7.1 Oral Anti-Diabetic Drugs

Blood glucose levels are mainly determined by absorption of glucose from gut, uptake of glucose by peripheral tissues (muscle, adipose tissue), hepatic glucose output, and the insulin secretion from the pancreas. Various oral anti-diabetic agents act by modifying the factors aiding in the control of hyperglycemia as shown in the Figure. Some of the oral anti-diabetic agents currently available are listed in the Table 1.

Figure: Primary action of oral anti-diabetic drugs
### Table 1: Types of oral anti-diabetic agents currently available in India

<table>
<thead>
<tr>
<th></th>
<th>Daily Dosage (mg)</th>
<th>Frequency per day</th>
<th>Duration of action (hrs)</th>
<th>Mode of excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Sulphonylureas (SU)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>a. First generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>100 – 500</td>
<td>1</td>
<td>24 – 60</td>
<td>Urine</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>500 – 2500</td>
<td>2 – 3</td>
<td>6 – 12</td>
<td>Urine</td>
</tr>
<tr>
<td><strong>b. Second generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>2.5 – 20</td>
<td>1 – 2</td>
<td>16 – 24</td>
<td>Urine (50%); Bile (50%)</td>
</tr>
<tr>
<td>Glipizide</td>
<td>2.5 – 20</td>
<td>1 – 3</td>
<td>8 – 12</td>
<td>Urine (80%); Bile (20%)</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>80 – 320</td>
<td>1 – 2</td>
<td>8 – 12</td>
<td>Urine (80%); Bile (20%)</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1 – 8</td>
<td>1</td>
<td>16 – 24</td>
<td>Urine (60%); Bile (40%)</td>
</tr>
<tr>
<td>Glipizide XL</td>
<td>5 – 20</td>
<td>1</td>
<td>24</td>
<td>Urine (80%); Bile (20%)</td>
</tr>
<tr>
<td>Gliclazide MR</td>
<td>30 – 120</td>
<td>1</td>
<td>24</td>
<td>Urine (80%); Bile (20%)</td>
</tr>
<tr>
<td><strong>II. Non-Sulphonylurea Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>a. Meglitinide analogs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1.0 – 6</td>
<td>2 - 3</td>
<td>2 – 4</td>
<td>Bile</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>120 – 360</td>
<td>2 - 3</td>
<td>2 – 4</td>
<td>Bile</td>
</tr>
<tr>
<td><strong>b. Biguanides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>250 – 2500</td>
<td>2 – 3</td>
<td>8 – 12</td>
<td>Urine (90%); Faeces (10%)</td>
</tr>
<tr>
<td>Metformin SR*</td>
<td>1 – 2</td>
<td>1</td>
<td>24</td>
<td>Urine (90%); Faeces (10%)</td>
</tr>
<tr>
<td>Phenformin</td>
<td>25 – 100</td>
<td>1 - 3</td>
<td>4 – 6</td>
<td>Urine</td>
</tr>
<tr>
<td>Phenformin TD</td>
<td>100-200</td>
<td>1 - 2</td>
<td>8–14</td>
<td>Urine</td>
</tr>
<tr>
<td><strong>c. Alpha glucosidase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td>25 – 150</td>
<td>1 - 3</td>
<td>4</td>
<td>Faeces</td>
</tr>
<tr>
<td><strong>d. Thiazolidinediones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>2 – 8</td>
<td>1 – 2</td>
<td>12 – 24</td>
<td>Urine</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>15 – 45</td>
<td>1</td>
<td>24</td>
<td>Urine</td>
</tr>
</tbody>
</table>

* Daily dosage in grams

In addition, various fixed dose combinations are also available such as Glibenclamide + Metformin, Gliclazide + Metformin, Glipizide + Metformin, Glimepiride + Metformin, Pioglitazone + Metformin, Rosiglitazone + Metformin, Glimiperide + Rosiglitazone, etc.
7.1.1 Sulphonylureas:

The sulphonylureas bind to specific sulphonylurea receptors on pancreatic β-cells and increase insulin secretion. First generation sulphonylureas are rarely used now days. Second generation sulphonylureas remain the mainstay of treatment of type 2 diabetes. Therapy should be initiated with the lowest effective dose and titrated upwards every two weeks until the desired control or maximal dosage is reached. Sulphonylureas are preferably given 15 to 30 minutes before meals. They can be combined with metformin, acarbose, glitazones or insulin to give synergistic effect. However, they should not be combined with another sulphonylurea or meglitinide, since they act similarly and there is no potentiation of action. Every year about 5% of people with diabetes stop responding to sulphonylurea therapy (secondary failure). There are factors which need to be considered before labeling as secondary failure as given in section 7.1.1 (i). Various clinical trials have failed to conclusively demonstrate superiority of one sulphonylurea over the other, when used in optimal doses. In individual cases, switching from one sulphonylurea to another may show some benefit, but this may not be long lasting.

