Updates in Therapeutics® 2015:

The Pharmacotherapy Preparatory Review & Recertification Course

Endocrine and Metabolic Disorders

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Conflict of Interest Disclosures

Dr. Irons has no conflicts of interest to disclose

Learning Objectives / Agenda

- **Review Diagnosis, Classification, Therapeutic agents, Treatment / Monitoring in Endo/Metabolic Disorders**

- Thyroid Disorders
  - Hypo-, Hyperthyroidism, Thyroid Storm
- Pituitary Disorders - Hyperprolactinemia
- Adrenal Disorders
  - Cushing's Disease, Hyperaldosteronism
- Obesity
- Diabetes Mellitus

Thyroid Disorders

Hyperthyroid Disorders

- Graves Disease
  - Autoimmune Disorder / Antibodies mimic TSH and stimulate T3 and T4 synthesis/release
- Thyroid Storm
- Pituitary Adenomas
  - Excessive TSH secretion with no shut off by negative feedback mechanisms
- Toxic Adenoma, Toxic Multinodular Goiter
- Painful Subacute Thyroiditis
- Drug-Induced (amiodarone, thyroid replacement tx)

Hyperthyroid Labs / Diagnosis

- Free T4 and TSH tell most of the story
- Graves Disease
  - Low TSH, elevated free T4

- TSH and T3/T4 elevated in pituitary adenomas
- Thyroid antibodies
- Radioactive iodine uptake

Hyperthyroid Clinical Presentation

- Appetite increased
- Weight loss
- Goiter
- Heat intolerance
- Fine hair
- Palpitations / tachycardia
- Anxiety / insomnia / nervousness
- Moist skin / sweating
- Exophthalmos (bulging eyes)

Thyroid Disorder: Goals

- Improve quality of life
- Minimize or eliminate symptoms
- Minimize long-term damage
- Normalize free T4 / TSH

Patient Case 1

43-year-old woman has diagnosis of Graves' disease. Does not want to undergo ablative therapy and wants to try medications instead. TSH = 0.22 mIU/L (0.5-4.5), free T4 = 3.2 ng/dL (0.8-1.9). Complaints of feeling anxious and warm.

Which if the most appropriate initial option?

a. Lugol's solution
b. Propylthiouracil
c. Atenolol
d. Methimazole

Treatment of Hyperthyroidism (Graves)

- Treatment of choice: ablative therapy with radioactive iodine
  - Surgical resection for most adenomas
- Pharmacotherapy reserved for:
  - Awaiting ablative therapy or surgery (depletes stored hormone)
  - Not a surgical or ablative candidate (or refuses)
  - If ablative therapy or surgery fails to normalize thyroid function

Thioureas (aka Thioamides)

- Propylthiouracil (PTU) and Methimazole
- Inhibit iodination and synthesis of thyroid hormones
- Efficacy
  - Methimazole is preferred agent (based on ADR profile)
  - Monthly dose titrations (guided by symptoms / TSH)
  - Low remission rate: 40-50% (1-2 years on therapy)
  - May take weeks for symptomatic improvement
  - 4-6 months for maximal effect
  - Neither drug appears more effective than the other
  - Mg-Mg: methimazole is 10x more potent

Thioureas (aka Thioamides): ADRs

- Hepatotoxicity with PTU (boxed warning): Obtain baseline LFTs
- Arthralgias
- Fever
- Rash
- Transient leukopenia
- Agranulocytosis: Obtain baseline CBC

Other Agents used in Hyperthyroidism

- **Beta-blockers**: Primarily for symptomatic improvements (e.g. propranolol/nadolol) (tachycardia / anxiety / tremor / palpitations)
  - Recommended in elderly, symptomatic patients or those with heart rates > 90 bpm

- **Iodines**: (Lugol's solution / SSKI)
  - Block release (not synthesis) of hormone / May help in reducing size and vascularity of gland prior to surgery
  - Only used short-term (1-2 weeks): Gland will eventually begin to leach hormone

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Thyroid Storm Therapy

- Life-threatening thyrotoxicosis
- Infection / Trauma common causes
- Fever / Tachycardia / N-V / Dehydration / Delirium / Tachypnea / Coma

Thyroid Storm Therapy

- PTU: 500-1000 mg loading dose, then 250 mg every 4 hours
- Iodide treatment: After PTU initiated
- Beta-blocker: (e.g. esmolol / propranolol)
- APAP: (avoid NSAIDs)
- Corticosteroid tx: 25-100 mg prednisone or equivalent

Hypothyroid Disorders

- Hashimoto's Disease
  - Autoimmune mediated
- Iatrogenic: Surgery / Ablative Therapy
- Iodine Deficiency
- Secondary Causes
  - Pituitary Insufficiency – Lack of TSH secretion
  - Drug-Induced: amiodarone, lithium

Hypothyroid Labs / Diagnosis

- Free T4 and TSH again tell most of the story
- Hypothyroid: High TSH (lack of negative feedback), suppressed free T4
  - TSH may be low or normal in secondary causes (e.g. pituitary cause)
- Thyroid antibodies
- Screen in 60+ (especially women)
  - Differing consensus recommendations

Hypothyroid Clinical Presentation

- Weight gain
- Dry skin
- Cold intolerance
- Weakness / fatigue / lethargy
- Bradycardia
- Slow reflexes
- Coarse skin / hair

Patient Case 2

63-year-old woman has Hashimoto's disease.
Recent TSH = 10.6 mIU/L (0.5-4.5) and free T4 = 0.5 ng/dL (0.8-1.9).

