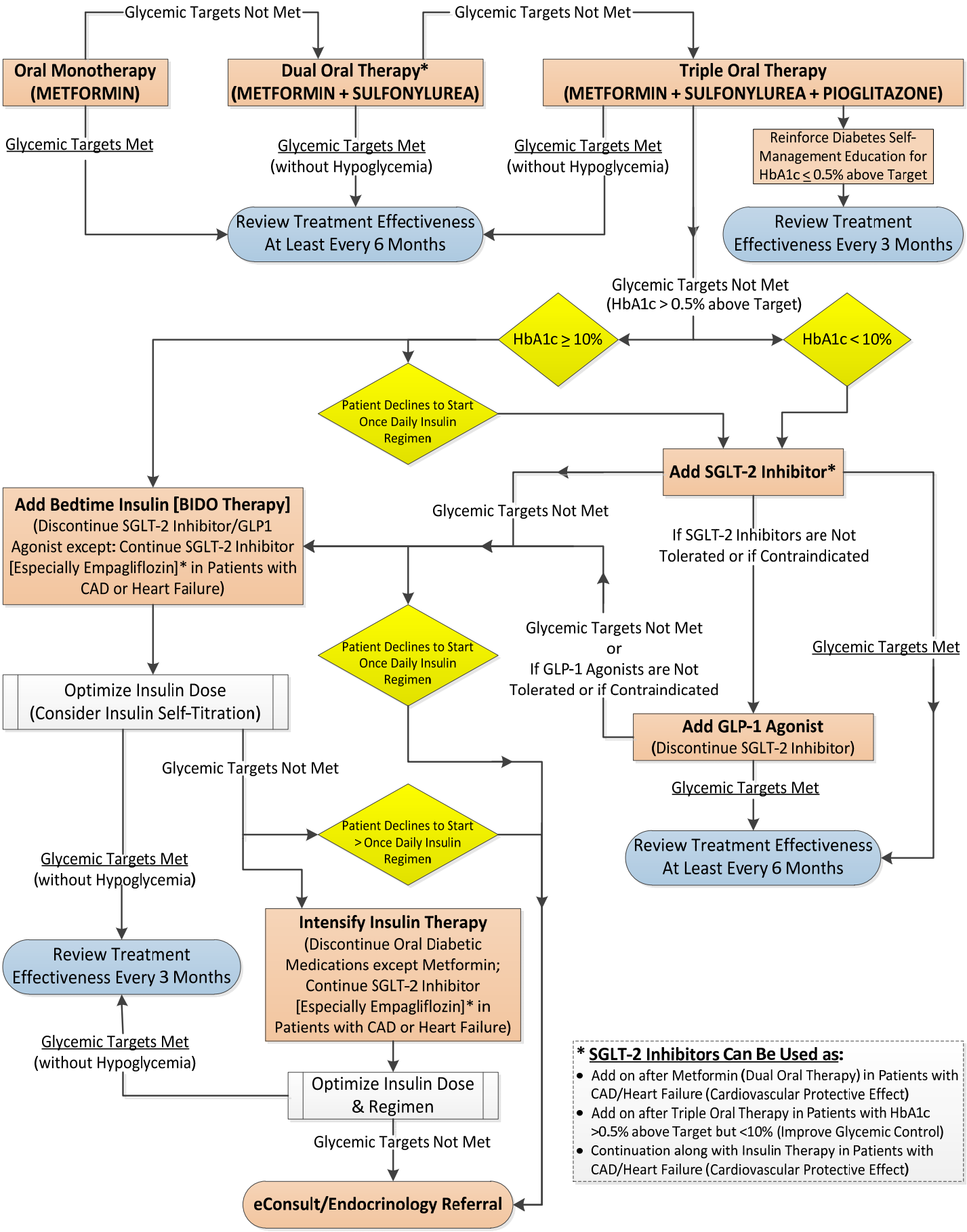
Health Services
LOS ANGELES COUNTY

DHS Best Practices

Outpatient Treatment and Management of Type 2 Diabetes Mellitus in Adults: Oral Agents, Non-Insulin Injectable, and Insulin Therapies

