# Update on Diabetes Medications California Area Office May 24, 2018

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Division of Diabetes Treatment and Prevention/Office of Information Technology



- Introduce the Glucose Management in Type 2 Diabetes treatment algorithm.
- Synthesize treatment recommendations for major glucose lowering therapies.

• Transform medication knowledge into clinical practice.





# Glucose Management in Type 2 Diabetes

#### IHS Home / Division of Diabetes Treatment and Prevention / Clinician Resources / Diabetes Treatment Algorithms

Division of Diabetes Treatment and Prevention	Diabetes Treatment Algorithms The Diabetes Treatment Algorithms were developed to provide clinicians with a quick reference to treatment algorithms based on national guidelines and the			
About Us				
raining	Standards of Care and Clinical Practice Recommendations: Type 2 Diabetes.         The algorithms are a collaborative effort between Indian health system professionals and have been reviewed by the IHS Division of Diabetes.         The algorithms provide the clinician with basic information needed at the point of patient care and also provide:         • Step-by-step management of the associated condition.			
HS Diabetes Audit				
Audit/SOS Login				
Clinician Resources				
Online CME/CE	<ul> <li>Dosing, common adverse reactions and contraindications for medications on the IHS National Core Formulary.</li> <li>Treatment targets and goals.</li> <li>Recommended monitoring parameters.</li> </ul> The Diabetes Treatment Algorithms are intended to serve as a tool to enhance the information required in treating patients with type 2 diabetes. It is not a substitute for the knowledge and information provided by complete national guidelines or the <i>IHS Diabetes Standards of Care for Patients with Type 2 Diabetes</i> . The algorithms will be updated periodically but changes in national practice may occur more quickly—users are advised to stay abreast of current clinical practice recommendations.			
Diabetes Standards of Care & Clinical Practice Resources				
Diabetes Treatment Algorithms				
Diabetes Education Lesson Plan Outlines				
Federal Partner Agency Resources				
Education Materials and Resources	Chronic Kidney Disease in Type 2 Diabetes	Foot Care in Type 2 Diabetes		
Online Catalog)	Download Algorithm [PDF – 229 KB]	Download Algorithm [PDF – 67 KB]		
Contact Us	Front   Back	Front		
Special Diabetes Program for Indians	Hypertension Management in Type 2 Diabetes	Insulin in Type 2 Diabetes		
	Download Algorithm [PDF – 417 KB]	Download Algorithm [PDF – 76 KB]		
	Front   Back	Front   Back		
	Lipid and Aspirin Therapy in Type 2 Diabetes <u>Download Algorithm</u> [PDF – 128 KB] Front I Back	Urine Albumin Screening and Monitoring in Type 2 Diabetes Download Algorithm [PDF – 45 KB]		

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https://www.ihs.gov/diabetes/clinician-resources/dm-treatment-algorithms/

Indian Health Service

Division of Diabetes and Prevention



Please Note: This algorithm is not intended for treatment and target selection in children or in women who are or could become pregnant.



# Diabetes Medications work best with...

...good nutrition and physical activity

Nutrition and physical activity are life-long interventions



### Diabetes is a Progressive Disease





#### Step 1: Determine Individualized Glycemic Target

 A1C Target Range: select based on age, duration of diabetes, patient preference, comorbidities, hypoglycemia risk, and other factors.







# Step 1: Determine Individualized Glycemic Target

Major Comorbidity	Microvascular Complications			
	Absent or Mild	Moderate	Advanced	
Absent (and/or >10-15 years of life expectancy)	6.0-7.0%	7.0-8.0%	7.5-8.5%	
Present (and/or 5-10 years of life expectancy)	7.0-8.0%	7.5-8.5%	7.5-8.5%	
Marked (and/or <5 years of life expectancy)	8.0-9.0%	8.0-9.0%	8.0-9.0%	

Major comorbidity includes but is not limited to significant CVD, severe CKD, severe COPD, severe chronic liver disease, recent stroke, and life-threatening malignancy. Microvascular disease includes retinopathy, neuropathy, or CKD. Adapted from the <u>VA/DoD Management of Diabetes Mellitus Guideline</u>.