Complains of dry skin and being rundown.

What is the best drug for initial treatment?

a) Levothyroxine
b) Liothyronine
c) Desiccated thyroid
d) Methimazole

Hypothyroid Pharmacotherapy

- Drug of Choice: Synthetic T4 (levothyroxine)
  - Cost / antigenicity profile / potency / ADR profile
- Initial dose: (a.m. 30-60 minutes before food)
  - 1.6 mcg/kg/day (IBW) in otherwise health adult
  - 50 mcg/day in those 50-60 years of age
  - 12.5-25 mcg/day in those with CVD
- Titrate (~ 4-8 weeks) based on T4/TSH and symptoms (~ 7 day half life)
- ADRs: Hyperthyroidism / angina / MI / bone fracture risk

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Myxedema Coma

- Misnomer as coma is uncommon / not required for diagnosis
- Life-threatening / severe hypothyroidism
- Causes: Trauma, HF, infection, medications
- Presentation
  - Mental status changes / elevated DBP / hypothermia / hypoventilation

Myxedema Coma

- IV Thyroid Hormone Replacement
  - T4 (lower initial doses in those with CAD or frailer patient)
  - T3 – T4 to T3 conversion may be suppressed so some advocate for T3 instead of T4 replacement
    - Higher Cost and Availability may limit its use
- Fix cause if known (antibiotics if infectious)
- Corticosteroid therapy

PITUITARY DISORDERS

Pituitary Disorders

- Hypersecretory
  - Acromegaly and Gigantism – Pituitary adenoma secreting excess Growth Hormone (GH)
  - Hyperprolactinemia
    - Prolactin-secreting pituitary tumor
    - Drug-Induced: SSRI, antipsychotics
    - CNS lesion
- Hyposecretory
  - GH Deficiency
  - Panhypopituitarism

ADRENAL DISORDERS

ADRENAL DISORDERS

Treatment Goals

- Reduce Morbidity and mortality
- Eliminate Cause (if known)
- Reverse clinical features
- Normalize biochemical changes
- Remission or long-term control without reoccurrence

Adrenal Disorders Classification

- **Hypersecretory**
  - ACTH-Dependent
    - Cushing's Disease – Pituitary adenoma / excessive ACTH secretion
    - Ectopic ACTH secreting tumor
  - ACTH-Independent
    - Adrenocortcial tumor
    - Adrenal hyperplasia
    - Excessive exogenous steroid intake
  - Hyperaldosteronism
- **Hyposecretory**
  - Addison's Disease – poor cortisol/aldosterone/androgen production
  - Exogenous steroid use / surgery / trauma

Patient Case 4

44-year-old man with consistently elevated blood pressure (172/98) despite 2 BP agents. Complains of HA, thirst, fatigue. Urine free-cortisol is 45mcg/24 hr (20-90) and plasma aldosterone: renin is 125 (<25). Which of the following is the most likely cause of his BP?

a. Cushing's disease
b. Addison's disease
c. Hyperprolactinemia
d. Hyperaldosteronism

Adrenal Disorders: Cushing's Disease

- Clinical Presentation
  - Central obesity / facial rounding
  - Peripheral obesity / fat accumulation
  - Myopathies
  - Osteoporosis / back pain / fracture
  - Glucose intolerance / diabetes
  - HTN

Adrenal Disorders: Cushing's Disease

- Treatment of choice:
  - Surgical resection
- Pharmacotherapy reserved
  - Not a surgical candidate
  - Prior to surgery
  - Surgical failure

Adrenal Disorders: Cushing's Disease Pharmacotherapy

- Block pituitary ACTH secretion
  - Pasireotide: somatostatin analogue (improved selectivity to pertinent somatostatin receptors than other analogs)
  - Significant ADR profile
    - Hyperglycemia, bradycardia, gallstones, HA
    - Baseline EKG, glucose, A1c, LFTs, gallbladder ultrasound

Adrenal Disorders: Cushing's Disease Pharmacotherapy

- Block adrenal cortisol production
  - Ketoconazole, Mitotane, Etomidate (IV reserved for rapid cortisol level control or po not an option)
- Treatment success measured by signs/symptom improvement and urine cortisol concentrations
- Treat sign/symptoms: BP, glucose, obesity, etc
  - Mifeprisone for Cushing's hyperglycemia

