New Drugs in the Management of Type 2 Diabetes

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Disclosure

I am or have been on the speaker’s bureaus for multiple pharmaceutical companies:

- Abbvie
- Astra-Zeneca
- Boehringer
- BMS
- Genzyme
- GSK
- Janssen
- Merck
- Novo-Nodisk
- Sanofi
- Veracyte
Outline

1. Background
2. Overview of diabetes treatment options
3. Discussion of newer classes of diabetes treatments and new additions to older classes
4. Recommendations for optimal diabetes treatments
5. Review current guidelines for management of Type 2 DM, and their limitations
Background
Diabetes is currently at epidemic levels in our country
Diabetes Mellitus in the US: Overview

Prevalence
- 25.8 million Americans (8.3% of the population)
  - 18.8 million diagnosed
  - 7 million not diagnosed
- Affects 27% of US population over 65 yrs of age

Incidence
- 1.5 million new cases diagnosed yearly
- Leading cause of
  - Blindness in adults
  - End-stage renal disease
  - Non-traumatic amputations
- Healthcare costs $172 billion annually

90% to 95% of cases are type 2 diabetes

Ref: National Diabetes Information Clearinghouse (NIDDK), 2011
What Is the Lifetime Risk for Diabetes for People Born in the United States in 2000?

1 of 3 Americans

1 of 2 Hispanic females

2 of 5 African Americans and Hispanics

Diabetes and Gestational Diabetes Trends Among Adults in the United States: Behavioral Risk Factor Surveillance System (BRFSS) 2006

Adapted from Mokdad AH et al. JAMA. 2003;289:76-79.
Root Cause: Obesity

- Over the past 50 years, two trends have contributed to the obesity epidemic:
  - More eating out
    - More calorie-dense foods
    - Resulting in 168-kcal/day excess intake in men and 335-kcal/day excess intake in women over past 30 yr
  - Less activity
    - Substantial decrease in calories burned per day

RH Unger, JAMA 299(10): 1185-1186
As a result, over 2/3 of the US population is overweight or obese.
Role of Insulin Secretion Defect in Type 2 Diabetes

Adapted from Bergenstal et al. 2000; International Diabetes Center.
Approximately 50% of β-Cell Function Has Already Been Lost at Diagnosis of Type 2 Diabetes

* Dashed line shows extrapolation backward from year 0 and forward from year 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS.
† The data points for the time of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model.
► All oral agents are “budget stretchers” for insulin

► The balance is decreasing, and eventually the account will run dry
However, there is no need to run to insulin at the onset of type 2 DM.

The non-insulin agents are convenient, and have certain other advantages.

But NEVER avoid insulin when it is needed!!
Diabetes Medications
Oral Meds for Type 2

- **Sulfonylureas:**
  - glipizide (Glucotrol)
  - glyburide (Glynase, Micronase)
  - glimepiride (Amaryl)

- **Biguanides:**
  - metformin (Glucophage)
  - metformin ER (Glucophage XL)

- **TZDs:**
  - pioglitazone (Actos)

- **Meglitinides:**
  - repaglinide (Prandin)
  - nateglinide (Starlix)

- **Alpha-glucosidase inhibitors:**
  - acarbose (Precose)
  - miglitol (Glyset)
Oral Meds for Type 2

- **DPP-4 inhibitors:**
  - sitagliptin (Januvia)
  - saxagliptin (Onglyza)
  - linagliptin (Tradjenta)
  - alogliptin (Nesina)

- **Bile acid sequestrant:**
  - colesevelam (Welchol)

- **Dopamine-agonist:**
  - bromocriptine (Cycloset)

- **SGLT-2 inhibitors:**
  - canagliflozin (Invokana)
  - dapagliflozin (Farxiga)
  - empagliflozin (Jardiance)

- **Various combination products**
GLP-1 mimetics:
- exenatide (Byetta, Bydureon)
- liraglutide (Victoza)
- albiglutide (Tanzeum)
- dulaglutide (Trulicity)

Amylin analog:
- pramlintide (Symlin)
**Injectable meds for Type 2**

- **Insulin**
  - Ultra-long acting basal
    - Degludec (Tresiba)
    - Concentrated glargine (Toujeo)
  - Long-acting basal:
    - Glargine (Lantus), detemir (Levemir)
  - Intermediate-acting
    - NPH
  - Rapid-acting at mealtime:
    - lispro (Humalog), aspart (Novolog), glulisine (Apidra)
  - Used less often, but available:
    - Regular instead of rapid-acting at mealtime
      - Timed 30-45 minutes before meals
    - Combinations: 75/25, 70/30, 50/50, with limited flexibility
► OK...