(i) Factors to be considered before labeling as secondary failure to sulphonylureas:

- Weightgain.
- Non-compliance to diet and exercise.
- Poor compliance to drugs.
- Inadequate dosage.
- Impaired absorption.
- Co-existing endocrine disorders such as thyroid disorders.
- Concomitant medications such as steroids.
- Infections, stress.

(ii) Side effects:

Hypoglycemia is the commonest side effect and is more likely to be prolonged and profound with long acting sulphonylureas, like chlorpropamide and glibenclamide and hence they should be used with extreme caution in the elderly. The side effects are:

- Mild nausea or vomiting and generally reversible with discontinuation of treatment.
• Rarely, skin rashes, leucopenia, anemia, thrombocytopenia, cholestatic jaundice, Steven-Johnson’s syndrome or granulomatous hepatitis may occur.
• Weight gain may be seen in people with diabetes on some sulphonylureas.
• Photosensitivity reactions to sulphonylureas (hyperpigmentation of exposed parts) may occur.

(iii) Contraindications:
• Type 1 diabetes.
• Renal insufficiency.
• Hepatic insufficiency, acute hepatitis.
• Pregnancy.
• Ketoacidosis.
• Acute myocardial infarction.
• Disseminated tuberculosis.
• History of adverse reactions to sulphonylureas.

7.1.2 Non-Sulfonylurea Agents:
(i) Meglitinide analogues: Meglitinide analogues (repaglinide and nateglinide) are non-sulphonylurea insulin secretagogues. They are benzoic acid derivatives, which act on separate non-sulphonylurea receptor binding sites on β-cell and enhance insulin secretion.

(ii) Repaglinide and Nateglinide:
These agents are absorbed rapidly (0.5-1 hr) and have a short half life (<1 hr). Thus they result in rapid but brief release of insulin, and hence may be useful in managing postprandial hyperglycemia. They have to be administered with each meal.
• They produce fewer and milder hypoglycemic episodes and other side effects compared to sulphonylureas.
• The indications and contraindications for these agents are similar to sulphonylureas.
• They may be used in mild renal insufficiency and elderly under supervision.

(ii) Biguanides: Metformin is the preferred biguanide. It mediates its effect by decreasing hepatic glucose output, as well as enhancing sensitivity of the hepatic and peripheral tissues to
circulating insulin. It also inhibits the intestinal absorption of glucose and exerts anorexic effect. The starting dose may be 250 mg twice a day after meals, which may be increased by 500 mg every two weeks until desired therapeutic goals are achieved or maximum daily doses (2500 mg), is reached. It can be used in combination with sulphonylurea and other oral hypoglycemic agents as well as insulin. Metformin, being an anti-hyperglycemic agent, rarely produces hypoglycemia when used as monotherapy. Weight loss is another feature with metformin and thus is now recommended as the first line treatment in obese type 2 diabetic people. Metformin has a favourable effect on lipids, decreasing triglycerides and LDL cholesterol. Metformin should be stopped at least three days before elective major surgery or use of radio contrast media. Metformin should be withdrawn if any contraindications to its use occur.

(ii) Side effects:
- Gastrointestinal side effects like abdominal discomfort and diarrhea may occur in some people with diabetes. These can be minimized if metformin is administered after meals and with slow titration of doses.
- Lactic acidosis is a rare side effect and is rare in the absence of other serious hypoxic medical disorders.