Adrenal Disorders: Hyperaldosteronism

- Primary aldosteronism
  - Bilateral adrenal hyperplasia: 70% of cases
  - Aldosterone-producing adenoma: 30% of cases
- Diagnosis / Clinical Presentation
  - Elevated plasma aldosterone:renin
  - Hypernatremia / hypokalemia / hypomagnesmia
  - HTN / HA / Muscle fatigue or weakness / Polydipsia / Nocturnal polyuria

Adrenal Disorders: Hyperaldosteronism

- Treatment
  - Aldosterone antagonists
    - Spironolactone (drug of choice) or Eplerenone
    - Hyperkalemia / Gynecomastia / GI discomfort
  - Amiloride
- Monitor
  - BP
  - Electrolytes
  - Symptomatic relief
  - Plasma aldosterone:renin

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Obesity

Recent Guidelines

- American College of Cardiology / American Heart Association
  - First significant guidelines since 1998
  - Very limited in pharmacotherapy
  - Stopped input in 2011, newer medications approved in 2012+
- Endocrine Society: Feb 2015
  - Pharmacotherapy focus
  - Good general overview of agents, no one agent stands out

Obesity - Classification

Classification	BMI
Normal	18.5-24.9
Overweight	25.0-29.9
Class I	30.0-34.9
Class II	35.0-39.9
Class III	40+

Patient Case 5

A patient is taking the maximum dose of phentermine/topiramate for obesity. Baseline BMI is 36 kg/m^2 and weight 255 lb. What is minimal weight loss expected to consider continuation of therapy after 12 weeks?

a. 7 lbs
b. 13 lbs
c. 17 lbs
d. 26 lbs

Obesity Guideline
Medication Recommendations

- Diet / Exercise always cornerstone of therapy
- Medications Reserved For:
  - Not achieving / sustaining weight reduction with adequate lifestyle modifications and:
  - Obese or,
  - BMI 27+ kg/m^2 with significant weight-related comorbidities (diabetes, hypertension)

Obesity Therapy

- Orlistat – Inhibits gastric and pancreatic lipases >> reduced fat absorption
  - Rx (Xenical): 120 mg three times daily (up to 1 hour prior to meals)
  - OTC (Alli): 60 mg three times daily (up to 1 hour prior to meals)
  - LOTS GI ADRs: flatulence, oily stool, loose stool
  - FDA 2012: Increased risk for kidney stones/liver injury

Obesity Therapy

- Lorcaserin (approved 2012)
  - Selective serotonin 2C agonist
  - ADRs: HA, dizziness, nausea, dry mouth, constipation, memory disturbances, hypoglycemia (in diabetes)
  - Efficacy: ~46% attain 5% wt loss, ~23% 10% loss (good A1c reduction in patients with diabetes)
  - Avoid use if also taking serotonergic agents (e.g. SSRIs)
  - Stop if < 5% weight loss after 12 weeks

Obesity Therapy

- Phentermine/extended-release topiramate (approved 2012)
  - ADRs: parathesia, dry mouth, constipation, insomnia, memory disturbances, dysgeusia, increased heart rate
  - Efficacy: 60+% attain 5% wt loss, 35-45% 10% loss
  - Women of childbearing age must have negative pregnancy test before and monthly after starting
  - Had been restricted to specific pharmacies
  - Stop if < 5% weight loss after 12 weeks of higher doses

Obesity Therapy

- Liraglutide (approved late 2014)
  - GLP-1 analog - Dosage is different than use in T2DM (3 mg once daily)
  - Similar precautions / contraindications as with DM formulation
  - Available in pre-filled, multi-dose pens
  - Similar GI side effects (N/V)
  - Initiate at 0.6 mg once daily (subcutaneous)
  - Increase weekly in 0.6 mg increments to attain 3 mg daily (lower doses not as effective for weight loss)

Not in Chapter

Obesity Therapy

- Naltrexone/Bupropion (approved Fall 2014)
  - Extended-release formulation
  - Weekly dose titration over four weeks to improve tolerability / limit ADRs
  - Reduce dose in moderate/severe renal impairment
  - ADR profile: nausea, constipation, HA, vomiting, insomnia, dry mouth, increased BP/pulse
  - Contraindications: seizure DO, uncontrolled HTN, eating DO, chronic opioid use, concurrent use of other products containing naltrexone or bupropion

Not in Chapter

Obesity Therapy Issues

- How long to treat for???
- Minimal comparative studies
- Long-term safety

Patient Case 5

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Diabetes Mellitus

The below follows the ADA's current recommendations unless otherwise mentioned

Diabetes Classification

- Type 1 Diabetes Mellitus (5-10% of DM)
  - Pancreatic beta-cell destruction / insulin required
- Type 2 Diabetes Mellitus (90-95% of DM)
  - Insulin resistance + decreased pancreatic insulin output
- Gestational diabetes
- Maturity-onset diabetes of the young (MODY)
- Others (pancreatitis, drug induced, genetic defects)

