International Journal of Community Research http://www.arpjournals.com
ISSN: 2315 – 6562 **E-ISSN: 2384 - 6828**

A SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF LIRAGLUTIDE FOR THE TREATMENT OF TYPE 2 DIABETES

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ABSTRACT

This is a systematic review of the clinical effectiveness of liraglutide in the treatment of adults with type 2 diabetes. The objective of this research is to systematically review the clinical effectiveness of liraglutide in the treatment of adults with type 2 diabetes. Studies were identified by searching seven electronic databases (Medline, EMBASE, CINAHL, CRD, Cochrane, MRC and UKCRN), secondary references of other studies and hand searching of two journals. Only randomised controlled trials were considered. Study quality was assessed using CASP, and data were extracted in a standard form. Analysis was by narrative synthesis and meta-analysis. Results showed that five studies (n = 1634) randomised to liraglutide were identified. Three of the studies: Harder (2004), Seino (2008), and Vilsbøll (2007) compared liraglutide with placebo; while two of the studies: Buse (2009) and Garber (2009) compared liraglutide with active control (exenatide or glimepiride). The results of the studies show that a minimum of 8 weeks liraglutide treatment provides evidence of clinical effectiveness in the reduction of HbA1c. Empirically liraglutide appears to be more effective than placebo, exenatide and glimepiride in the treatment of type 2 diabetes; but this evidence is provided by few studies and therefore requires strengthening by more studies if policy change is to be considered.

Key words: **systematic review, effectiveness, liraglutide, type 2 diabetes**

Received: 17th August, 2014 **Accepted: 30th August, 2014** **Published: 31st October, 2014**

INTRODUCTION

Diabetes Mellitus is a chronic condition encompassing a wide range of diseases characterized by abnormal levels of blood glucose which can result in increased risk of heart disease, stroke, renal disease, blindness and peripheral neuropathy. Diabetes arises from a dysfunction in the production/action of insulin -a hormone produced by the β-cells of islets of langerhans in the pancreas that is essential for blood glucose metabolism (ADA, 2012). This condition creates abnormal metabolism of blood glucose (Boyer and Paharia, 2008).

It was previously considered a disease of little importance, but with an explosive rise in the number of people diagnosed with the disease in the past 20 years, it has become a major public health challenge, affecting both the developed and the developing countries of the world (Thévenod, 2008). According to Wild *et al.* (2004), the prevalence of global diabetes for all age groups has been estimated at 2.8% in 2000, and is projected to rise to 4.4% by 2030; translating to a rise from 171 million in 2000 to 366 million by 2030. This systematic review focused on the effectiveness of liraglutide for the treatment of type 2 diabetes.

A systematic review on diabetes is necessary due to its increasing incidence in all populations. The choice of liraglutide is because of the manufacturer's claim of its high effectiveness in the treatment of type 2-diabetes with concomitant weight reduction based on clinical trials (Marre et al., 2009). In this review, liraglutide was compared with placebo, exenatide and glimepiride. The comparison with placebo is based on the fact that a placebo-controlled randomised clinical trial is considered as the most reliable method for exact representation of things in clinical practice (Kaptchuk, 2001).

A double-blinded placebo-controlled randomised controlled trial is the gold standard of clinical evidence (Bailey et al., 2006). However, the use of placebo alone as a comparator may lead to overestimation of the effectiveness of a new drug. Van Luijn et al. (2008) therefore recommended the use of a standard treatment as an active comparator in a randomised trial when a therapeutic indication of a new medicine is being studied; not only for the demonstration of the efficacy and safety of the new medicine, but also for the assessment of its place in therapy when compared with existing medicines. Exenatide is a good choice of an active comparator because it belongs to the same class with liraglutide

and is similar to it, and has been recommended by the National Institute for Health and Clinical Excellence (NICE) as a third line medicine for the treatment of type 2 diabetes (NICE, 2009). Glimepiride was chosen as another active comparator because it is a very potent anti-diabetic medicine in the class of sulphonylureas. It is considered as the most effective of all the sulphonylureas in glycaemic control at the lowest dose of 1.8 mg per day (Draeger, 1995); and recommended by NICE as a second line treatment for type 2 diabetes (NICE, 2009).

LITERATURE REVIEW

Diabetes is a major cause of morbidity and mortality worldwide. Some of its complications include cardiovascular diseases, hypertension, retinopathy, neuropathy and uropathy (Watkins, 2004). The risk of developing heart disease is 2-4 times higher among diabetic patients and hypertension is present in 70% of cases. Over 50% suffer neuropathy. Diabetes has also been implicated in blindness and end stage renal disease among patients between 20 and 74 years (CDC, 2003). Available report shows that an individual's risk of dying at any age is doubled by diabetes, thus in the US alone half a million deaths occur among those with diabetes; accounting for approximately 20% of all deaths among those aged 25 years and above (ADA, 2007). The diagnosis of diabetes (types 1 & 2) is based on blood glucose levels (ADA, 2012). Diagnostic threshold is taken as fasting blood glucose (FBS) ≥7 mmol/l (126 mg/dl) or 2-hour (after meal) blood glucose ≥11.1mmol/l (200 mg/dl) for symptomatic cases (WHO, 2006). The gold standard for the diagnosis of diabetes is oral glucose tolerance test (OGTT). OGTT is used in the diagnosis of asymptomatic cases, where blood glucose level is at borderline between the levels that establish or exclude diabetes (WHO, 2006; ADA, 2013).

