Abstract
The glucagon-like peptide-1 receptors agonists (GLP1RA) are a relatively new class of drugs, used for management of type 2 diabetes. This review studies the characteristics of these drugs, focusing upon their mechanism of action, intra-class differences, and utility in clinical practice. It compares them with other incretin based therapies, the dipeptidyl peptidase-IV inhibitors, and predicts future developments in the use of these molecules, while highlighting the robust indications for the use of these drugs.

Keywords: Glucagon-like peptide-1, Drugs.

Introduction
Recent advances in the pathophysiology of diabetes have been accompanied by improvements in the pharmacological options available to tackle the condition. One such relatively recent addition is a class of drugs whose mechanism of action is based upon the incretin pathway. These drugs include the injectable glucagon-like peptide 1 receptor antagonists (GLP1RA) and as well as the orally administered dipeptidyl peptidase-IV inhibitors [DPP (IV)]

This review discusses recent advances in the use of GLP1RA.

Glucagon-Like Peptide-1 (GLP-1)
GLP-1, a member of the glucagon peptide family, is released from the neuroendocrine L-cells in the small intestine. It acts through the GLP-1 receptors, which are found in organs as varied as the brain, lung, pancreatic islets, stomach, hypothalamus, heart, intestine, and kidney. As native GLP-1 has a very short plasma half-life, it cannot be used therapeutically, except by continuous intravenous infusion. Modifying the two sites in the GLP-1 molecule which are susceptible to cleavage: the position 8 alanine, and the position 34 lysine, can help prolong the half-life of GLP-1. These, and other chemical modifications, help in creating compounds known as GLP-1 receptor agonists, which have a longer half-life, and can be used for therapeutic purposes.

Classification of Gp1ra
The various GLP1RA can be classified based upon their chemical structure, their major mechanism of action, and their duration of action (Table-1). All GLP1RA are injected subcutaneously, and cannot be administered orally.

GLP1RA Available or Soon to be Available in Pakistan
The three GLP1RA currently available in global markets are exenatide, exenatide LAR (long acting release), and liraglutide.

Exendin-4 is a naturally occurring peptide of 39-amino acids obtained from the venom of "Heloderma lizard venom," bearing a 53% homology to human GLP-1. The second amino acid residue in N-terminal region, (alanine for human GLP-1), is replaced by glycine in exenatide and exenatide LAR (long acting release). LAR preparations are based on microsphere-based technology, which
incorporates drug molecules into a matrix of poly-D, L-lactide-co-glycolide, and allows once weekly administration.\textsuperscript{2}

Liraglutide ([(Arg (34) Lys (26)-(N-epsilon-(gamma-Glu (N-alpha-hexadecanoyl))]), has only one amino acid substitution (Lys34Arg) with the addition of a C-16 acyl group (palmitoyl) attached to Lys 26 via a glutamate linker. It retains 97\% sequence homology to human GLP-1. Acylation prolongs the half-life of GLP-1 by slowing release from the injection site; and extensive binding to albumin, which protects it from degradation by DPP-4 and reduced renal clearance). These characteristics allow liraglutide to be administered once daily.\textsuperscript{3}

**Mechanism of Action**
GLP1RA act by increasing the concentration of GLP 1 to supra-physiological or pharmacological levels (80 pmol/l). This in turn stimulates GLP1 receptors, present in various organs of the body, to elicit beneficial glycaemic effects.

The beneficial glycaemia related effects include:

1- Brain /hypothalamus: reduced appetite
2- Liver: decreased hepatic gluconeogenesis
3- Pancreas: alpha cells: reduced glucagon
4- Pancreas: beta cells: increased insulin
5- Gastrointestinal tract: delayed gastric emptying

GLP1RA target both fasting glycaemia and postprandial glycaemia. While most GLP1RA work mainly by increasing insulin, and decreasing glucagon levels, exenatide and lixisenatide act mainly through inhibition of gastric emptying.

**GLP1RA vs. DPP IV Inhibitors**
Though both belong to the group of incretin-based drugs, GLP1RA and DPP (IV) I work through different mechanisms of action, and have different effects on physiology. Some of these contrasts are highlighted in Table-2. Both classes of drugs have distinct advantages and shortcomings, and both have a distinct place in diabetes pharmacotherapy.