(ii) Contraindications:
- Renal insufficiency
- Hepatic insufficiency
- Respiratory insufficiency
- Hypoxemic conditions
- Acute myocardial infarction
- Congestive cardiac failure
- Alcohol abuse
- Ketoacidosis
- Pregnancy
- Severe infections
(iii) **Alpha-glucosidase inhibitors**: Alpha-glucosidase inhibitors such as acarbose acts by competitively inhibiting alpha-glucosidase, the enzyme in the small intestine brush border, which breaks down oligosaccharides and disaccharides into mono-saccharides. Thus the absorption of glucose is delayed. Acarbose is especially useful in decreasing post-prandial glucose levels. It can be combined with sulphonylureas and biguanides but its hypoglycemic potency is much less in comparison with these compounds. The starting dosage is 25-50 mg once daily, which is increased to 50 mg two to three times in a day. It must be ingested with the first bite of food, as the drug must be present in the small bowel with the food for proper effect. Hypoglycemia rarely occurs if used as monotherapy. If hypoglycemia results from combination therapy, treatment should be with oral glucose rather than sucrose.

**(iii)a Side effects:**

Gastrointestinal side effects like bloating, abdominal discomfort, diarrhea and flatulence are common.

**(iii)b Contraindications:**

- Inflammatory bowel disease.
- Cirrhosis of liver.
- Malabsorption syndromes.

(iv) **Thiazolidinediones (Glitazones):** These agents act by improving insulin sensitivity in adipose tissue and skeletal muscles. This effect is brought about by binding to nuclear peroxisome proliferator activated receptor-gamma (PPAR-γ) leading to increased glucose transporter expression. The action on adipocytes reduces plasma free fatty acids. This is a major mechanism for restoring insulin sensitivity. It also inhibits hepatic glucose output. Pioglitazone has partial PPAR-alpha agonist activity, which accounts for its beneficial effects on lipid profile. The dosage of rosiglitazone is 2-8 mg in one to two divided doses while that of pioglitazone is 15 to 45 mg once a day. The onset of action of these drugs start from 2-4 weeks of therapy and the maximum effect is observed after 8-12 weeks. These can be combined with sulphonylureas, meglitinides or metformin; however, combination with insulin may be used with caution. The women with anovulatory cycles may ovulate; hence adequate contraceptive advice should be given.
(iv) **Side effects:**

- Mild to moderate hypoglycemia has been reported in people with diabetes undergoing therapy with glitazone in combination with a sulphonylurea or insulin.
- Weight gain may be quite significant in many people with diabetes and is dose related.
- Edema and cardiac failure are reported in some people with diabetes, especially when combined with insulin.
- Other adverse events of glitazone include anemia and haemodilution.
- Liver dysfunction is relatively rare with rosiglitazone and pioglitazone compared to troglitazone.

(iv) **Contraindications:**

- Type 1 diabetes.
- Liver insufficiency.
- History of cardiac failure.
- Pregnancy and lactation.
- Moderate to severe anemia.
- History of familial cancers.

7.1.3 **General Guidelines for using oral anti-diabetic agents:**

The treatment should be individualized and the points mentioned below are only broad based Guidelines. The necessity of diet, exercise and life style modifications needs to be emphasized; in some cases these measures alone would suffice. When pharmacological treatment becomes necessary, the following points may be considered:

(i) **Non-obese people with type 2 diabetes:**

- In non-obese people with diabetes, start with a sulphonylurea / meglitinide or glitazone. If even after two to four weeks of initiation of treatment, symptoms still persist or blood sugar is not sufficiently controlled then a drug from another group like metformin can be added. If the initial blood sugar levels are very high, the symptoms are very severe or acute complications like ketosis are present, insulin has to be considered for treatment even at the onset, for a brief period.
• If the initial assessment shows presence of complications like diabetic retinopathy or nephropathy, this indicates a long period of undiagnosed diabetes and insulin therapy on a continuous basis should be considered.

(ii) Obese people with type 2 diabetes:
• In obese people with diabetes, the starting drug is ideally metformin.
• Similar Guidelines as mentioned above can be used to achieve good metabolic control with addition of other drugs like sulphonylureas/ meglitinides or glitazones and/or insulin.

(iii) Lean people with type 2 diabetes:
• In India, many subjects with type 2 diabetes are lean or low body weight (BMI <18.5kg/m²). In these people with diabetes, metformin is better avoided and the use of glitazones and sulphonylureas may be considered as first line of management. Quite often, such people with diabetes may require insulin for better control.
• With increasing duration of diabetes, most oral anti-diabetic agents tend to be less effective and hence poly-pharmacy becomes inevitable, with use of drugs from multiple classes. However, insulin use should not be delayed and, if and when necessary, insulin should be introduced for tight glycemic control.