The negative economic impact of diabetes has also been acknowledged (ADA, 2003) but glycaemic control has been associated with improved quality of life and the attendant economic benefits (Stratton et al., 2009; Wagner et al., 2001). Prevention of diabetes can be achieved through behavioural changes that support weight loss; increased physical activity; and intake of low saturated fats and high fibre diets (Lindström et al., 2006). But with the inclusion of age, sex, family history, genetic markers and ethnicity as uncontrollable risk factors of diabetes, it becomes necessary to establish an effective therapy, especially for type 2 diabetes which accounts for 90% - 95% of all cases of diabetes worldwide (CDC, 2005; The Decode Study Group, 2003; Oldroyd et al., 2005). Liraglutide is therefore a considerable option. Liraglutide is a long-acting glucagon-like peptide-1 analogue (GLP-1) developed by Novo Nordisk (Novo Nordisk, 2007). GLP-1 is one of two insulinotropic hormones secreted in response to oral intake of glucose (Doyle & Egan, 2007). Naturally, a GLP-1 (see figure 1) is a 30-amino acid peptide formed from the cleavage of the transcription product of the preproglucagon gene (Bell et al., 1983).

Liraglutide forms when Lys on position 34 is substituted with Arg, and then introducing a C16 fatty acid at position 26 using a γ-glutamine acid spacer. Native GLP-1 has a very short half-life of less than 2 minutes after administration (Russell-Jones, 2009), but the structural modification in the liraglutide molecule supports its long half-life of up to 20 hours (Madsen et al., 2007). Liraglutide acts by stimulating insulin production and secretion from the pancreatic β-cells in response to high oral glucose intake. It also suppresses glucagon secretion and hepatic glucose output, causes delay in gastric emptying, reduces food intake, and promotes glucose distribution into the peripheral tissues (List and Habener, 2004). These activities are mediated by the stimulation of the growth and differentiation of pancreatic β-cells, and cytoprotective antiapoptotic effects on the β-cells.

There is evidence that liraglutide (GLP-1 agonist) acts on receptors on pancreas-derived stem cells to initiate their differentiation into β-cells (List and Habener, 2004). These actions of liraglutide lead to high degree of glycaemic control. Liraglutide's stimulation of insulin secretion is glucose dependent as demonstrated in a study by Nauck et al. (2003) where insulin secretion increased with liraglutide at higher glucose levels but not vice versa. These actions have also been shown to be beneficial to body weight (Raun et al., 2007). Since clinical trials have been undertaken on liraglutide involving individuals

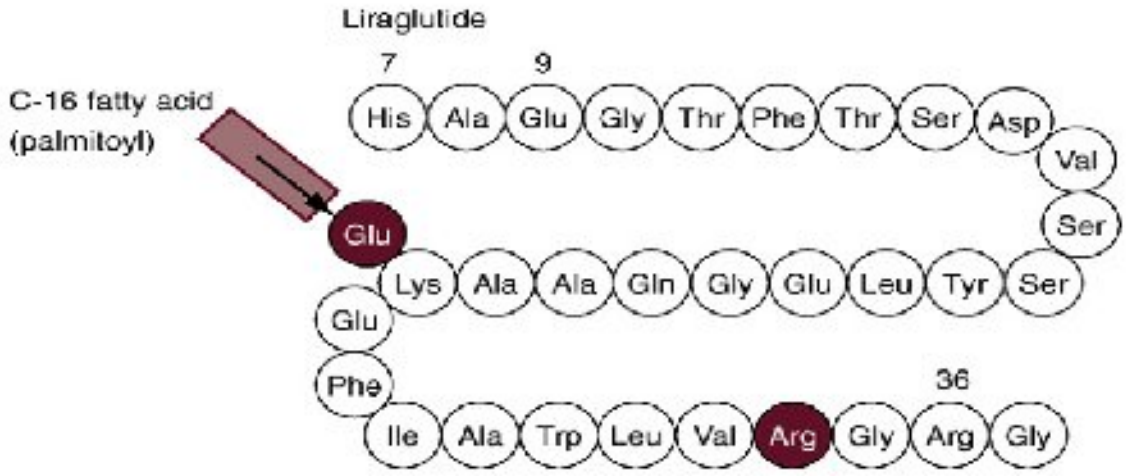


Figure 1: Structure of Liraglutide, a once-daily human GLP-1 analogue (Source: Russell-Jones (2009): Molecular and Cellular Endocrinology)

with type 2 diabetes, undertaking a systematic review in this research area will add to and strengthen the current body of evidence available as to whether this drug is effective in the treatment of type 2 diabetes.