- Patients with type 2 diabetes mellitus often require more than one medication to reach glycemic controls.
- Insulin may be considered as an initial therapy for patients who, at the time of diagnosis, are symptomatic and/or have markedly elevated hemoglobin A1c (HbA1c) (>10%), **although most patients with new-onset type 2 diabetes can achieve euglycemia with oral medications**.
- Insulin therapy may be required when non-insulin therapy fails to achieve the glycemic targets and based on patient preference, can be added at any time.
- 'Glycemic Targets' should be individualized; for most patients HbA1c target is < 7%.
  - As patients age, the HbA1c target should be raised because of increased chance of hypoglycemia.
  - For most patients > 70 years of age, HbA1c target is >7% and < 8%, depending on other health conditions.
- Treatment decisions should be patient-centered based upon:
  a) Patient characteristics: age, body weight, comorbidities, lifestyle, meal pattern, disease duration, risk for hypoglycemia and adverse drug effects,
  b) Presence of prior cardiovascular disease (CVD) and/or chronic kidney disease (CKD),
  c) Patient attitude, preferences, needs, values, cultural heritages, and challenges in health literacy, and
  d) Resources, costs, living environment, and support system related to social determinants of health.
- Educating patients on medications that can cause hypoglycemia (sulfonylureas and insulin) and about the signs, symptoms, and treatment of hypoglycemia should be a top priority.
- Educating patients that diabetes self-management, (e.g., healthy eating/diet, physical activity/exercise, stress management, and most importantly, medication adherence) complements any prescribed therapy.
- Community based resources should be accessed using One Degree (https://www.1degree.org/org/city-of-los-angeles) and 211 (https://www.211la.org) as needed.
- Team-based care should be incorporated, for diabetes self-management education/support, lifestyle interventions, or for medication dose titrations, as needed.
- Treatment effectiveness should be re-evaluated frequently, as clinically appropriate, guided by the current medication regimen, glycemic control, and patient's personal factors.
- Patients should be appropriately managed for underlying diabetes distress disorder, anxiety, or depression.

Type 2 Diabetes Mellitus: Outpatient Treatment Algorithm



Oral Monotherapy — Metformin

- Maximize dose as tolerated: 1000 mg BID if estimated glomerular filtration rate (eGFR) > 45; 500 mg BID if eGFR 30 – 45.
- Do not use if eGFR < 30 (or if eGFR < 45 and patient is not currently taking metformin).
- Switch to metformin XR if patient has GI side effects.
- Monitor eGFR: every 12 months if eGFR > 60; every 6 months if eGFR 45 - 60; every 3 months if eGFR 30 – 45.
- Metformin may cause vitamin B12 deficiency - monitor B12 levels in patients presenting with anemia, macrocytosis, neuropathy, or other clinical stigmata for deficiency; supplement vitamin B12 as needed.
- Metformin may cause slight weight loss.
- Metformin initiation and dose titration: step up interval 14 days.

Dual Oral Therapy — Metformin + Sulfonylurea (Glimepiride/Glipizide)

- If glycemic targets not met, add sulfonylurea.
- Start glimepiride unless eGFR<60.
- Up titrate glimepiride as needed to max dose of 8 mg once daily (4 mg/day max dose for ages 65 and older), although it could also be given at a maximal dose of 4 mg bid with metformin.
- For patients with eGFR <60: start glipizide.
- Up titrate glipizide as needed to max dose of 20 mg BID.
- Sulfonylurea may cause weight gain, although this is less frequent with glimepiride.
- Educate patients about signs, symptoms, and treatment of hypoglycemia.
- If hypoglycemia occurs: reduce sulfonylurea dose or may need to discontinue it.
- Glimepiride/Glipizide initiation and dose titration: step up interval 14 days.

Triple Oral Therapy — Metformin + Sulfonylurea + Pioglitazone

- Pioglitazone is the preferred thiazolidinedione
- If glycemic targets not met, add pioglitazone.
- The recommended starting dose of pioglitazone is 30 mg/day, although 15 mg/day can be used in those close to target and in whom there is a greater concern of a weight gain, while 45 mg/day can be used in those farther from target.
- Pioglitazone should be up-titrated to a max dose of 45 mg/day as tolerated.
- Do not use pioglitazone in patients with history of heart failure (New York Heart Association Functional Class III or IV), macular edema, bladder cancer, or at increased risk of bone fracture. Use with caution in patients with fluid retention/edema.
- Counsel patients to report any symptoms of heart failure.
- Check liver function tests (LFTs) prior to initiating treatment. Do not start pioglitazone if aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (i.e., AST/ALT) > 3 times normal.
- Pioglitazone may cause weight gain and lower extremity edema.
- Pioglitazone initiation and dose titration: step up interval 30 - 60 days.