► ... how do I fit these together?
Goals of glycemic control

- ADA recommends a general A1C target of <7%
- The goal of therapy for the individual patient is to achieve an A1C as close to normal (<6%) as possible without hypoglycemia
- More stringent glycemic goals may reduce the risk of serious diabetes-related complications
- Less stringent treatment goals may be appropriate for certain patient populations and patients with severe or more frequent hypoglycemia
  - ACCORD
- ALARA
T2DM treatment strategies revisited

*Individualise

Adapted from Riddle M. Endo Metab Clin NA 1997;26:659–77.
Incretins
Incretins

- **GLP-1 agonists**
  - Exenatide
    - immediate-release (Byetta)
    - extended release (Bydureon)
  - Liraglutide (Victoza)
  - Albiglutide (Tanzeum)
  - Dulaglutide (Trulicity)

- **DPP-4 inhibitors**
  - sitagliptin (Januvia)
  - saxagliptin (Onglyza)
  - linagliptan (Tradjenta)
  - alogliptin (Nesina)
Explains why the insulin response to an oral glucose load is greater than the response to an equivalent amount of IV glucose infusion.

Approximately 60% of post-meal insulin secretion is due to the effects of incretins.¹

These effects are diminished in patients with type 2 diabetes.²


The Incretin Effect in Healthy Subjects

N = 6; Mean (SE); *P ≤ 0.05
Data from Nauck MA, et al. J Clin Endocrinol Metab. 1986;63:492-498
The best characterized incretins are:
- Glucagon-like peptide-1 (GLP-1)
- Glucose-dependent insulinotropic peptide (GIP)
GLP-1

- Secreted from L cells of the intestines
- Most well-characterized incretin
- Levels are decreased in type 2 diabetes

- GLP-1 acts by binding to specific receptors on the surface of the beta cell, as well as other tissues, and has a very short half-life (less than 2 minutes in the circulation)
- GLP-1 is the signal to body that food has arrived
GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

Beta cells: Enhances glucose-dependent insulin secretion

Exenatide Reduced Beta-Cell Workload in Type 2 Diabetes

Data from Kolterman OG, et al. J Clin Endocrinol Metab. 2003;88:3082-3089

N = 20; Mean (SE)

Plasma Glucagon (pg/mL)

Plasma Glucose (mg/dL)

Time (min)

Standardized Breakfast Exenatide or Placebo

Standardized Breakfast Exenatide or Placebo
GLP-1 agonists: Exenatide

- Exenatide is derived exendin-4, which is found in Gila Monster saliva
- Mimics GLP-1
  - Longer serum half-life
- Leads to increased *regulated* insulin release
  - Low risk for hypoglycemia if not used with SU or insulin
GLP-1 agonists: Exenatide

- **Contraindications**
  - Gatroparesis
  - Chronic nausea or vomiting / motility issues
    - Use of metoclopramide / motility agents
  - History of pancreatitis
  - GFR < 30

- **Precautions**
  - Chronic diarrhea
  - IBS
  - GFR < 60
Immediate-release exenatide

- Dose 30-60 minutes before a meal
  - Less nausea, more weight loss
- Inform patient that they should expect to eat less
  - Some have never felt full before
Advantages
- Dose once per week, with at least 3 days between doses
- Slowly builds up in system, so less nausea than IR
- More potent than IR in terms of A1c and FBS

Disadvantages
- Larger needle than IR
- Takes a while to mix
- Leaves small nodule under skin for several weeks
- Black box warning about risk of thyroid tumors in rats
- Contraindicated if h/o medullary thyroid CA or MEN-2
GLP-1 agonists: Liraglutide

- **Advantages**
  - Once per day injection
  - Slightly stronger than ER exenatide and albiglutide
  - Less nausea than IR exenatide, more than ER exenatide
  - Already in solution; no mixing needed
  - Easy to inject, small needle

- **Disadvantages**
  - Black box warning about risk of thyroid tumors in rats
  - Contraindicated if h/o medullary thyroid CA or MEN-2
GLP-1 agonists: Liraglutide

- A long-term CV trial (LEADER) was recently completed and top-line results indicate superiority of liraglutide over usual diabetes care for all 3 components of the endpoint (MACE)
  - CV death
  - Nonfatal MI
  - Nonfatal stroke
GLP-1 agonists: Albiglutide

- **Advantages**
  - Once per week injection
  - Less nausea than other GLP-1 agents

- **Disadvantages**
  - Not as potent as liraglutide
  - Takes a while to mix
  - Black box warning about risk of thyroid tumors in rats
  - Contraindicated if h/o medullary thyroid CA or MEN-2
GLP-1 agonists: Dulaglutide