This research is further supported by the fact that systematic reviews are ranked highest in the hierarchy of evidence in the evaluation of effectiveness of health care interventions (Evans, 2003). This review will be of benefit to clinicians by providing sound evidence on the effectiveness of liraglutide in the treatment of type 2-diabetes, and highlight areas for further research on liraglutide in type 2 diabetes. The objective of this research is to systematically review the clinical effectiveness of liraglutide in the treatment of adults with type 2 diabetes.

METHODS

Protocol and Ethical Concern: A protocol was developed to serve as a guide in line with Schlosser (2007) to avoid unnecessary changes and minimize bias. Ethical approval is not required since it is a systematic review and not a primary research dealing with human subjects, or secondary research requiring confidentially held data,

Criteria for Consideration of Studies for this Review:

Types of Studies: Only Randomised Controlled Trials (RCTs) were included and in line with the gold standard for intervention studies (Muir, 1997; Mulrow and Oxman, 1997). All studies done in parts of the world and reported in English or otherwise translated in English were included in this review.

Types of Participants: Participants were adults aged 18 years and above with type-2 diabetes and diagnosed based on WHO recommendations (WHO, 2006).

Types of Intervention: Liraglutide given as a monotherapy at doses ranging from 0.1 mg to 1.90 mg single dose per day for at least 8 weeks. The evaluations were based on the following comparisons: Liraglutide versus placebo; Liraglutide versus exenatide and Liraglutide versus glimepiride.

Excluded Studies: Non RCTs (cohort, case-control, quasi-experimental and observational studies) were excluded from this review. This is because these studies do not provide the highest level of evidence for evaluation of effectiveness and are viewed as being liable to greater risk of systematic errors than RCTs (Miller et al., 1989).

Excluded Population: Studies whose populations comprised adults with type 1 diabetes and those involving children below 18 years of age were excluded.

Excluded Interventions: Studies with combination therapies made up of various compounds in the treatment arms (liraglutide plus rosiglitazone versus metformin or liraglutide plus metformin versus rosiglitazone) and studies including other type 2 diabetes interventions like insulin, meglitidine

analogues, biguanides, thiazolidinedione and glucosidase inhibitors were excluded.

Types of Outcome Measure: The primary outcome measure of interest is glycated haemoglobin (HbA1c) reduction measured by whole blood (not plasma) using high performance liquid chromatography (HPLC) (Jeppsson et al., 2002). HbA1c is a gold standard for measuring the degree of glycaemic control in both type 1 and type 2 diabetes treatment monitoring, and decision regarding therapy is based on it, since it is not affected by daily fluctuation in blood glucose, but rather depends on accumulated build-up over a period of time (Little, 2000; Sacks et al., 2002; Goldstein et al., 2004). The secondary outcome measure is weight reduction measured by any standard weighing scale. Other outcome measures which include reduction in FBS, antihypoglycaemic effects, and adverse events (nausea, vomiting and diarrhoea) were excluded.

Search Strategy for Identifying Studies: Seven databases were searched to ensure a comprehensive retrieval of titles and citations of relevant studies. A search strategy was developed for use in the various electronic databases searched. The search strategy was designed to filter only the randomised controlled trials. The search filter used was adopted from the Scottish Intercollegiate Guidelines Network (SIGN) which has been updated (SIGN, 2009). References of systematic reviews, literature reviews and those of identified studies were carefully scrutinized for identification of more studies. The databases searched include, Centre for Reviews and Dissemination (DARE, NHS EED & HTA), Cochrane Central Registers of Controlled Trials (CDSR & Central), CINAHL (Cumulative Index to Nursing and Allied Health Literature), EMBASE, Medical Research Council (MRC) trials register, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and UK Clinical Research Network (UKCRN). The searches were meant to identify current and ongoing trials. Hand searching of the two selected journals (*Diabetes Care* and *Journal of Diabetes*, *metabolic Syndrome and Obesity: Targets and Therapy*) was carried out electronically on the journals' websites.

Study Selection and Eligibility: Potentially relevant titles, citations and abstracts were screened following the standard process that ensures minimising bias (CRD, 2009). This procedure used was in conformity with standard procedure for the conduct of systematic reviews (SCIE, 2006).

Quality Assessment: This procedure was carried out in line with standard procedures for conducting systematic reviews (West et al., 2002; Jüni et al., 2006; Petticrew and Roberts, 2006; Herbison et al., 2006; Wells & Littell, 2009). For this review, the quality of selected studies was assessed based on the Critical Appraisal Skill Programme (CASP) checklist (Public Health Resource Unit, 2006). CASP was chosen because it is among the standard popular tools with a good number of items that address validity issues in a study (Hejri, 2005). There are ten screening questions for the assessment of RCTs using CASP checklist.