7.1.4 Combination of oral drugs with insulin
When the glycemic control is not achieved with the maximum dose of an oral agent/combination therapy, this is called “secondary failure to oral hypoglycemic agents (OHA).

It has been the experience of most physicians in India that combination of oral drugs and insulin helps to achieve good control of diabetes. While using combination therapy, the oral drugs may be continued in optimal doses, while intermediate acting/long acting/short acting insulin is added either at bed time or in the morning depending on the blood sugar profile of person with diabetes. However, if indicated, one should not hesitate to use insulin in multiple doses to achieve tight metabolic control.
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7.1.5 Use of indigenous drugs

Many people with diabetes in our country use some indigenous drugs from other systems of medicine like Ayurveda, Homeopathy, Unani etc. Several herbal products have been advocated for the treatment of diabetes such as *Pterocarpus marsupium*, *Gymn sylvestre*, *Mormordica chirantica*, *Eugenia jambolana* etc. These drugs by themselves or in combination have hypoglycemic effects. Their exact mechanism of action is being worked out. There is a common belief that all herbal drugs are safe and non-toxic which is not necessarily true.

In view of the widespread use of these indigenous medicines, physicians should be aware of the herb-drug interactions. There is ample scope for research and careful evaluation of these agents needs to be done in the management of diabetes.

7.2 Insulin therapy

7.2.1 Indications for the use of insulin in type 2 diabetes mellitus at the time of diagnosis:

(i) If person with diabetes presents with complication such as

- Infection.
- myocardial infarction.
- history of weight loss > 5 kg with osmotic symptoms.

(ii) If

- person with diabetes is younger than 30 years with significant, symptomatic hyperglycemia and loss of weight.
- fasting plasma glucose > 270 mg/dl.

7.2.2 Other situations where insulin is indicated:

- Not responding to optimal doses of OHA alone or in combination.
- Acute hyperglycemia - Diabetic keto-acidosis / hyperglycemic-hyperosmolar state / lactic acidosis.
- Stressful situations such as acute myocardial infarction, stroke, acute infections, tuberculosis* and trauma.
- Pregnancy and lactation.
Section 7 Pharmacological Treatment For Diabetes

- Peri-operative state.
- Intolerant / contraindications to OHA.
- Hepatic and renal decompensation.
- Renal transplantation.
- Person with diabetes on steroids.

* Decision left to discretion of treating physician.

7.2.3 Types of insulin preparations:
Different types and species of insulin are available. They have different pharmacokinetic properties. Different insulin preparations can be divided based on the species, duration of action and impurities present. Insulin type, species, injection technique, insulin antibodies, site of injection and individual patient response differences can affect the onset, degree and duration of insulin activity.

(i) **Available insulin preparations:** The available insulin preparations are divided into three categories based on insulin source, pharmacokinetic properties and purity:

(i)a **Insulin source**
- Bovine
- Porcine
- Human (semi-synthetic or by rDNA technology)

(i)b **Pharmacokinetic properties**
- Short acting (bovine, porcine, human).
- Intermediate acting (bovine, porcine, human).
- Premixed (bovine, porcine, human).
- Long acting (bovine, human), currently not available in our country.

(i)c **Purity**
- Highly purified with impurities < 10 ppm pro-insulin.
- Monocomponent with impurities < 1 ppm pro-insulin.

The purity of currently available insulin varies from < 10 ppm to < 1 ppm pro-insulin.
(i) **Insulin analogues:**

- **Rapid acting** (e.g. Lyspro, Aspart): It is useful in children and in situations where other methods have failed to control post-prandial hyperglycemia.
- **Long acting** (Glargine). It is used to treat type 1 diabetes. It is also used to treat people with type 2 diabetes who need long-acting insulin to control their diabetes.

7.2.4 **Insulin action profiles:**

![Insulin Action Profiles Diagram]

7.2.5 **Storage of insulin:**

Vials of insulin not in use should be refrigerated. They should not be kept in the freezer compartment.

- Insulin should not be exposed to direct sunlight / heat.
- Excess agitation should be avoided to prevent loss of potency, clumping, frosting or precipitation.
- Insulin in use may be kept at room temperature and used within 30 days. If refrigerated, bring to body temperature before use.
- If refrigeration is not available, insulin should be stored in a cool place.
- If regular insulin shows haziness, it should not be used. If cloudy insulin cannot be re-suspended, it should not be used.