- **Advantages**
  - Once per week injection
  - At least as potent as liraglutide
  - Already in solution; no mixing needed
  - Very easy to inject, small needle

- **Disadvantages**
  - Increased HR (2-4 bpm) and sinus tachycardia
  - Increased PR interval (2-3 ms) and first degree AV block
  - Black box warning about risk of thyroid tumors in rats
  - Contraindicated if h/o medullary thyroid CA or MEN-2
Oral incretins: DPP-4 inhibitors

- DDP-4 is enzyme on surface of most cells that deactivates many peptides, including GIP & GLP-1
- Oral inhibitors of DPP-4 have been developed
  - sitagliptin (Januvia)
  - saxagliptin (Onglyza)
  - linagliptin (Tradjenta)
  - Alogliptin (Nesina)
- Not as potent as GLP-1 agonists, but lack the GI side effects
- Still give regulated increase in insulin secretion
  - Low risk of hypoglycemia unless used with SU or insulin
Incretins Are Degraded by DPP-4

DPP-4 enzyme

Active GLP-1 and GIP

Rapid inactivation

Inactive metabolites

Oral incretins: DPP-4 inhibitors

- Very clean side effect profile
  - No major hypoglycemia
  - No effect on weight

- Sitagliptin, saxagliptin and alogliptin dose needs to be decreased with decreasing renal function
  - But OK to use through ESRD

- Pancreatitis risk is same as with GLP-1 agonists

- Minor increase in CHF seen with saxagliptin and alogliptin but not with sitagliptin
SGLT-2 inhibitors
SGLT-2 inhibitors

- Canagliflozin, dapagliflozin and empagliflozin

Mechanism of action
- Blocks sodium-glucose cotransporter-2 in the proximal convoluted tubule
- Blocks reabsorption of glucose from the urine back into the blood
- No effect on insulin production
- Lose lots of sugar (and about 400 calories per day) into the urine
SGLT-2

= glucose
SGLT-2 inhibitor = SGLT-2 inhibitor
-glucose = glucose
SGLT-2 inhibitors: Canagliflozin

Dose

- Start at 100 mg daily before breakfast
- Increase to 300 mg daily as needed
- Limited to 100 mg daily if GFR 45-59 (CKD 3A)
SGLT-2 inhibitors: Dapagliflozin

- **Dose**
  - Start at 5 mg daily before breakfast
  - Increase to 10 mg daily as needed
  - Contraindicated if GFR < 60 (CKD 3)
SGLT-2 inhibitors: Empagliflozin

- **Dose**
  - Start at 10 mg daily before breakfast
  - Increase to 25 mg daily as needed
  - Contraindicated if GFR < 45 (CKD 3B)
EMPA-REG study showed a significant mortality benefit from this drug

- Primary endpoint was CV death, nonfatal MI and nonfatal stroke
  - RRR 14%, ARR 1.6%, NNT 63
- CV death
  - RRR 38%, ARR 2.2%, NNT 45
- CHF hospitalization
  - RRR 35%, ARR 1.4%, NNT 71
- Overall mortality
  - RRR 32%, ARR 2.6%, NNT 38
Advantages

- No increase in hypoglycemia when used alone
- Weight loss (4-6#)
- Decreases blood pressure by about 5 points
  - Basically, a diuretic effect
- Canagliflozin is more effective at max dose than sitagliptin
  - By about 50%, in terms of A1c (1.03% vs 0.66% drop)

Schernthaner G, et. al., *Diabetes Care*. 2013 Sep;36(9):2508-15
SGLT-2 inhibitors

- **Contraindications**
  - GFR < 45 (or 60 for dapagliflozin)

- **Precautions**
  - Age > 75
  - GFR 45-59 (CKD 3A)
  - Dehydration
  - Use of loop diuretics
SGLT-2 inhibitors

Side Effects

Common:
- Genital yeast infections
  - More common in women who already have frequent yeast infections and in uncircumcised men
  - Up to 15.3% in women (11% more than placebo) and 9.2% in men over 1 year
- Cystitis
  - Small increase vs. placebo
- Pyelonephritis
  - Very small increase seen
- LDL increase of about 4-8 points
- Increase in creatinine, especially in CKD 3
- Constipation, thirst, increased urination
SGLT-2 inhibitors

Side Effects

Serious:

- Orthostasis
  - More common in dehydrated, CKD and elderly (> 75 yo)
  - Especially on full dose
  - Especially if they were also on loop diuretic, ACE or ARB
  - I do advise patients to drink 1-2 glasses extra of water per day while on these medications