These are summarized as follows: 1)Whether a clearly-focused question was raised by the study in terms of population studied, intervention given and outcome measured; 2) If it is a randomised controlled trial and appropriately carried out as such, and if this design is suitable to address the question raised; 3) whether the allocation of participants to intervention and control groups was appropriate in terms of randomisation; 4) whether participants, staff and personnel were blinded to study groups; 5). whether all the participants that entered the trial were accounted for at the end; 6) whether the participants in all the groups were followed up in a similar manner and if collection of data was done in a similar way; 7) whether enough participants were used for the study to minimize the play of chance, and if power calculation was carried out to determine the required number of participants for the study; 8) How the results were presented and what the main result was; 9) The precision of the result in terms of decision making and if confidence interval was reported or p-value in its absence; 10)Whether all important outcomes were considered for the application of the results, and if the result can be applied widely.

The quality of the selected studies was assessed by descriptive analysis of their compliance to the individual items on the CASP checklist, as recommended by Wells and Littell, rather than by scoring (rating) which is discouraged by the Cochrane Collaboration due to its possibility of introducing bias (Higgins and Green, 2006; Wells and Littell, 2009). This process was conducted in consistence with conventional practice (Wilby et al., 2003).

Data Extraction: Data extraction was carried out in compliance with the recommendation by Kitchenham on data extraction for systematic reviews

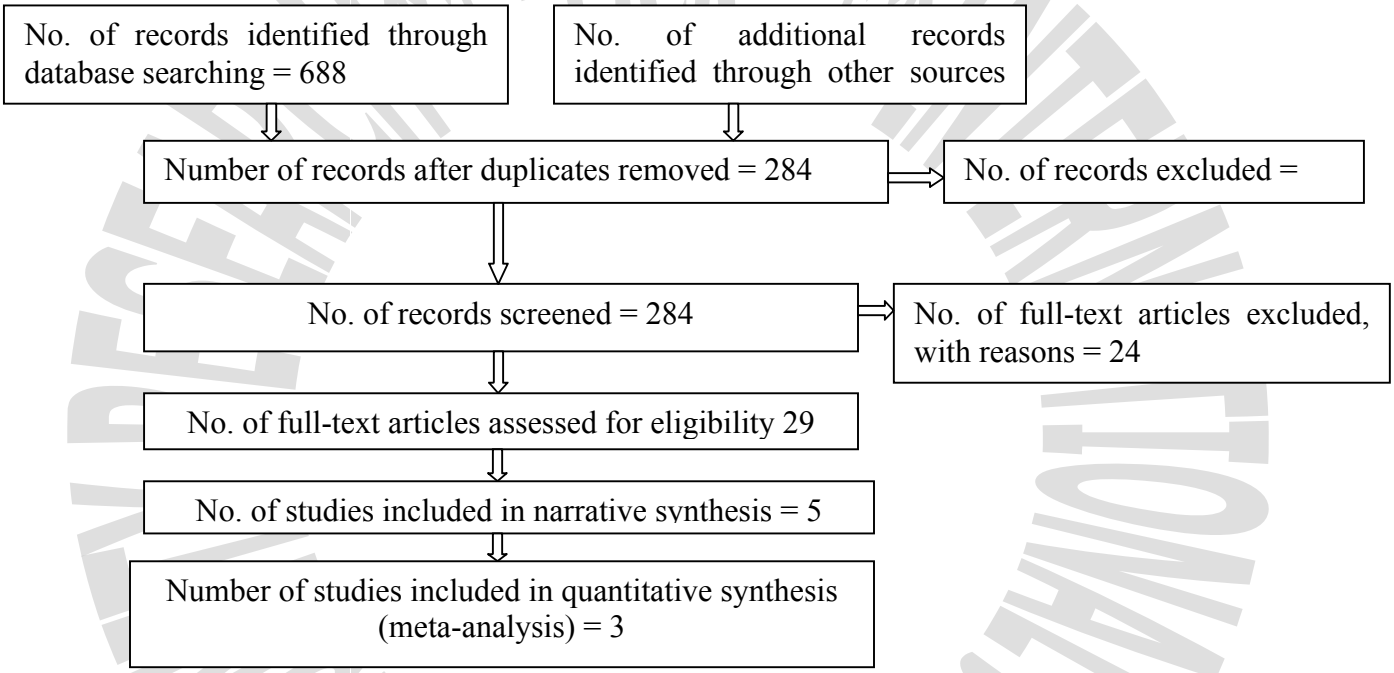
(Kitchenham, 2004). The data extraction form used in this review conforms with SCIE (SCIE, 2006).