**Placing GLP1RA in Clinical Practice**
International guidelines now recommend GLP1RA as one of the second line drugs for use after metformin monotherapy.\textsuperscript{4} This suggestion is based on robust clinical evidence which supports the efficacy, safety and tolerability of GLP1RA. This class of drugs is non-inferior to maximum dose metformin, pioglitazone, sulfonylurea, and insulin (biphasic and long-acting), in glycaemic

<table>
<thead>
<tr>
<th>GLP1RA</th>
<th>DPP (IV) I</th>
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<tbody>
<tr>
<td>Predominant mechanism</td>
<td>Stimulation of GLP1 receptor</td>
</tr>
<tr>
<td>Effect on GLP 1 concentration</td>
<td>Increase to supra-physiological levels (80 pmol/l)</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Varies from twice daily (exenatide) to once daily (liraglutide, lixisenatide) to once weekly (exenatide LAR, others)</td>
</tr>
<tr>
<td>Efficacy: effect on</td>
<td></td>
</tr>
<tr>
<td>- HbA1c</td>
<td>Greater</td>
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<tr>
<td>- Fasting glycaemia</td>
<td>Equal</td>
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<tr>
<td>- Post prandial glycaemia</td>
<td>equal</td>
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<tr>
<td>Tolerability</td>
<td></td>
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<tr>
<td>- Body weight</td>
<td>Reduced</td>
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<tr>
<td>- Appetite</td>
<td>Reduced</td>
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<tr>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>- Hypoglycaemia</td>
<td>Low</td>
</tr>
<tr>
<td>- Gastrointestinal effects</td>
<td>Possible; transient</td>
</tr>
<tr>
<td>- Cardiovascular risk</td>
<td>Reduced</td>
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<tr>
<td>Pleiotropic effects</td>
<td></td>
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<tr>
<td>- Use as anti-obesity drug</td>
<td>Marked benefit</td>
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<tr>
<td>- Lipid lowering effect</td>
<td>Marked benefit</td>
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<tr>
<td>Use in combination</td>
<td></td>
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<tr>
<td>- With insulin</td>
<td>Yes</td>
</tr>
<tr>
<td>- With oral hypoglycaemics</td>
<td>Yes</td>
</tr>
<tr>
<td>- As fixed dose combination</td>
<td>No</td>
</tr>
<tr>
<td>- As fixed proportion combinations</td>
<td>Yes (In development)</td>
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</table>
control. Especially noteworthy is the ability of GLPRA1 to achieve composite end points, i.e., lowering of HbA1c, without causing hypoglycaemia, without causing weight gain. It is this multifaceted, three-pronged, efficacy which suggests that GLP1RA have a cardiovascular friendly profile. Another noteworthy characteristic of GLP1RA is the sustainability of action, proven in studies of up two years duration. GLP1RA have been studied in combination with various oral hypoglycaemic agents, as well as with basal insulin. Their mechanism of action is complementary to that of most other drugs.

**Robust Indications for GLP1RA**

While GLP1RA can be used in all persons with type 2 diabetes, its cost limits its universal use, especially in pay-from-pocket markets such as South Asia.

Persons with robust indications for GLP1RA use include:

- Type 2 diabetes not responding to metformin monotherapy; dual therapy; or insulin, if
  - Obese/overweight
  - Unable to control appetite
  - At high risk of cardiovascular disease
  - At high risk of hypoglycemia
  - Requiring high doses of insulin

**Posology**

The doses and frequency of administration vary for each GLP1RA. Exenatide is prescribed as 5mcg twice daily, before meals, up-titratable to 10mcg twice daily. Liraglutide is begun at 0.6mg once daily, without regard to meal times, and may be increased to 1.2 or 1.8mg. Exenatide LAR is a fixed dose of 2mg, once a week. Though GLP1RA are injectable drugs, just like insulin, there are subtle differences in counseling patients being prescribed these drugs. A greater emphasis on the mechanism of action, and potential pleiotropic effects, is needed.