Patient Case 6

64-year-old AAF with a 27 pound increase in weight over the last year due to poor diet and activity. BMI = 44 kg/m^2. Both her mother and sister have type 2 diabetes. Fasting glucose today = 212 mg/dL. Which of the following is the best course of action?

a. Diagnose type 2 diabetes and begin to treat
b. Diagnose type 1 diabetes and begin to treat
c. Obtain another glucose concentration today
d. Obtain another glucose concentration another day

Screening for Type 1 Diabetes

- If symptomatic (polyuria / polyphagia / polydipsia / weight loss): Blood glucose
- High risk asymptomatic (e.g. family history of type 1 DM): Islet autoantibodies
  - If screen positive: Counsel on hyperglycemia symptoms and risk of DM

Screening for Type 2 Diabetes

- Every 3 years starting at age 45
- Earlier if BMI $\geq$ 25 kg/m^2 ($\geq$ 23 kg/m^2 in Asian-Americans) and any of the below:
  - h/o CVD
  - IGT / IFG / mild increase in A1c (aka prediabetes)
  - Polycystic ovary syndrome
  - Low HDL or elevated TG
  - Hypertension
  - h/o gestational DM (or delivery of large baby)
  - High-risk ethnicity
  - First-degree relative with DM
  - Physically inactive

Screening for Gestational Diabetes

- Previously dependent on risk (high / average / low)
- Recommendations by ADA
  - 24-28 weeks of gestation (at early prenatal visit if type 2 DM risk factors present)
  - One Step: 75 gram Oral Glucose Tolerance Test
  - Two Step: 50 gram, if abnormal 100 gram

Type 1 and 2 DM Diagnosis (Based on glycemia)

- Fasting Plasma Glucose ≥ 126 mg/dL
- Random Plasma Glucose ≥ 200 mg/dL and symptomatic
- Elevated Plasma Glucose Post-OGTT
  - 2 hours after 75 g oral glucose ingestion
  - ≥ 200 mg/dL

Type 1 and 2 DM Diagnosis

- Hemoglobin A1c ≥ 6.5%
- Plasma Glucose if abnormal should be repeated on subsequent day (same test preferred)

Patient Case 6

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Patient Case 7

56-year-old man with recent type 2 DM diagnosis. Has no other chronic diseases or h/o CVD. BP = 148/78 mm Hg, A1C = 6.9%, LDL-C = 112 mg/dL, TG = 174 mg/dL. Which is considered under good control?

a. Blood Pressure
b. A1C
c. LDL-C
d. Triglycerides

Goals of Therapy in DM

- Prevent acute and chronic complications
- **Acute**: Hypoglycemia / DKA / HHNS
- **Chronic**:
  - Microvascular: Retinopathy / Neuropathy / Nephropathy
  - Macrovascular: Cardiovascular / Cerebrovascular / Peripheral vascular disease

ADA's Glycemic Goals (non-pregnant adult)

- Fasting/Pre-meal Plasma Glucose: 80-130 mg/dL
- A1c: < 7.0% (< 6.5% per AACE/ACE)
  - Obtain every 3 months if uncontrolled
  - Obtain every 6 months if at goal
  - Can be less stringent in some patients
- Post-prandial (1-2 hours after meal): < 180 mg/dL
- Glycemic goals in gestational DM much more aggressive

Other Goals of Therapy

- Blood Pressure < 140/90 mm Hg
  - ADA changed goal in 2015 to be consistent with JNC
  - Consider < 130/80 in younger patients to reduce renal damage, existing renal disease, or patients at high stroke risk
- Lipids
  - ADA changed stance on LDL/TG/HDL goals to be more consistent with ACC/AHA
  - No specific targets/goals

Benefits of Good DM Control

- **Glycemic Control**
  - Reduces microvascular complications
  - ? Effect on CV outcomes ?
- **Cholesterol Control**
  - Reduces macrovascular complications
- **Blood Pressure Control**
  - Reduces both microvascular and macrovascular complications