Data Synthesis: Data synthesis was carried out by both meta-analysis and narrative synthesis. Where studies were sufficiently similar in terms of population, intervention, comparator and outcome, meta-analysis was carried out. Statistical heterogeneity was tested using the standard mean difference. Meta-analysis was performed for the primary outcome (HbA1c reduction) of three studies. Meta-analysis was conducted using a Review Manager 5 (RevMan 5) (CIMS, 2008).

RESULTS

The studies' selection process is presented in a PRISMA flow diagram adapted from Moher et al. (2009) (See figure 1 below). However, figure 2 below represents the prisma flow diagram for the studies' selections.

FIGURE 2: PRISMA FLOW DIAGRAM FOR STUDIES' SELECTION



Measurement of Outcome: All the studies specified the range of HbA1c index of diabetic patients, but none of the studies gave details of type 2 diabetes diagnostic criteria. One study: Harder (2004) specified that the primary outcome (HbA1c) was measured by HPLC, ion-exchange chromatography assay (normal range 4.3 – 5.8%); however, the instrument for body weight measurement was not stated. Three studies: Buse (2009), Garber (2009), and Seino (2008) stated that the outcomes were measured in central laboratories, but the specific methods used were not stated. One study: Vilsbøll (2007) did not mention where, and how the outcomes were measured. All the studies had HbA1c reduction as the primary outcome measure and the unit of measurement was consistently expressed in percentage (%). All the studies also included weight reduction among the secondary outcome measures, and this was expressed in kilograms (kg).

TABLE 1: A SUMMARY OF STUDY CHARACTERISTICS OF INCLUDED STUDIES

Author	Study design/ Country	Population baseline characteristics	Intervention	Comparator	Outcome Primary:HbA1c Secondary: Weight
Buse et al., (2009)	RCT/Austria, Denmark, Finland, France, Germany, Ireland, Macedonia, Norway, Poland, Romania, Slovenia, Spain, Sweden, Switzerland, and United States	Liraglutide Age (yrs) 56.3±9.8; Sex(M/F) 114/119 BMI 32.9 ± 5.5; HbA1c (%) 8.2 ± 1.0 Weight (kg) 93.1± 20.1 Exenatide Age 57.1 ± 10.8; Sex 127/104 BMI 32.9 ± 5.7; HbA1c 8.1 ± 1.0 Weight 93.0 ± 19.5	Liraglutide 1.8mg once daily No. of participants N = 235 Duration = 26 weeks	Exenatide 10µg twice daily N = 232 Duration = 26 weeks	Liraglutide to Exenatide diff: HbA1c -0.29% (-0.45 to -0.13); P <0.0001. Weight: Liraglutide to Exenatide difference: -0.38kg (-0.99 to 0.23), P = 0.2235
Garber et al., (2009)	RCT/ Mexico and USA	Liraglutide Age 53.7 ±11.0; Sex(M/F) 117/134 BMI 33.2 ±5.6; HbA1c 8.3 ±1.0 Weight 92.5 ±19.2 Glimepiride Age 53.4 ±10.9; Sex (M/F) 133/115 BMI 33.2 ±5.6; HbA1c 8.4 ±1.2 Weight 93.4 ±19.2	Liraglutide 1.2mg or 1.8mg once daily N = 497 Duration = 52 weeks	Glimepiride 8 mg once daily N = 248 Duration = 52 weeks	Liraglutide to Glimepiride diff: HbA1c: -0.62% (-0.83 to -0.42), P<0.0001 Weight: -3.48 kg, CI, p N/R
Harder et al., (2004)	RCT/ Denmark	Liraglutide Age 59.9 ±11.0; Sex (M/F) 11/10; BMI 36.8 ±4.6 HbA1c 7.37 ±0.21 Weight 106.9 ±2.9 Placebo Age 60.1 ± 6.7; Sex (M/F)1/11 BMI 36.1 ± 3.4; HbA1c 7.68 ±0.47 Weight 98.0± 3.8	Liraglutide 0.6 mg once daily N = 21 Duration = 8 weeks	Placebo N = 12 Duration = 8 weeks	Liraglutide to Placebo difference: HbA1c: -0.80, P = 0.02; CI N/R Weight: +0.2, P = 0.505 ; CI N/R
Seino et al., (2008)	RCT/ Japan	Liraglutide 0.6 mg Age 60.0 ± 7.0; Sex (M/F) 28/17 BMI 23.74 ± 2.78; HbA1c 8.21±0.83 Weight 61.52±9.46 Placebo Age 57.5 ±8.7; Sex (M/F) 29/17 BMI 23.77 ±2.63; HbA1c 8.43± 1.02 Weight 62.0±10.97	Liraglutide 0.1, 0.3, 0.6 or 0.9 mg N =180 Duration = 14 weeks	Placebo N = 46 Duration = 14 weeks	Liraglutide 0.6 mg to placebo diff: HbA1c: -1.64, P< 0. 0001 CI N/R Weight N/R, CI N/R, P = 0.2481
Vilsbøll et al., (2007)	RCT/ Denmark	Liraglutide (0.65 mg) Age 56.5 ±9.3; Sex (M/F) 27/13 BMI 28.9 ±3.9; HbA1c 8.1 ±0.6 Weight N/R Placebo Age 57.7 ±8.2; Sex (M/F) 19/21 BMI 30.4 ±4.0; HbA1c 8.2 ±0.7 Weight N/R	Liraglutide 0.65, 1.25 or 1.90 mg once daily N = 123 Duration = 14 weeks	Placebo N = 40 Duration = 14 weeks	Liraglutide (0.6 mg) to Placebo diff: HbA1c: -1.27 (-1.72 to -0.82), p<0.0001 Weight N/R, p = 0.039, CI N/R