**Non-Glycemic Benefits**

Some of the pleiotropic effects of GLP1RA include:

1. Cardiovascular System: positive effect on myocardial contractility, hypertension (natriuretic/diuretic effect), endothelium (anti-atherosclerotic), and lipid profile.
2. Nervous system:
   - a. neuronal protection, resulting in an improvement in cognition, memory, and spatial learning.
   - b. modification of eating behavior by inducing satiety, thereby reducing energy intake by approximately 12%.
   - c. gastric slowing via interaction with the peripheral nervous system (vagus), thus inducing a post-prandial satiety.
3. Obesity: Weight loss is dose dependent and progressive. Liraglutide has shown to induce a mean weight loss of approximately 6.0 kg with >35% of the subjects achieving >= 10% reduction of weight.
4. Insulin Resistance: restoration of insulin signaling and reduction of hepatic gluconeogenesis. Reduced insulin resistance, locally at the level of beta-cell and fat cell (reduced release of free fatty acids), and systemically (down-gradation of markers of inflammation).
5. Gastrointestinal/Hepatobiliary system:
   - a. delays gastric emptying via "ileal-break mechanism;"
   - b. improves hepatosteatosis.
7. Bone health: improve bone mass, via its antagonistic action on neuropeptide Y.
8. Skin: potential beneficial role of liraglutide and exenatide in psoriasis via influence on natural killer cells (implicated in pathogenesis of psoriasis).

**Choosing a GLP1RA**

All GLP1RAs are not alike. Three drugs of this class are available in the world presently. Exenatide needs to be injected twice daily, 30 to 60 minutes prior to meals, and is associated with a high risk of nausea, vomiting, antibody formation. Liraglutide is a once daily injection, which causes mild, transient nausea and vomiting, and leads, to minimal antibody formation. Exenatide LAR has a once weekly dose, and may lead to local injection site-related adverse events.

Various head to head comparative studies have been shown a superior HbA1c lowering of liraglutide as compared to exenatide (LEAD-6), exenatide LAR (DURATION-6), and albiglutide (Harmony-7). LEAD-6 results reveal that reduction in HbA1c is 0.33% greater with liraglutide compared with exenatide. Further benefits are obtained with fasting plasma glucose (0.9mmol/l), body weight (0.9kg), and systolic blood pressure (3.8mmHg) with minimal minor hypoglycemia (1.30 episodes/patient-year) or nausea (3.2%) in patients switched onto liraglutide from exenatide. Pancreatic [beta]-cell function (proinsulin : insulin ratio and HOMA-beta) also improved, and triglycerides and free fatty acids...
reduced, to a greater extent with liraglutide than exenatide. The gastrointestinal side effects were most pronounced with exenatide BID (28%-nausea, 9.9%-vomiting) compared to liraglutide (25.5%-nausea, 6.0%-vomiting). Liraglutide was found to be less immunogenic than exenatide.\textsuperscript{9} Similarly, better efficacy of liraglutide is also reported by researchers from DURATION -6 abd Harmony-7, comparing it with exenatide LAR and albiglutide.

**Adverse Events**

The commonest events noticed with GLP1RA use are gastrointestinal in nature. Concerns have been raised regarding the possibility of pancreatitis, malignancy, and thyroid disease with GLP1RA, but seem to be overhyped.

**Recent Trends**

Liraglutide has been used, with beneficial effects, in patients with type 1 diabetes as well.\textsuperscript{12} Both exenatide and liraglutide are being studied as anti-obesity drugs, to be used in non-diabetic persons as well. A fixed proportion combination of liraglutide with detemir, and lixisenatide with glargine, is under development.\textsuperscript{13} GLP1RA are also being suggested as drugs with potential for use in coronary syndromes.

**Future Trends**

The GLP1RA molecules, currently exemplified by liraglutide, exenatide, and exenatide LAR, are welcome additions to the fast-expanding anti-diabetic pharmacopoeia. Though they will not displace insulin, their use, especially that of liraglutide, is bound to grow in the near future. They will be used not only in diabetes, where they help achieve composite endpoints of glycemic control, weight loss and lack of hypoglycemia, but also in non-diabetic persons with obesity.

**References**