Patient Case 7

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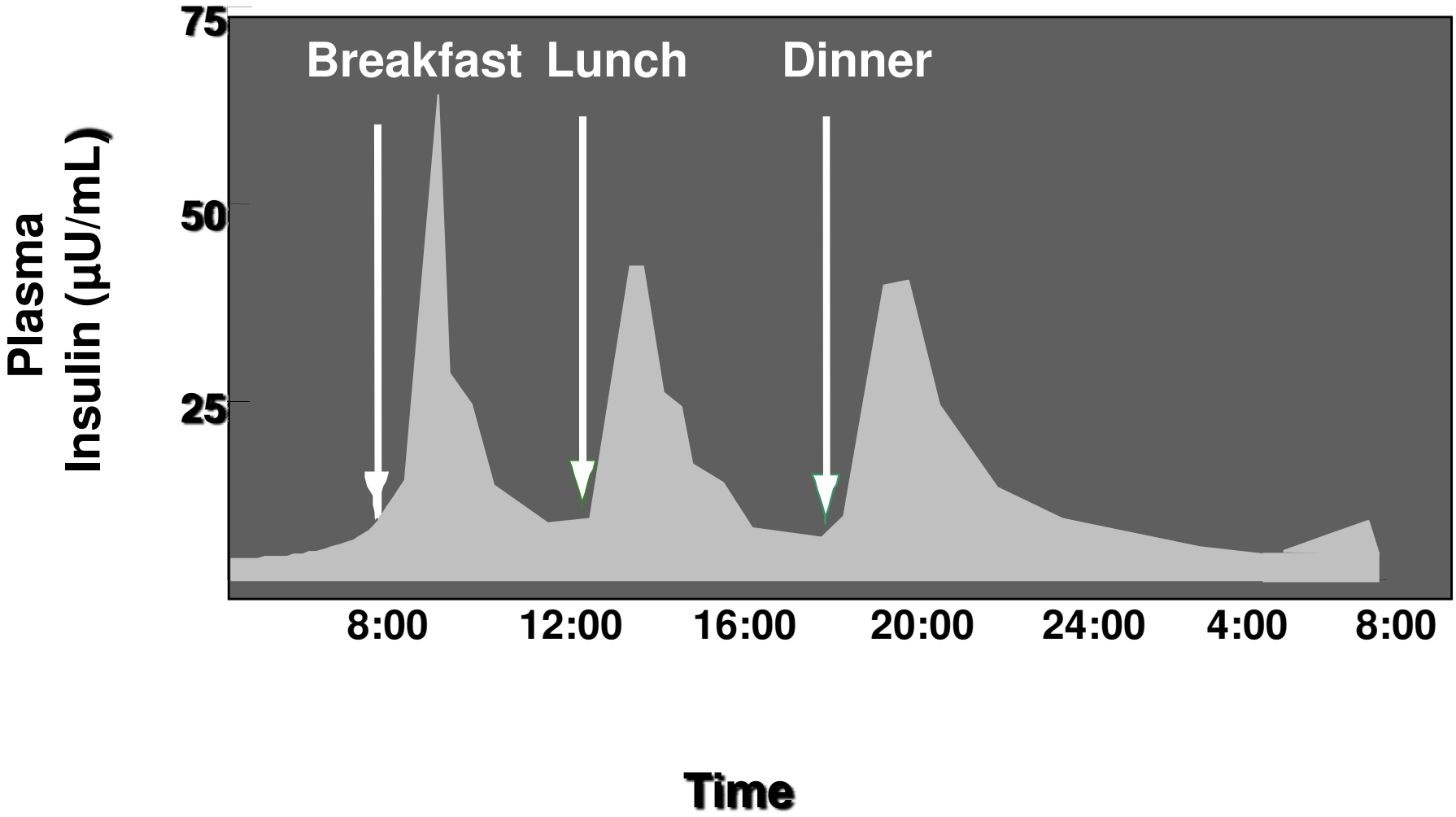
Treating Type 1 Diabetes Mellitus

Natural Insulin Secretion



Insulin Kinetics

Type	Drug Name	Onset	Peak	Duration
Rapid-Acting	Inhaled Insulin	2-3 minutes	15 minutes	2-3 hours
	Glulisine Aspart Lispro	5-15 minutes	1-2 hours	4-6 hours
Short-Acting	Regular	0.5-1 hour	1-5 hours	6-10 hours
Intermed-Acting	NPH	1-2 hours	4-8 hours	10-20 hours
Intermed - Long Acting	Detemir	2-4 hours	6-8 hours 3-4h (0.2-0.4)	5.7-23.2 hrs
Long-Acting	Glargine	1-2 hours	Not significant (Flat)	~24 hours

Treating Type 1 DM

- Basal / Bolus Insulin Regimens (mimic nature)
  - Basal to prevent ketosis and control fasting BG
    - Detemir / Glargine / (NPH)
  - Bolus to control post-prandial glucose excursions
    - Glulisine / Aspart / Lispro / Inhaled (Regular)

Treating Type 1 DM

- Initial treatment often weight-based estimate
  - e.g. 0.6 units / kg / day = total daily insulin (TDI) needs
- Basal is 50% of total daily insulin needs
- Bolus is 50% of total daily insulin needs split three ways and given prior to each meal
- "Correctional Dosing": 1800/TDI = # mg/dL estimate decrease by 1 unit of rapid insulin