### 7.2.6 Mixing of insulin:
- Administration of mixtures of short and intermediate insulin will produce better glycemic control in some patients than use of single insulin.
- It is recommended that insulin of the same species should be used for mixing.
- Regular and lente insulin can be mixed but must be injected immediately.

### 7.2.7 Use of syringes:
- Conventional insulin administration involves subcutaneous injection with syringes marked in insulin units.
- There may be differences in the way units are indicated (U-40, U-100) and in India both are available in 1-ml syringe. Fixed needle (single unit) syringes are desirable.
- It is important to make sure that there is no syringe-vial mismatch as far as insulin concentration is concerned e.g. U-40 syringe must be used only for U-40 insulin.
- Syringes must never be shared with another person.
- Syringes may be reused at the patient’s discretion with appropriate precautions.
- If reuse is planned, the needle must be carefully recapped after each use. The needle should not be wiped or washed.
- Most insulin preparations have bacteriostatic additives that inhibit growth of bacteria commonly found on the skin.
7.2.8 *Insulin administration*

(i) **Insulin dose preparation**

- Before each injection, the hands and the injection site should be cleaned.
- The top of the insulin vial should be wiped with spirit.
- For all insulin preparations, except rapid and short acting, the vial should be gently rolled in the palms of the hands (not shaken) to re-suspend the insulin.
- An amount of air equal to the dose of insulin required should first be drawn up and injected into the vial to avoid creating a vacuum.
- For a mixed dose, putting sufficient air into both bottles before drawing up the dose is important.
- In case, insulin has to be mixed in the same syringe, (the mixing of rapid or short acting insulin with intermediate) the clear rapid or short acting insulin should be drawn into the syringe first.

(ii) **Sequence of mixing insulin**

(iii) **Injection procedures**

- Injections are given into the subcutaneous tissue.
- Inject insulin by lifting up a fold of skin and inject at a 90° angle.
• Thin individuals or children may need to pinch the skin and inject at a $45^\circ$ angle to avoid intramuscular injection, especially in the thigh area.

(iv) Injection site

• Insulin may be injected into the subcutaneous tissue of the upper arm, the anterior and lateral aspects of the thigh, the buttocks and the abdomen. For self injection, abdomen and thigh are the convenient sites.

• Rotation of the injection site is important to prevent lipohypertrophy or lipoatrophy. Rotating within one area is recommended (e.g. rotating injections systematically within the abdomen) rather than rotating to a different area with each injection. This practice may decrease variability in absorption from day to day.

• Site selection should take into consideration the variable absorption between sites. The abdomen has the fastest rate of absorption followed by the arms, thighs and buttocks.

• Exercise increases the rate of absorption from the injection sites.

• The most commonly recommended interval between injection of short acting (regular) / premixed insulin and a meal is 30 min.
(v) **Adverse effects associated with insulin use**

- The main problems associated with insulin use are hypoglycemia and weight gain.
- Weight gain can be significant and is generally well correlated with the total daily dose of insulin.

(vi) **Insulin pens**

- Several pen like devices and insulin containing cartridges are available that deliver insulin subcutaneously through a needle.
- They are easy to use.

(vii) **Insulin pumps**

- Insulin pump for continuous subcutaneous insulin infusion is currently available in the country.
- Its use may be restricted to diabetes specialists with relevant experience.
(viii) Disposal of needles

- Used needles must be disposed off in a bio-safe manner. For initiating insulin, it is not necessary to hospitalize the patient. It can be done on out patient basis.
- The dose has to be individualized depending upon the blood glucose profile and clinical setting.
- It is better to start with small doses and modify accordingly every three days.
- Generally, the starting dose of insulin should be 0.2 units/kg/day.

(ix) Adding insulin to OHA

When combinations of OHA no longer maintain the level of control desired, insulin is needed (see section 7.1).

(x) Multiple insulin injections

- When a single insulin injection plus one or more oral agents no longer maintains good glucose control, two or more injections are needed.
- A regimen containing mixtures of NPH and regular insulin mixed in different ratios (e.g. 30:70, 50:50) either mixed by the individual or premixed, taken before breakfast and dinner is a reasonable way to start multiple injections.
- Older persons need careful monitoring to avoid hypoglycemia.
- Combination of glitazone and insulin is not routinely recommended.