- Hyperkalemia
  - Especially in CKD 3

- DKA
  - NORMOGLYCEMIC (sugars do not need to be elevated)
  - Can occur in type 1 or type 2 (LADA?)
  - Mechanism not fully understood
  - Appears to be very rare in type 2
Think about insulin when

- Hemoglobin A1c is > 9%
- Quickly failing oral agents
- Suspicion of Type 1 DM
- Contraindications to oral agents
  - ESRD
  - Severe liver disease
- Steroid use
- Failing 2 or more other agents at max doses
  - Especially if failing 3 drugs

Never avoid insulin when it is indicated
By concentrating insulin glargine (U-300), an extended profile of action was achieved.

A “smoother” profile also resulted, with duration of activity of up to 36 hours post-injection.

Steady-state is achieved in 5 days.
Concentrated Insulin Glargine

Toujeo® Has a Flatter and More Prolonged PK/PD Profile than Lantus®

Copied from Google Images
Also, 67% less injection volume

However, 12-18% more insulin is required vs normal glargine

Possibly because the longer subcutaneous residence time allows more time for proteases to act

Recommended conversion is 1:1 from normal glargine or detemir

Pens available as 1350 units per box

Maximum of 80 units per dose from pen
Extended insulin activity due to
- Polymerization in the subcutaneous tissue and slow dissociation of hexamers due to release of zinc
- Binding to albumin in the blood

- Half-life is 25 hours
- Duration of action is > 42 hours
- Steady-state achieved after 3-4 days
Insulin Degludec

Relative serum trough concentrations of once-daily dosing in adults with type 1 diabetes

STeady state achieved after 3 to 4 days

Copied from Google Images
Highly extended and stable insulin activity allows for dosing flexibility

One study showed no significant difference in hypoglycemia or in A1c when injections were alternated between 40 hours and 8 hours apart vs. being given every 24 hours (!!)
Available in U-100 and concentrated (U-200) pens.

U-200 pens allow delivery of up to 160 units per injection

1500 units per box of U-100 or 1800 units per box of U-200

Pens can be used for up to 8 weeks after first use

Convert glargine or detemir doses at 1:1
Bariatric Surgery

- The “atom bomb” of diabetes therapy
- The only therapy that addresses the root cause of diabetes
  - Excess energy consumption / caloric ingestion
- Sends diabetes into **remission** over 66% of the time
  - *NOT a “cure”*
- Lots of potential side effects
- Can be a life-altering therapy
Multiple studies show this to overall be more effective at controlling blood sugar than standard medical therapy
- Swedish Obesity Study

Several studies show better CV and mortality outcomes with surgical vs medical management of DM2
- JAMA. 2015;313:62-70

Should be offered to all patients with Type 2 DM and BMI > 35
- Especially if > 40
- Maybe on less obese patients (BMI > 30) in the future
Current guidelines
Current guidelines

- American Diabetes Association (ADA)
  - Provides a menu of choices, but not much guidance

- American Association of Clinical Endocrinologists (AACE)
  - Values therapies that do not cause hypoglycemia or weight gain
  - These are major safety and compliance barriers
    - Reflects US endocrine ideal practice

- Both of these were recently revised, and revised versions are shown here

- Both agree that you start with metformin (when possible) and end with insulin
Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

Entry A1c < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- AGI
- TZD
- SU/GLN

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- AGI
- TZD
- Basal Insulin
- Colesvelam
- Bromocriptine OR
- SU/GLN

If not at goal in 3 months proceed to Double Therapy

Entry A1c ≥ 7.5%

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- AGI
- TZD
- Basal Insulin
- Colesvelam
- Bromocriptine OR
- SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPE THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- AGI
- TZD
- Basal Insulin
- Colesvelam
- Bromocriptine OR
- SU/GLN