# Updates to GPRA

- GPRAMA: Diabetes Good Glycemic Control
  - Current: Good control: A1c less than (<) 8
  - Future: Poor control: A1c greater than (>) 9





- Lisa is a 28 year old female who was diagnosed with type 2 diabetes three months ago. She is taking metformin XR 1500mg daily. She has no other medical problems.
- What is a reasonable A1C target for Lisa?



- 25 years later, Lisa has developed hypertension, rheumatoid arthritis, congestive heart failure, and chronic kidney disease. She is now taking detemir insulin BID and regular insulin before breakfast and supper.
- Is a target A1C range of 6-7 still appropriate?



# Step 2: Initiate Medication Therapy

- If significant weight loss or ketonuria, use insulin
  - Hospitalize if acidotic



- Otherwise:
  - Start **metformin** if A1C above patient's target but <9%.
  - Start metformin and a second medication if A1C ≥9% (see Step 3).





# **Metformin Dosing**

- Start with 500mg once a day with largest meal of the day.
- Regular Release
  - Increase to 1 tablet 2 times a day for at least 1 week.
  - Increase by 1 tablet weekly if able.
  - Maximum dose 2550mg per day (5 tablets)

#### • XR (Extended Release)

- Increase to 2 tablets with largest meal for at least 1 week.
- Increase by 1 tablet weekly if able.
- Maximum dose 2000mg per day (4 tablets)
- Do not cut, break, or crush XR tables









#### **Metformin Benefits**





#### Metformin Side Effects





- Marge is a 28 year old female who was diagnosed with type 2 diabetes 3 months ago. She wanted to try lifestyle management to lower her A1C before starting medications. She has no other medical problems and her eGFR >60ml/min. Her target A1C is 6-7%.
- Today her A1C is 7.8%. She decided that she would like to start medication therapy.
- What medication is the best first choice?





# 6 weeks later...

- Marge is involved in a serious automobile accident. The accident caused some physical trauma to her kidneys but the surgeons feel that she will fully recover with time.
- Her eGFR is currently 48ml/min. What recommendations do you have regarding her metformin therapy?



#### Metformin Lactic Acidosis Risk





# Metformin Lactic Acidosis Risk

#### Contraindications

- Severe renal impairment: eGFR < 30 mL/min
- Acute or chronic metabolic acidosis

#### Temporarily discontinue

- Radiologic studies using iodinated contrast media
- Hold for non-minor surgery restart when eating and renal function normal

#### Cautions

- Hypoxia (shock, CHF, AMI)
- Hepatic dysfunction
- Excessive alcohol intake
- Severe renal impairment: eGFR 30-45 mL/min



# Step 3: Intensify Therapy

If A1C above patient's target range, increase dosage(s) and/or add another medication

- Select additional medication(s) based on:
  - Formulary options
  - Side effects
  - Comorbidities
  - Cost
  - Medication regimen complexity
  - Patient preference



# Medication Options: National Core Formulary



The primary responsibility of the NPTC is to ensure that the IHS Malcoal Core Formulary (NCF) remains up to date with changes the knowledge and practice and provides IT/U clinicians with the tools to deliver evidence-based and cost-effective pharmacoulical services. The NPTC meets quartery to discuss eviding research and practice guidelines for conditions addressed by the NCF. In review the status of national contracts and other pharmacoeconomic data, to consult with subject matter experts on formulary and guidelines issues and to modify the NCF and ended.

- The NPTC Identifies the minimal drugs that must be stocked in federal IHS facilities.
- Local P&T Committee identifies the medications that will be stocked locally based upon resources and needs.





# Medication Options: Effects and Cost

Medication	A1C	Weight	Risk of Hypoglycemia	Cost
Metformin	$\downarrow \downarrow \downarrow$	-/↓	-	$\uparrow$
Alpha Glucosidase Inhibitor	$\downarrow$	-	-	$\uparrow$
Amylin Analog	$\downarrow$	-	-	$\uparrow\uparrow$
DPP-4 Inhibitor	$\downarrow$	-	-	$\uparrow\uparrow$
GLP-1 Receptor Agonist	$\downarrow \downarrow \downarrow$	$\downarrow \downarrow$	-	$\uparrow\uparrow\uparrow$
Insulin	$\downarrow \downarrow \downarrow \downarrow$	ተተ/ተተ	$\uparrow \uparrow \uparrow \uparrow$	$\uparrow\uparrow$
SLGT2 Inhibitor	$\downarrow$	-/↓	-	$\uparrow\uparrow\uparrow$
Sulfonylurea	$\downarrow \downarrow \downarrow$	$\uparrow\uparrow$	$\uparrow \uparrow$	$\uparrow$
Thiazolidinedione	$\downarrow\downarrow\downarrow$	$\uparrow$		$\uparrow \uparrow$