Assessing Therapy and Dosage Adjustment

- Know your goal fasting and post-prandial BGs
- Identify where in the day problems occur
- Determine which insulin(s) can affect problem areas
- Adjust medication (or behavior)

Treating Type 2 Diabetes Mellitus

Type 2 DM Treatment Concepts

- Metformin usual initial drug of choice (barring tolerability / contraindications)
- Metformin monotherapy likely to fail over time
- Build upon existing therapy (unless significant ADRs or contraindications appear)
- The higher the baseline A1c the larger the drop in expected A1c with any therapy
- ADA recommends more ‘patient-focused’ approach to care/decisions

Type 2 DM Treatment Concepts

- Additions to metformin (or in lieu of)
  - How high is the A1c
  - Fasting and / or post-prandial hyperglycemia
  - What precautions / contraindications exist
  - Hypoglycemia risk
  - Is weight an issue
  - Cost issues
  - Oral vs injection preferences

Type 2 DM Treatment Concepts

- Additions to metformin (or in lieu of)
- 'Preferred' options: SUs, TZDs, basal insulin, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors
- 'Not favored' options: GI, Bromocriptine, colesevelam
  - ADR profile, efficacy, administration issues

ADA. Diabetes Care 2015;38 (Suppl 1): S41-S48.
ADA. Diabetes Care 2015;38:140-149

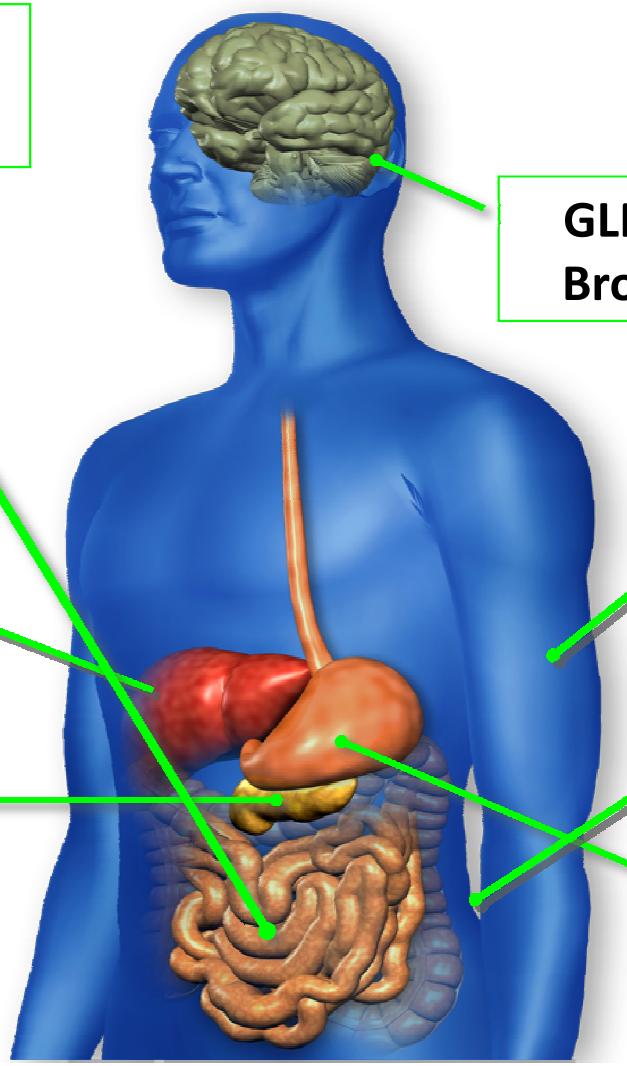
Type 2 DM Treatment Concepts

- Early / Initial Use of Insulin Therapy
  - 10+% A1c
  - Glucose > 300-350 mg/dL
  - Symptoms of hyperglycemia exist
  - Positive for urine ketones

AGENTS TO TREAT TYPE 2 DM

Benefits vs Risks

Areas of Action for DM Meds



Glucosidase Inhibitors
Colesevelam

GLP-1 Analogs
Bromocriptine

Metformin
TZDs

TZDs
Metformin

SGLT2
Inhibitor

Sulfonylureas
Meglitinides
DPP-4 Inhibitors
GLP-1 Analogs
Amylin Analog

GLP-1 Analogs

Patient Case 9

A 52-year-old woman received a diagnosis today of type 2 DM. Her A1C is 7.8%, and FBG is 186 mg/dL. She has no other chronic disease states or history of cardiovascular disease. According to the current ADA guidelines, which would be considered the best initial treatment of choice for this patient?

a. Implement changes in lifestyle (diet and exercise), and initiate metformin 500 mg once daily.

b. Implement changes in lifestyle (diet and exercise).

c. Implement changes in lifestyle (diet and exercise), and initiate sitagliptin 100 mg once daily.

d. Implement changes in lifestyle (diet and exercise), and initiate insulin glargine 10 units once daily.