Missing Data/Information: The lead investigators for all the included studies were contacted for missing data/information. However, the required information were not provided. Response was only received for one study: Vilsbøll (2007) after a reminder was sent, but the required information was not supplied.

Risk of Bias/ M*ethodological Quality of Included Studies*: The methodological quality of included studies was assessed based on CASP checklist (PHRU, 2006). Three of the studies: Buse (2009), Garber (2009) and Seino (2008) were of high quality addressing over three-quarters of the criteria; while the other two studies: Harder (2004) and Vilsbøll (2007) were of moderate quality addressing about three-quarters of the criteria.

Meta-analysis of Outcome (Statistical Summary): The primary outcome, HbA1c of three studies: Harder (2004), Seino (2008) and Vilsbøll (2007), involving 204 participants were pooled together in a meta-analysis (see hybrid figure 3 below). The secondary outcome of these studies could not be subjected to meta-analysis due to lack of data. Meta-analysis showed a significantly negative association between liraglutide and placebo with a difference (d) of -1.54 (95% CI: -2.21 to -0.88). The magnitude of this relationship suggests a large effect, $p<0.00001$; but the 95% CI cannot exclude a slightly small -0.88 or a very good -2.21 effects. The inconsistency in this result occurring as a result of variation across the studies rather than chance was found to be 75%. This is higher than the recommended 50% limit in heterogeneity. Subgroup analysis (see hybrid figure 4) of two of the studies: Seino (2008) and Vilsbøll (2007) also showed a significantly negative association between liraglutide and placebo with a d of -1.84 (95% CI: -2.26 to -1.42). The magnitude of this relationship suggests a large effect, $p<0.00001$; but the 95% CI cannot exclude a not too good -1.42 or a very good -2.26 effects. However, the inconsistency of the studies' results reduced to 26%.

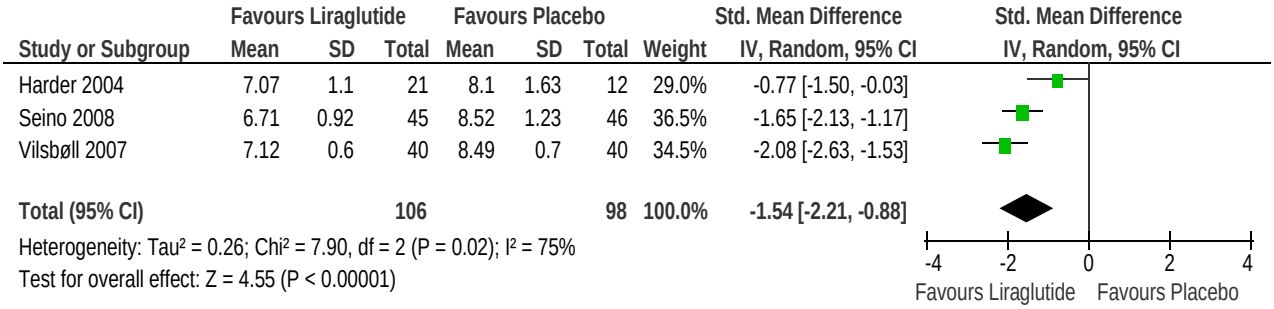


Figure (hybrid) 3: Meta-Analysis of HbA1 Reduction with Liraglutide versus Placebo

Heterogeneity: Meta-analysis shows that the variation across three studies: Harder (86), Seino (2008) and Vilsbøll (2007) measured by I^2 was 75% (see hybrid figure 3 above). This could be attributable to the small sample size, unequal distribution of participants in the intervention and control groups and short study period (8 weeks) in one of the studies: Harder (86). Subgroup analysis was therefore undertaken leading to a significant reduction of heterogeneity to 26% (see hybrid figure 4 below).