# Medication Options: Comorbidities (sample)

- Cardiovascular disease: empagliflozin, liraglutide
- Polycystic Ovary Syndrome (PCOS): metformin
- Liraglutide: weight loss (Marketed as Saxenda)
  - Same as Victoza but dosed higher at 0.6-3mg/day



- Heart Failure: avoid Thiazolidinediones
- Osteoporosis/fracture risk: avoid Thiazolidinediones and SGLT2 Inhibitors
- Liver disease: avoid metformin
- Pancreatitis: avoid GLP-1 Receptor Agonists



# Medication Options: Pregnancy

Medication	Pregnancy Category	Breastfeeding
Metformin	В	Enters breast milk
Alpha Glucosidase Inhibitor	В	Unknown; avoid
Amylin Analog	C	Unknown; use caution
DPP-4 Inhibitor	Unknown/B for saxagliptin	Unknown
GLP-1 Receptor Agonist	C may cause fetal harm	Unknown; use caution
Insulin	B/C	Generally safe/Unknown
SLGT2 Inhibitor	C/Ertugliflozin & Empalgiflozin not recommended during 2 <sup>nd</sup> and 3 <sup>rd</sup> trimester	Unknown
Sulfonylurea	C	Unknown
Thiazolidinedione	C; Limited Data	Limited Data; discontinue



# **Medication Options: Patient Preference**

- Patient Engagement
  - Clear Communication
  - Health Literacy Universal Precautions
  - Explain risks & benefits of therapeutic options



# Medications

- GLP-1 Receptor Agonists
- DPP-4 Inhibitors
- SGLT2 Inhibitors
- Sulfonylureas
- Thiazolidinediones
- Newer Basal Insulins

# Glucagon Like Peptide-1 Receptor Agonist





## Glucagon Like Peptide-1 (GLP-1) Receptor Agonist



Albiglutide (Tanzeum®) – withdrawn

Dulaglutide (Trulicity®)

Exenatide (Byetta®)

Exenatide (Bydureon®)

Liraglutide (Victoza®)

Lixisenatide (Adlyxin®)

Semaglutide (Ozempic®)



# **GLP-1** Receptor Agonist Benefits







#### **GLP-1** Receptor Side Effects





# **GLP-1** Receptor Agonist Dosing

Medication	Starting Dose	Maximum Dose
Albiglutide	30mg weekly	Increase to 50mg weekly
Dulaglutide	0.75mg weekly	Increase to 1.5mg weekly
Exenatide	5mcg Q12 hours 60 minutes before meals	Increase to 10mcg after 1 month
Exenatide weekly	2mcg weekly	
Liraglutide	0.6mg daily x 7 days	1.8mg daily
Lixisenatide	10mcg daily	20mcg daily after 14 days
Semaglutide	0.25mg weekly	1mg weekly

Avoid using with patients who have family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.



# **GLP-1** Receptor Agonist Dosing

Exenatide:CrCl 30-50:Use caution<br/>CrCl <30: Not recommended</th>Lixisenatide:CrCl <15: Not recommended</td>No change for other GLP-1 Receptor Agonists

No dose adjustment



# Weekly Doses

Bob is a 48 year old man with type 2 diabetes for six years. He is takign glipizide 10mg BID, metformin 1000mg BID, and exenatide 2mg weekly every Monday.

He calls on Thursday and tells you that he forgot to take his exenatide and wants to know what he should do?

Should he take it now or just wait until Monday?



# **GLP-1** Agonists

 Missed weekly doses: take when remembered if ≤ 3 days of the next dose (semaglutide may be administered within 5 days)

• Switching days: after at least 4 days of last dose







# **DPP-4** Inhibitors





## **GDPP-4** Inhibitors




### **GDPP-4** Inhibitors

#### **DPP-4** Inhibitor



Do not use GLP-1 Receptor Agonists and DPP-4 inhibitors together.