Next Step: New Oral Agent — SGLT-2 (Sodium-Glucose Co-Transporter 2) Inhibitor

Drug	Starting Dose	Maximum Dose	Renal Adjustment
canagliflozin	100 mg daily	300 mg daily	**GFR 45 - 59 ml/min**: dose should not exceed 100 mg a day **GFR < 45 ml/min**: DO NOT USE
dapagliflozin	5 mg daily	10 mg daily	**GFR < 60 ml/min**: DO NOT USE.
empagliflozin	25 mg -1/2 pill daily	25 mg -1/2 pill daily	**GFR < 45 ml/min**: DO NOT USE

Next Step: New Oral Agent (continued)

- If HbA1c > 0.5 above target but < 10% on triple oral therapy, provider can add an SGLT-2 inhibitor
- Recommended doses and use in renal insufficiency are given in the Table.
- Do not add SGLT-2 inhibitor in patients with history of recurrent urinary tract infection (UTI), vaginitis or balanitis.
- Use with caution in uncircumcised males, and patients ages 75 or older.
- SGLT-2 inhibitors may cause hypotension, ketoacidosis, acute renal failure, UTI, or genital mycotic infection. In nearly everyone, it causes increased urination.
- Empagliflozin reduces risk of CVD death in patients with prior CVD and slows renal decline in patients with CKD.
- Counsel patients to maintain adequate hydration and good genital hygiene.
- Reduce sulfonylurea dose by 50% when starting SGLT-2 inhibitor, to reduce the risk of hypoglycemia.
- If glycemic response remains inadequate after 1 month of starting the SGLT-2 inhibitor, and there are no hypoglycemic episodes, the sulfonylurea dose can be maximized.
- HbA1c should reach < 8% after 6 months of SGLT-2 inhibitor therapy to qualify for its continued use, except in patients with known coronary artery disease or heart failure where SGLT-2 inhibitors (especially empagliflozin) may be continued for its cardiovascular protective effects, irrespective of the HbA1c targets achieved.
- SGLT-2 inhibitors can also be used as 2nd line agent with metformin (Dual Oral Therapy) in patients with known coronary artery disease or heart failure.
- SGLT-2 inhibitors may cause weight loss.

Next Step: Non-Insulin Injectable GLP-1 (Glucagon-Like Peptide-1) Receptor Agonists:

Drug	Starting Dose	Maximum Dose	Renal Use	Warnings**
exenatide	5 mcg subcutaneously twice daily 60 minutes prior to a meal	10 mcg subcutaneously twice daily 60 minutes prior to a meal	**GFR < 30**: not recommended	1
liraglutide	0.6 mg subcutaneously daily for 1 week	1.8 mg subcutaneously daily	Use caution when initiating or escalating doses in patients with renal impairment.	1, 3, 4, 5
lixisenatide	10 mcg subcutaneously daily for 14 days	20 mcg subcutaneously daily starting on day 15	**eGFR > 15**: no adjustment recommended	1, 2
exenatide ER	2 mg subcutaneously weekly	2 mg subcutaneously weekly	**GFR < 30**: not recommended	1
albiglutide	30 mg subcutaneously weekly	50 mg subcutaneously weekly	**eGFR > 15**: no adjustment recommended	1
dulaglutide	0.75 mg subcutaneously weekly	1.5 mg subcutaneously weekly	No restrictions	1
semaglutide	0.25 mg subcutaneously weekly	1.0 mg subcutaneously weekly	No restrictions	1

** Warnings:
1) History of or family history of medullary thyroid carcinoma (MTC); patients with multiple endocrine neoplasia syndrome type 2 (MEN2).
2) Pancreatitis.
3) Increase in the heart rate.
4) Increase in acute gallbladder disease
5) Increase in suicidal behavior and ideation.

Next Step: Non-Insulin Injectable (continued)

- If HbA1c > 0.5 above target but < 10% on triple oral therapy, and patient unable to take SGLT-2 inhibitor (due to intolerance, contraindication, or no preference), a GLP-1 receptor agonist can be added.
- See the above table for restrictions.
- Reduce sulfonylurea dose by 50% when starting GLP-1 receptor agonist, to reduce the risk of hypoglycemia.
- If glycemic response remains inadequate after 1 month of starting a GLP-1 receptor agonist, and there are no hypoglycemic episodes, the sulfonylurea dose can be maximized.
- HbA1c should reach < 8% after 6 months of GLP-1 receptor agonist therapy for its continued use.
- GLP-1 receptor agonists may cause weight loss.