If not at goal in 3 months proceed to or intensify Insulin therapy

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

Entry A1c > 9.0%

SYMPTOMS
NO
YES

DUAL Therapy
OR
TRIPLE Therapy

INSULIN ± Other Agents

LEGEND
- Few adverse events or possible benefits
- Use with caution

* Order of medications listed represents a suggested hierarchy of usage

PROGRESSION OF DISEASE

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## Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>DPP-4i</th>
<th>GLP-1 RA</th>
<th>TZD</th>
<th>AGI</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>SU</th>
<th>GLN</th>
<th>INSULIN</th>
<th>SGLT-2</th>
<th>PRAML</th>
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<tr>
<td><strong>HYPO</strong></td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>GLN Moderate to Severe</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
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<tr>
<td><strong>WEIGHT</strong></td>
<td>Slight Loss</td>
<td>Neutral</td>
<td>Loss</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
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<td>Gain</td>
<td>Gain</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>RENAL/GU</strong></td>
<td>Contraindicated Stage 3B,4,5</td>
<td>Dose Adjustment May be Necessary (Except Linagliptin)</td>
<td>Exenatide Contraindicated CrCl &lt; 30</td>
<td>May Worsen Fluid Retention</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>More Hypo Risk &amp; Fluid Retention</td>
<td>Infections</td>
<td>Neutral</td>
<td></td>
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<tr>
<td><strong>GI Sx</strong></td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
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<td>Mild</td>
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<td><strong>CVD</strong></td>
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<td>Safe</td>
<td>Safe</td>
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<td>Safe</td>
<td>Neutral</td>
</tr>
<tr>
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<td>Neutral</td>
<td>Moderate Bone Loss</td>
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<td>Neutral</td>
<td>Bone Loss</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

- **Few adverse events or possible benefits**
- **Use with caution**
- **Likelihood of adverse effects**

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My practice is generally similar to AACE guidelines, HOWEVER:

First step is to evaluate for **contraindications**
- Metformin in CKD, pioglitazone in CHF, etc.

Next is to evaluate **patient values / preferences**
- Desire for weight loss?
- Fear of hypoglycemia?
- Fear of injections?

Evaluate agents in this light
- We have lots of agents now, and can individualize therapy
- Get patient “buy-in”. It helps a lot with compliance

Recent CV benefits do sway things
- I favor liraglutide and SGLT-2 agents partially for this reason
Start with **metformin** (if not contraindicated)
- If intolerable diarrhea, can add colesevelam (Welchol)

Add **GLP-1 agonist** if they are willing
- If they lose weight, everything gets better (BP, lipids, etc)

Or try **SGLT-2 inhibitor** if renal function is normal

Otherwise, try a **DPP-4 inhibitor**
Start with **metformin** (if not contraindicated)
- If intolerable diarrhea, can add colesevelam (Welchol)

Add **GLP-1 agonist** if they are willing
- If they lose weight, everything gets better (BP, lipids, etc)

Or try **SGLT-2 inhibitor** if renal function is normal

Otherwise, try a **DPP-4 inhibitor**

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My view on life (continued)

- Metformin
  - Esp. needs more wt loss
  - Esp. needle phobia
  - Esp. frail, elderly, CKD

- GLP-1

- SGLT-2

- DPP-4
If FBS or A1c is very high (> 300, >9%), then consider insulin along with metformin.

- Alternative is to start metformin plus GLP-1 agonist, SGLT-2 inhibitor or DPP-4 inhibitor
- Or, metformin + SU

Consider insulin if failing 2-3 drugs at maximal doses
After starting insulin, can continue the following:

- Metformin
- Incretins
- SGLT-2 inhibitor
- Bromocriptine
- Colesevelam
- SU (with basal insulin, with caution)
My view on life – Special circumstances

- If too poor to afford co-pay but too rich for drug assistance, consider SU after metformin
  - glimepiride is the best in the SU class

- If need more LDL lowering on max tolerated dose of statin, consider colesevelam (Welchol)
If old and frail, think DPP-4 inhibitor
If CKD stage 4+, think DPP-4 inhibitor or insulin
If CHF, consider SGLT-2 inhibitor, incretin and/or insulin
Offer bariatric surgery consult to all who qualify
- BMI > 35
- especially if BMI > 40

All patients get referred to diabetic educator and dietician...
... multiple times

Weight loss and exercise are KEY in type 2 DM therapy
- But if it was easy, we’d all be thin.
“Mr. Osborne, may I be excused? My brain is full.”
END
Complications-Centric Model for Care of the Overweight/Obese Patient

**Step 1: Evaluation for Complications and Staging**

**Cardiometabolic Disease**
- **No Complications**
  - BMI 25–26.9, or BMI ≥ 27

**Biomechanical Complications**
- **BMI ≥ 27 with Complications**
  - Stage Severity of Complications
    - Low
    - Medium
    - High

**Step 2: Select:**

- **Lifestyle Modification:**
  - MD/RD counseling; web/remote program; structured multidisciplinary program

- **Medical Therapy:**
  - Phentermine; orlistat; lorcaserin; phentermine/topiramate ER

- **Surgical Therapy (BMI ≥ 35):**
  - Lap band; gastric sleeve; gastric bypass

**Step 3:**

If therapeutic targets for improvements in complications not met, intensify lifestyle and/or medical and/or surgical treatment modalities for greater weight loss

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