Patient Case 10

A 66-year-old man has had type 2 DM for 4 years. His A1C today is 7.7%. He has altered his diet, and he states that he has been exercising regularly for months now. He is taking metformin 1000 mg twice daily. Which would be the best choice to help optimize his glycemic control?

A. Continue current medications and counsel to improve his diet and exercise.

B. Discontinue metformin and initiate exenatide 5 mcg twice daily.

C. Add bromocriptine 0.8 mg at bedtime.

D. Add sitagliptin 100 mg once daily to his metformin therapy.

Metformin

- Initial Drug of Choice per leading guidelines
  - Good A1c reduction
  - Cheap
  - Well tolerated
  - Some weight loss
  - Some lipid benefits
  - Possible CV benefit (obese patients)

Metformin

- Side Effect Profile
  - Common
    - Gastrointestinal: Cramping, Diarrhea, N/V
  - Severe (but rare)
    - Lactic acidosis
  - Other
    - Hypoglycemia (uncommon with monotherapy)

Metformin

- Contraindications
  - Increased serum creatinine
    - 1.4+ in women, 1.5+ in men
  - eGFR may be better than Cr cutoffs
    - Avoid < 30 ml/min
- In-Patient Metformin Issues:
  - Hold if undergoing radiological study using IV iodinated contrast dye (hold x 48 hr and get Cr before restarting)
  - Hold if undergoing surgery (>minor)

Sulfonylureas

- May affect both fasting and post-prandial glucose
- Cheap
- Good A1c decrease
- Side Effect Profile
  - Weight gain
  - Hypoglycemia
  - Rash
  - HA
  - GI complaints
  - SIADH (rare)
- Beta-cell fxn loss

Meglitinides

- Better Focus on post-prandial BG than sulfonylureas
- Activity not glucose dependent (less hypoglycemia)
- Can use if renal impairment exists
- Weight gain
- Cost
- Mealtime dosing

Thiazolidinediones (TZDs)

- Good A1C reduction
- Affects fasting and post-prandial BGs
- Beta-cell fxn
- Improved insulin sensitivity
- Cost
- ? CVD benefit
- Weight gain
- Edema
- Avoid in CHF
- ? Bladder CA risk ?
- ? CHF risk ?
- Proximal bone fracture risk

Alpha Glucosidase Inhibitors

- Focus on post-prandial BGs
- No systemic absorption
- Lots of GI ADRs
- Slow titration
- Avoid in IBS, colitis, etc
- Mealtime admin
- Modest A1c decrease

DPP-4 Inhibitors

- Focus on post-prandial glucose (has some effect on fastings)
- Once daily administration
- Well tolerated
- Weight neutral
- Modest reductions in A1c
- No titration
- Cost
- Most require renal dose adjustment
- ? CHF risk ?
  - “Cautious, if at all” in patients with HF

Colesevelam

- Oral
- Prandial focus
- Mild lipid benefit
- No systemic absorption

- Small reductions in A1c
- Side Effects
  - Constipation / dyspepsia / nausea / myalgia
- Pill size / #

Bromocriptine

- Oral, once daily
- ? CV benefit ?

- Cost
- Dosage timing
- Small A1c decrease
- ADRs
  - CNS
  - Fatigue
  - N/V

Sodium-glucose co-transporter-2 (SGLT2) inhibitors

- Oral, once daily
- Moderate A1c reductions
- Fasting and post-prandial BGs
- Weight reduction
- Minimal hypoglycemia
- Cost
- Unknown long-term safety
- Urinary tract and genital mycotic infections
- Diuresis

GLP-1 Agonists

- Exenatide twice daily (2005)
- Liraglutide once daily (2010)
- Exenatide once weekly (2012, pen 2014)
  - Embedded in microspheres degradable material
- Dulaglutide once weekly (2014)
  - Dimer fused to modified human immunoglobulin
- Albiglutide once weekly (2014)
  - Dimer fused to human albumin

GLP-1 Agonists

- Side Effect Profile
  - Hypoglycemia (increased with sulfonylurea)
  - Weight Loss
  - Nausea (usually improves)
  - Vomiting (usually improves)
  - GI discomfort
  - Injection site discomfort
  - Pancreatitis risk ? not likely)

GLP-1 Agonists

- Precautions
  - Existing gastroparesis
  - History of pancreatitis
  - Exenatide: Moderate renal impairment (<50 ml/min)
- Contraindications
  - Exenatide: CrCl<30 ml/min
  - Liraglutide/Albiglutide/Dulaglutide: Medullary thyroid carcinoma

Patient Case 9

A 52-year-old woman received a diagnosis today of type 2 DM. Her A1C is 7.8%, and FBG is 186 mg/dL. She has no other chronic disease states or history of cardiovascular disease. According to the current ADA guidelines, which would be considered the best initial treatment of choice for this patient?

a. Implement changes in lifestyle (diet and exercise), and initiate metformin 500 mg once daily.

b. Implement changes in lifestyle (diet and exercise).

c. Implement changes in lifestyle (diet and exercise), and initiate sitagliptin 100 mg once daily.

d. Implement changes in lifestyle (diet and exercise), and initiate insulin glargine 10 units once daily.