GLP-1 Receptor Agonists are not affected by DPP-4.

Combining DPP-4 Inhibitors and GLP-1 Receptor Agonists do not provide additional A1C lowering, but does increase the risk of side effects.

**GLP-1** Receptor Agonist



# Dipeptidyl Peptidase-4 (DPP-4) Inhibitors





#### **DPP-4** Inhibitors Benefits and Risks



#### Increased Risk of Heart Failure with Saxagliptin and Alogliptin

FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin

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This is an update to the FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drug saxagliptin (marketed as Onglyza and Kombiglyze XR) issued on February 11, 2014.

[4-5-2016] A U.S. Food and Drug Administration (FDA) safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. Heart failure can result in the heart not being able to pump enough blood to meet the body's needs. As a result, we are adding new warnings to the drug labels about this safety issue.





# **DPP-4** Inhibitors Dosing

Medication	Starting/Usual Dose	Modify Dose if:
Saxagliptin	2.5-5mg daily	GFR ≤45 – 2.5mg daily Strong CP450 3A4/5 inhibitors – 2.5mg daily
Alogliptin	25mg daily	CrCl ≥30 but < 60 - 12.5mg daily CrCl <30 - 6.25mg daily
Linagliptin	5mg daily	
Sitagliptin	100mg daily	CrCl ≥30 but <50 - 50mg daily CrCl <30 - 25mg daily



- Robert is a 52 year old man with type 2 diabetes for 11 years and hypertension. He had an MI two years ago. He is taking metformin 1,000mg BID, glipizide 10mg BID, and saxagliptin 5mg daily.
- A1C is 8.4% (Target A1C is 7-8)
- Refuses to use an injectable medication
- What treatment options does Robert have?





# Sodium Glucose Co Transporter 2 Inhibitors



Canagliflozin (Invokana®)

Dapagliflozin (Farxiga®)

Empagliflozin (Jardiance®)

Ertugliflozen (Steglatro®)



# SGLT2 Inhibitors





#### SGLT2 Inhibitors Benefits





#### SGLT2 Inhibitors Risks







#### SGLT2 Inhibitors Risks: Ketoacidosis



# SGLT2 Inhibitors

Medication	Starting/Usual Dose	Max Dose
Canagliflozin	100mg daily before the first meal	300mg daily
Dapagliflozin	5mg daily with or without food	10mg daily
Empagliflozin	10mg daily with or without food	25mg daily
Ertugliflozin	5mg daily	15mg daily



# SGLT2 Inhibitors

Medication	Renal Dosing
Canagliflozin	GFR 45-60: max dose 100mg/day GFR <45: do not initiate GFR <30: do not use
Dapagliflozin	GFR <60: do not initiate GFR 30-60: not recommended GFR <30: do not use
Empagliflozin	GFR <45: do not use
Ertugliflozin	GFR <30: do not use



# Sulfonylureas/Meglitinides

Sulfonylurea	Starting Dose	Max Dose	Duration
Tolbutamide	0.25-3g divided doses	2-3g	6-12 hours
Tolazamide (Tolinase®)	0.1-1g single or divided doses	0.75-1g (500mg BID)	10-14 hours
Chlorpropamide	0.1-0.5g single dose	0.5g	72 hours
Tolbutamide	0.25-3g divided doses	2-3g	6-12 hours
Glyburide (Diabeta®, Micronase®)	1.25-10mg daily (single or divided dose)	20mg daily	24 hours
Glyburide (Glynase®)	0.75-12mg daily	12mg daily	
Glipizide (Glucotrol® Glucotrol XL®)	2.5-20mg daily (single or divided dose)	40mg (20mg if XL)	12-16 hours
Glimepiride (Amaryl®)	1-4mg daily	8mg daily	24 hours
Repaglinide (Prandin®)	0.5-4mg before meals	16mg per day	2-3 hours
Nateglinide (Starlix®)	120mg before meals	120mg	2-3 hours