DISCUSSION

Overview of this Review: Five studies which met the inclusion criteria, involving 1634 participants, comparing liraglutide versus placebo, or liraglutide versus active control (exenatide or glimepiride), were selected and systematically reviewed. The baseline characteristics of participants in three studies: Buse (2009), Garber (2009), and Seino (2008) were balanced. This ensured that factors such as age, HbA1c, BMI and weight of participants at the beginning of the study did not vary widely as to affect the result of the study. Follow-up of participants as well as data collection were carried out in similar ways. However, there were potential sources of bias in these studies. The studies did not describe the recruitment setting of the participants, except one study: Harder (2004) which stated that the participants were recruited from patients' register. It is therefore not certain whether the study populations were representative of the general populations where the studies was carried out. Four of the studies reported carrying out double-blinding, but it was not explicitly stated whether blinding involved participants, investigators or personnel.

One study, Buse (2009), was an open-label even though blinding was possible. This has the potential of introducing information bias as mere knowledge of a particular treatment may affect patients' feeling. Methods of treatment allocation were not described

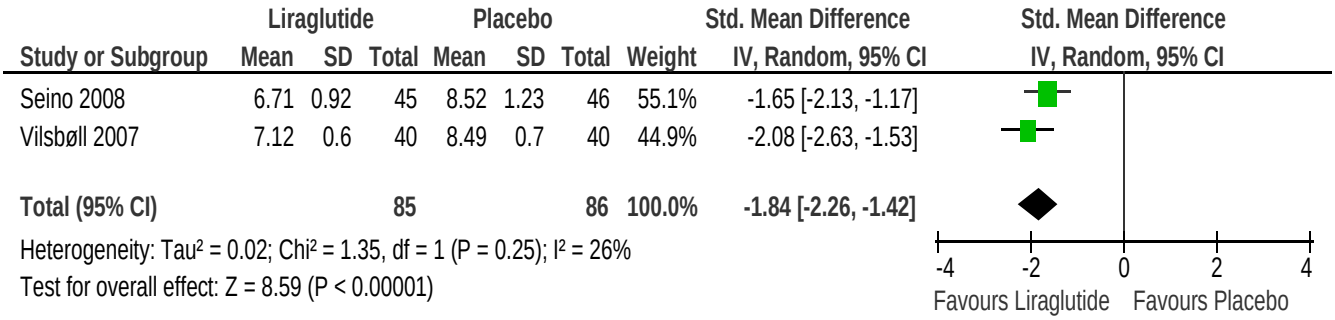


Figure (hybrid) 4: Meta-analysis of HbA1c Reduction with Liraglutide versus Placebo- subgroup Analysis

in four studies: Garber (85), Harder (2004), Seino (2008) and Vilsbøll (2007), so it was not certain whether concealment of allocation was properly carried out. Buse (2009), Garber (2009), Seino (2008) and Vilsbøll (2007) recorded high dropout rates of 78, 17, 16 and 25 participants respectively; translating to 16.7%, 2.3%, 7.1%, and 15.3% respectively. In two studies: Buse (2009) and Vilsbøll (2007) dropout rates were comparable in the study groups, but in one study: Garber (2009) it affected the intervention groups alone, while in another study: Seino (2008) it was more in the control group. Three studies: Buse (2009), Garber (2009) and Seino (2008) estimated 30%, 25% and 15% dropout rate respectively; while one study: Vilsbøll (2007) did not report expected dropout rate.

Although the dropout in three studies was less than what was expected, it was substantial enough to create an imbalance in the study groups which can affect the results. Buse (2009), Garber (2009), Seino (2008) and Vilsbøll (2007) carried out intention-to-treat analysis; but one study: Harder (2004) did not report carrying out such analysis. Power calculation was not reported by Harder (86) and Vilsbøll (2007). It is not possible to comment on whether these two studies recruited the required number of participants necessary to detect a difference in treatment. Garber (2009), Buse (2009) and Seino (2008) defined the primary endpoint in association with power calculation. Harder (2004) and Vilsbøll (2007) did not do so. This has the potential of introducing measurement bias due to uncertainty about the number of participants required to detect a difference in treatment. Also methods used in measuring outcomes were not described by Buse (2009), Garber (2009), Seino (2008) and Vilsbøll (2007). Only Harder (2004) gave a full description of how the primary outcome (HbA1c) was measured, but no information on how the secondary outcome (weight) was measured. Although Buse (2009), Garber (2009) and Seino (2008) stated that measurement of the outcomes were carried out in central laboratories, it would have been necessary to describe the methods used in order to ascertain whether they complied with the standard method.

A random effect approach was employed in the meta-analysis conducted on the primary outcome of three studies: Harder (2004), Seino (2008) and Vilsbøll (2007). Random effect approach was considered above fixed effect because it is more natural since it allows for variation in study outcomes between studies in a normal distribution (Higgins, 2008). Statistical heterogeneity was high (I^2= 75%). This may have been due to the small sample size, uneven distribution of the number of participants between the intervention and control groups and the short treatment duration (8 weeks) in one of the studies: Harder (2004). Subgroup analysis was therefore undertaken and there was significant reduction in the heterogeneity to 26% when one study, Harder (2004) was removed. Two studies: Vilsbøll (2007) and Seino (2008) did not report their funding sources; but three of the studies: Buse (2009), Garber (2009) and Harder (2004) were funded by Novo Nordisk, the manufacturers of liraglutide. This may have influence on the investigators with the possibility of introducing bias.