Patient Case 10

A 66-year-old man has had type 2 DM for 4 years. His A1C today is 7.7%. He has altered his diet, and he states that he has been exercising regularly for months now. He is taking metformin 1000 mg twice daily. Which would be the best choice to help optimize his glycemic control?

A. Continue current medications and counsel to improve his diet and exercise.

B. Discontinue metformin and initiate exenatide 5 mcg twice daily.

C. Add bromocriptine 0.8 mg at bedtime.

D. Add sitagliptin 100 mg once daily to his metformin therapy.

Treatment / Screening Diabetes Complications

Hypoglycemia

- Treatment depends on degree of hypoglycemia
- Plasma glucose < 70 mg/dl (+/- symptoms)
- Mild-moderate low BGs: 15-20 gm oral glucose or equivalent
- Severe (cognitive impairment, requires help):
  - 1 mg IM glucagon
  - IV Dextrose

Diabetic Ketoacidosis

- Significantly elevated BG / ketoacidosis / dehydration
- Signs/symptoms: Thirst, abdominal pain, mental status changes, fruity breath, tachycardia, low Na / high K, ketones in urine/serum
- Most common causes: infection/acute illness or inappropriate/inadequate insulin therapy

DKA-Treatment (see ADA statement)

- Find and fix underlying cause (if known)
- NOT about normalizing blood glucose
- Fluid Replacement (IV Na% depends on serum Na)
- IV insulin: 0.1 unit/kg bolus, 0.1 unit/kg/hr drip (double drip rate if minimal response)
  - Hold if baseline serum K < 3.3 meq/L until corrected
- Potassium supplementation: Depends on baseline K

DKA Treatment Goals

- Serum glucose < 200 mg/dL and at least 2 of the following:
  - pH > 7.3
  - Serum bicarbonate ≥15 meq/L
  - Anion gap ≤ 12 mEq/L
- Convert IV drip to subcutaneous insulin

Screening for DM Microvascular Complications

- Type 2 DM: At diagnosis
- Type 1 DM: At 5 years post-diagnosis
- Screen yearly thereafter

Diabetic Nephropathy

	Urine albumin / creatinine (mg/g or mcg/mg)
Normal	< 30
Increased urinary albumin excretion	30 +

Per ADA update in 2013: No longer using terms 'microalbuminuria' or 'macroalbuminuria', still common in literature

Treatment DM Nephropathy

- Up to 2011 ADA had differing recommendations for Type 1 vs 2 depending on micro- or macroalbuminuria
- 2012+ Guidelines – ACE-I or ARB for non-pregnant patients with increased urinary albumin excretion

Diabetic Neuropathic Pain

- TCAs (smaller doses than in depression)
  - Desipramine / Nortriptyline / Amitriptyline
- Anticonvulsants
  - Gabapentin / Lamotrigine / Pregabalin
  - May be better tolerated than TCAs
- SSRIs / SSNRI
  - Duloxetine
- Tramadol/APAP
- Opioids (tapentadol approved)

Cardiovascular Disease Prevention

- Blood pressure control:
  - Regimen ideally contains an ACE-Inhibitor or ARB
  - Take 1+ BP med at bedtime?

Cardiovascular Disease Prevention

- **Lipid Management**
  - **Cardiovascular Risk Factors: HTN, smoking, overweight/obese, LDL cholesterol ≥ 100 mg/dL**
  - **Overt CVD: Previous cardiovascular event or acute coronary syndromes**
  - **Age Groups: < 40, 40-75, > 75 years**
  - **Statin Dose: Moderate or High (don't define)**

Cardiovascular Disease Prevention

- **Lipid Management**
  - High dose statin in all patients with overt CVD
  - If CVD risk factors present
    - Age < 40 or > 75 years: Moderate or High dose statin
    - Age 40-75 years: High dose statin
  - If no risk factors present
    - Age < 40: No statin therapy
    - Age 40+: Moderate dose statin

ADA. Diabetes Care 2015;38 (Suppl 1): S49-S57.

Cardiovascular Disease Prevention

- Antiplatelet Therapy:
  - Aspirin Therapy (75-162 mg daily)
    - Secondary prevention: All, unless contraindicated
    - Primary prevention
      - 10-year risk for cardiovascular event is > 10%
      - Will include most men > 50 and women > 60 with at least one other CVD risk factor
  - Clopidogrel is alternative in ASA allergy/intolerance

QUESTIONS??