#### Sulfonylurea Effects





# Thiazolidinediones (TZD)



#### Pioglitazone (Actos®)



Rosiglitazone (Avandia ®)

Medication	Starting/Usual Dose	Max Dose
Pioglitazone	15mg daily	30-45mg daily
Rosiglitazone	4mg daily	8mg daily

May take up to 12 weeks for maximal A1C lowering to occur



#### Thiazolidinedione Benefits





#### Thiazolidinedione Risks







Bladder Cancer (pioglitazone)

#### May stimulate ovulation in

premenopausal anovulatory women





# **Basal Insulin**

- Intermediate Acting
  - NPH
- Long Acting
  - Glargine (Lantus®, Basaglar®)
  - Detemir (Levemir®)
- Ultra Long Acting
  - Glargine U300 (Toujeo®)
  - Degludec (Tresiba®)





# What makes insulin different?

- How long it takes to work (onset)?
- When (if) the insulin spikes (peak)?
- How long it works (duration)?



• How concentrated is the insulin?





#### **Insulin Concentrations**

#### U-100 U-200 U-300 U-500



1mL U-100 contains 100 units of insulin 1mL U-200 contains 200 units of insulin 1mL U-300 contains 300 units of insulin 1mL U-500 contains 500 units of insulin





#### Intermediate Acting Insulin



Type of Insulin	Onset	Peak	Duration
NPH	1-2 hours	4-12 hours	12-16 hours



## Long-Acting Insulin



Type of Insulin	Onset	Peak	Duration
Glargine (Basaglar®, Lantus ®)	1-2 hours	None	20-26 hours
Detemir (Levemir®)	1-2 hours	6-8 hours	18-24 hours



# Ultra-Long-Acting insulin

- Steady insulin levels for over 24 hours
- Injected once daily
- May be combined with short-acting insulin to cover meals

Type of Insulin	Onset	Peak	Duration
Glargine U300 (Toujeo®)	1-2 hours	None	Up to 36 hours
Degludec (Tresiba®)	30-90 min	None	>42 hours



# Insulin Glargine U300 (Toujeo®)

- 1ml of Glarine U100 contains 100 units
- 1ml of Glargine U300 contains 300 units





### Insulin Degludec (Tresiba®)

- Available as:
  - U100 (100 units/mL)
  - U200 (200 units/mL)
- Good for 8 weeks after opening







#### What to do with other medications when starting Insulin?





#### What to do with other medications when starting Insulin?

- Metformin: Recommend that it be continued
- Sulfonylureas: questionable benefit
- **TZD**: May increase risk of edema and weight gain; may reduce insulin resistance
- SGLT2 Inhibitors: Lower risk of hypoglycemia compared with other agents and less weight gain
- **DPP4 Inhibitors**: Modest A1C lowering; may be weight neutral
- **GLP-1 Agonist**: Can reduce A1c and body weight; longer acting have more effect than shorter acting; low risk of hypoglycemia



- Patricia is a 63 year old woman with type 2 diabetes for eight years.
- She is taking metformin 1000mg BID and glipizide10mg BID.
- She was started on saxagliptin 5mg 3 months ago with no change in A1C.
- Her doctor started insulin detemir 10 units at bedtime.
- Her last A1C is 8.6
- Today her A1C is 8.7
- What is the next step?



# Drugs don't work if.... ...people don't take them!

#### **Medication Adherence**



100 Prescriptions written

88 are filled at the pharmacy

76 are taken by the patient

49 are refilled after the prescription runs out



### **Medication Adherence**

• Proportion of Days Covered (PDC)



#### Total days must be $\geq 80\%$ (> 292 days supply)



### Proportion of Days Covered





# Gaps in Therapy





# Addressing Adherence

- Simplify the regimen
- Impart knowledge
- Modify patient beliefs and human behavior
- Provide communication and trust
- Leave the bias
- Evaluate adherence







# Thank you!



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#### Resources

- Division of Diabetes Treatment and Prevention <u>https://www.ihs.gov/diabetes/</u>
- Continuing Education <a href="https://www.ihs.gov/diabetes/training/">https://www.ihs.gov/diabetes/training/</a>
- Diabetes Listserv <u>https://www.ihs.gov/diabetes/ihs-diabetes-listserv/</u>