Irrespective of the potential sources of bias identified in the included studies, they provided strong evidence of effectiveness of liraglutide in the treatment of adults with type 2 diabetes. The studies considered in this review had a follow-up duration of 8 weeks which was the minimum period required for liraglutide therapy to produce a clinically significant difference in HbA1c and body weight. It may be argued theoretically that studies lasting for longer period will likely produce a more significant effect on these outcomes. The chances that this assumption is possible are slim, considering the fact that significant detectable difference was recorded in the shortest study, Harder (2004) that lasted for 8 weeks, as well as the longest study, Garber (2009) that lasted for 52 weeks. All the included studies consistently reported liraglutide as clinically effective in the

treatment of type 2 diabetes. Moreover, these studies were carried out by different groups of investigators at different times. The consistency of their results couldn't have arisen by chance. The result of meta-analysis of three of the studies in this review which also supported the findings of these studies provided a statistical evidence to rule out the play of chance ($p<0.00001$). As this is a new area and studies may be ongoing to explore further, few available reviews by Crom and McCormack (Crom & McCormack, 1985), Deacon (Deacon, 2009) and Montanya and Sesti (2009) are consistent with the findings of this review. An evaluation by Mikhail (2010) also reported high effectiveness of liraglutide in reducing HbA1c and body weight, but expressed concern about the high degree of adverse events such as nausea, vomiting and diarrhoea experienced by 44% - 56% of patients treated with liraglutide.

Strengths and Weaknesses of this Review

A good number of sources were extensively searched, and a meta-analysis was successfully completed. The studies used in this review were RCTs which are regarded as gold standard in establishing the effectiveness of health care interventions (Muir, 1997). The studies included in this review investigated the effectiveness of liraglutide as a monotherapy. This is to ensure that the estimated effect is attributable to liraglutide alone, and not due to the synergistic or antagonistic effect of any other compound. This approach has the benefit of eliminating any ambiguity about the effectiveness of liraglutide. Time posed a big challenge in this review, as the reviewers have to screen a large volume of titles and citations within the time limit prescribed in the protocol.

Implication for Patients, Practice and Policy/Decision

From the result of the five studies reviewed, it appears that a minimum of 8 weeks treatment with liraglutide provides evidence of clinical effectiveness in the improvement of patient-oriented outcomes such as glycaemic control, measured by HbA1c reduction, and weight reduction in adults with type 2 diabetes, compared to placebo, exenatide and glimepiride. However, recommendation cannot be made based on this finding, as this evidence is provided by few studies. This therefore requires strengthening by more studies. Patients should as a matter of fact not use this evidence as the basis for advancing self-medication. Clinical effectiveness is only one aspect of multifaceted criteria required in changing decisions regarding patient management. Clinicians may have to consider other factors such as adverse events, tolerability and patient satisfaction before deciding on change of treatment. In addition to clinical considerations, it is advisable for decision makers to seek further information from subsequent systematic reviews, health technology assessments and economic evaluations of cost-effectiveness before deciding on funding liraglutide as a new treatment regimen for type 2 diabetes.

Implication for Further Research:

Efforts should be made by subsequent systematic reviews to include studies published in languages other than English. Most importantly, further primary studies with larger sample sizes should be carried out in this area.

Conclusion

Type 2 diabetes can be managed in various ways ranging from healthy eating plans, weight reduction plans, exercise and the use of hypoglycaemic agents. This systematic review focused on the clinical effectiveness of liraglutide compared with placebo, exenatide or glimepiride in the treatment of adults greater than 18 years of age with type 2 diabetes. Based on the evidence available from 5 studies, liraglutide appears to be more effective than placebo, exenatide or glimepiride in the treatment of type 2 diabetes; and provides better glycaemic control by enhancing HbA1c reduction. Its effectiveness in weight reduction, is, however, uncertain as some of the studies actually showed weight gain. However, recommendation cannot be made based on this finding, as this evidence is provided by few studies and therefore requires strengthening by more studies if change in policy and practice is to be considered. Decision makers are therefore advised to seek further information from subsequent systematic reviews, health technology assessments and economic evaluations of cost-effectiveness before deciding on funding liraglutide as a new treatment regimen for type 2 diabetes. Further primary studies with larger sample sizes should be carried out; and the study population should spread across all the continents by conducting multi-centre studies internationally.

ACKNOWLEDGEMENT

We thank Agbo, Gloria (Research Assistant, Anthonio Research Publications) for reading through the scripts and making useful corrections.

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AUTHORS CONTRIBUTION