986	3700.26816
Armstrong and Talley et al, 2(	434	0.728	0.04095631	0.001677419	596.1538462	434	315.952	355399.4	191.5832293	139.472591	101.53605	36704.1338
Kahrilas and Falk et al, 2000	650	0.869	0.036563959	0.001336923	747.986191	650	564.85	559483.3	204.9530059	178.1041622	154.77252	42005.7346
Lightdale and Schmitt et al, 2	588	0.883	0.038751783	0.001501701	665.9116648	588	519.204	443438.3	198.2575194	175.0613896	154.57921	39306.044
Schmitt and Lightdale et al, 2	572	0.855	0.038662065	0.001494755	669.005848	572	489.06	447568.8	198.5308934	169.7439139	145.13105	39414.5156
Chen and Lu et al, 2005	23	0.5	0.147441956	0.02173913	46	23	11.5	2116	39.55481118	19.77740559	9.8887028	1564.58309
k	6			Sums:	2802.594608	2335	1960.202	1814018	893.7092888	735.5072227	612.69351	162695.279
df	5									v	0.0045383	
Q	14.781501			Q_v	7.383835319							
I^2	66.173937			I^2_v	32.28451361							
es (fixed)	0.8331565			es (random)	0.822982632							
SEes (fixed)	0.0188895			SEes (random)	0.033450442							
CI (fixed)	0.7961332	0.8701799		CI (random)	0.757419765	0.888545						

Study	Outcome (**Eso**)	Sample Size	SE	Outcome (**Ome**)	Sample Size	SE	OR	SE (OR)	CI lower	CI upper
Zheng, 2009	0.911	68	0.115745664	0.877	68	0.113565218	1.038768529	0.087395674	0.867473	1.210064
Armstrong and Talley et al, 2(	0.735	425	0.041586197	0.728	434	0.04095631	1.009615385	0.034283204	0.94242	1.07681
Kahrilas and Falk et al, 2000	0.899	654	0.037075838	0.869	650	0.036563959	1.03452244	0.028166388	0.979316	1.089729
Lightdale and Schmitt et al, 2	0.906	588	0.039253233	0.883	588	0.038751783	1.026047565	0.029537932	0.968153	1.083942
Schmitt and Lightdale et al, 2	0.87	576	0.038864079	0.855	572	0.038662065	1.01754386	0.029771836	0.959191	1.075897
Chen and Lu et al, 2005	0.722	25	0.169941166	0.5	23	0.147441956	1.444	0.173445477	1.104047	1.783953
Summary	0.8405		0.073744363	0.785333		0.069323549	1.095082963	0.063766752	0.9701	1.220066