Next Step: Add Basal Insulin

Bedtime Insulin & Daytime Orals (BIDO): Basal NPH / Glargine

- Initiate BIDO therapy if HbA1c not at target but < 10% on triple oral therapy, for patients who are unable to take SGLT-2 inhibitor or GLP-1 receptor agonist (due to intolerance, contraindication, or no preference).
- Initiate BIDO therapy if HbA1c does not reach target after addition of SGLT-2 inhibitor /GLP-1 receptor agonist
- Start bedtime insulin NPH (Insulin Human Isophane).
- For patients with frequent overnight hypoglycemic episodes on Insulin NPH: switch to bedtime insulin glargine
- BIDO initiation/titration: adjust weekly until pre-breakfast self-monitoring blood glucose (SMBG) 100 – 140.
- Patients may be given daily self-titration instructions: increase insulin dose for SMBG >130 before breakfast, or decrease insulin dose for SMBG <70 before breakfast, by 1 unit for lean patients and 2 units for obese patients; discontinue self-titration if there are no changes to insulin dose for one week.
- Pioglitazone should be discontinued or dose reduced to 15 mg/day, if edema or other symptoms of fluid overload occur when initiating BIDO.
- SGLT-2 inhibitors and GLP-1 receptor agonists should be discontinued when initiating BIDO, except in patients with known coronary artery disease or heart failure, when SGLT-2 inhibitors (especially empagliflozin) may be continued.
- Educate patients about signs, symptoms, and treatment of hypoglycemia.
- Educate patients on eating small (100-150 calories) protein-containing healthy bedtime snacks if they develop overnight hypoglycemia.
- Initiate BIDO therapy for patients with HbA1c > 10% on triple oral therapy.

Next Step: Intensify Insulin Therapy

Self-Mixed Split vs. Premixed vs. Basal/Bolus Insulin Regimens

- Consider intensifying insulin therapy, if HbA1c does not reach target after 6 months of BIDO therapy.
- Self-mixed split insulin regimen (NPH + Regular) is preferred over premixed regimen (Insulin 70/30) and is the most cost-effective option for most patients with Type 2 DM.
- Basal/Bolus insulin regimen may be a preferred option for patients when switching from BIDO therapy, for those with variable eating/exercise pattern, or for those with frequent hypoglycemic episodes on self-mixed split insulin regimen.
- Basal/Bolus regimen with human insulin (NPH & Regular) is a preferred cost effective option over glargine & lispro.
- Glargine may be substituted for patients who have frequent overnight hypoglycemic episodes on basal NPH Insulin.
- Lispro may be substituted for patients who have frequent daytime hypoglycemic episodes on bolus regular insulin.
- When switching to an insulin regimen (other than BIDO), oral diabetic medications other than metformin, and the injectable non-insulin medication of GLP-1 receptor agonist should be discontinued, except SGLT-2 inhibitor (especially empagliflozin) may be continued in patients with known coronary artery disease or heart failure.
- Insulin therapy may cause weight gain.
- Educate patients about signs, symptoms, and treatment of hypoglycemia and be provided with glucose tablets. Patients with hypoglycemic unawareness should be provided with glucagon kits.
- Educate patients on eating small (100-150 calories) protein-containing healthy bedtime snacks if they develop overnight hypoglycemia.
- Adjust insulin dose weekly until SMBG within target range.

Insulin Preparation	Time Injected	Period of Activity	SMBG Test (To check for insulin effect)
Regular / Lispro	Before Breakfast	Morning	Before Lunch
Regular / Lispro	Before Lunch	Afternoon	Before Supper
Regular / Lispro	Before Supper	Evening	Before Bedtime Snack
NPH Insulin	Before Breakfast	Afternoon	Before Supper
NPH Insulin	Before Supper / Bedtime	Overnight	Before Breakfast
Glargine	Bedtime	Overnight	Before Breakfast
Premixed (70/30)	Before Breakfast	Morning + Afternoon	Before Lunch + Before Supper
Premixed (70/30)	Before Supper	Evening + Overnight	Before Bedtime Snack + Before Breakfast

Refer to a Diabetes Specialist+

- For any management advice.
- Type 1 diabetes or latent autoimmune diabetes of adults (LADA)
- Lean type 2 diabetes (BMI < 25%) and HbA1c > 9% or frequent hypoglycemia
- On insulin and dialysis or symptomatic gastroparesis requiring hospital admissions
- Undergoing non-emergency surgery soon and has poorly controlled diabetes (HbA1c > 9%)
- On U-500 insulin or may require it (i.e., >100 units per injection or > 150 – 200 units per day of insulin)
- Type 2 diabetes PLUS other endocrinopathies, e.g., adrenal or pituitary insufficiency
- Recurrent unexplained hypoglycemia
- Presence of major disabilities that affects ability to adequately manage diabetes (e.g., blind, deaf, neurological issues, etc.)

+ Pregnant patients should be sent to high risk obstetrics.

References

1. American Diabetes Association. (2018). Standards of Medical Care in Diabetes. *Diabetes Care,* Jan; 41(Supplement 1): S1-S159.
2. American Association of Clinical Endocrinologists and American College of Endocrinology. (2018). Comprehensive Type 2 diabetes Management Algorithm Executive Summary. *Endocrine Practice,* Jan: 24 (1):91-120. doi:10.4158/CS-2017-0153