Addison’s Disease and Cushing’s

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Addison’s Disease

- Defined by a deficiency in cortisol (from adrenal gland)
  - Corresponding aldosterone deficiency
- Results in; - possible adrenal crisis
  - Low blood pressure
  - Hyperkalemia
  - Hyponatremia
  - Hypoglycemia
  - Skin darkening

Management

- Treatment with steroid replacement (hydrocortisone)
  - 15-25 mg in 2-4 divided doses (adult starting dose)
  - Lifelong therapy likely unless identifiable/treatable reason for deficiency
- Mineralocorticoid replacement may be necessary to help with hyponatremia
  - i.e. fludrocortisone
  - Side note - May be considered in hypotension due to dialysis
- Avoid spironolactone as can exacerbate hyperkalemia and hyponatremia as well as oppose effects of mineralocorticoids

Adrenal Crisis

- Acute, severe, symptomatic adrenal gland failure
  - Hypotension
  - Loss of consciousness
  - Hyperkalemia, hyponatremia
  - N/V
- IV glucocorticoid (hydrocortisone)
- Fluid replacement
- Sodium monitoring
- Dextrose – to treat hypoglycemia

Cushing's

- Opposite of Addison's
  - Excessive corticosteroid (cortisol)
  - Caused by oversupply of exogenous
- Weight gain
- Hyperglycemia
- Moon face/buffalo hump – fat distribution changes
- Acne
- HTN
- Osteoporosis

Treatment – Cushing's

- Remove exogenous steroids
  - SLOWLY!!!
- Abrupt discontinuation of long term steroids
  - Adrenal insufficiency
- Treat underlying cause if not due to excessive supplementation of steroid
  - I.e. cancer
  - Surgery, radiation
- Cabergoline – may help normalize production of cortisol
  - Low success rate
  - Dopamine agonist
    - May see used for elevated prolactin levels
    - Psych/GI adverse effects

Diabetes: Compelling Indications, Complications, and Goals

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Diabetes Monitoring

- A1C target of less than 7 in most nonpregnant patients (ADA)
- A1C target less than 6.5 can be considered so long as risks of hypoglycemia are minimal and adverse effects are minimized
- Age greater than 65 with few chronic conditions who have good cognitive function and functional status may have a goal of <7.5
- Risk of hypoglycemia, older age, cognitive impairment, limited life expectancy are all examples of situations where relaxed A1C goals may be appropriate (i.e. A1C less than 8 or even <8.5)
- Blood sugars
- Kidney, eye, feet

Complications

- Cardiovascular Disease
- Neuropathy
- Nephropathy
- Retinopathy
- Gastroparesis
- Amputation risk
- Infection risk

Preventative Medications

- Remember cardiovascular risk factors and use of statins, antihypertensives, and aspirin
  - Moderate to high intensity statin is indicated (age 40-75) for primary prevention in patients with diabetes
  - <7.5% 10 year ASCVD risk – moderate
  - >7.5% - high
- Majority of diabetics with latest guidelines based upon CV risk calculation will have a BP target goal of <130/80
  - ACE Inhibitor or ARB will be the first line antihypertensive with dihydropyridine calcium channel blocker (i.e. amlodipine) being the second best alternative

Preventative Medications (cont.)

- Aspirin
  - Most likely, but:
  - Consider risk with other medications (i.e. Warfarin, NSAIDs, etc.)
  - Past history
  - Bleeding
  - Risk calculators (See CHD lecture)
  - Dose of aspirin @ 81 mg is usually sufficient barring other rationale

Table 1. Statin Therapy

Intensity	Definition	Dosage
Low	Daily dose lowers LDL-C by <30%, on average	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg
Moderate	Daily dose lowers LDL-C by approximately 30% to <50%, on average	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg
High	Daily dose lowers LDL-C by approximately ≥50%, on average	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

Courtesy:
uspharmacist.com

Hypertension

- ACE OR ARB
  - Renal protection
- CCB
- Thiazide

Diabetic Neuropathy

- Gabapentin/pregabalin
- SNRI’s
- Topical Lidoderm
- TCA’s

Gastroparesis

- Cause of GI nausea/upset in diabetes patients
- Metoclopramide
  - Parkinson’s disease risk
- Erythromycin
  - Drug interaction risk
- Be careful with anticholinergics
  - Exacerbate gastroparesis

Changes That Can Impact Diabetes

- Steroids
- Beta-blockers
- Infections
- Dementia
- Medications that suppress or stimulate appetite

Treatment of Hypoglycemia

- Glucagon
  - Alertness compromised
  - <54
  - Nasal and injection available
  - Still need to give sugar (IV or oral)
- Sugar replacement
  - Aspiration
  - Choking

Diabetes: The Medications

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Type 2 Diabetes Pharmacotherapy

Adapted from the 2025 ADA Standards of Care in Diabetes

Page 1

Healthy lifestyle behaviors, self-management education/support, and social determinants of health should be considered in all patients

First-line pharmacotherapy (metformin or other agents) should be selected based upon patient-specific factors
(e.g., glycemic goals, weight goals, comorbidities, tolerability, cost)

Consider **combination pharmacotherapy** at initiation if A1C ≥1.5% above target goal

Consider **early insulin initiation** if A1C >10%, BG ≥300 mg/dL, or symptoms of hyperglycemia
(e.g., polydipsia, polyuria, unexpected weight loss)

Page 2

Reassess treatment plan every **3-6 months** and modify, if appropriate

Glycemic Treatment Goals
Must be individualized and periodically reassessed after considering patient-specific characteristics

POPULATION	A1C	PREPRANDIAL	2-HR PPG
Most patients*	<7%	80-130 mg/dL	<180 mg/dL
Certain patients^	<8%	--	--

* Stricter goals may be reasonable for certain patients, if achievable without significant hypoglycemia risk
^ e.g., risk of severe hypoglycemia, limited life expectancy, significant comorbidities

Established ASCVD/High Risk, Heart Failure, or Chronic Kidney Disease? — No
Recommended irrespective of A1C or use of metformin

Select therapies with **adequate efficacy** to achieve and maintain **treatment goals**
Do not combine DPP-4i, GLP-1 RA and/or tirzepatide (GIP/GLP-1 RA)

ASCVD
(established or high risk†)

GLP-1 RA or **SGLT2i** with proven CVD benefit

If A1C above target
- On **GLP-1 RA?** Consider adding **SGLT2i** with CVD benefit *(or vice versa)*
- Consider low-dose pioglitazone

Heart Failure
(preserved or reduced EF)

SGLT2i (or SGLT1/2i) with proven HF benefit

Or

GLP-1 RA with proven HF benefit in those with symptomatic **HFpEF** and **obesity**

Chronic Kidney Disease
(eGFR <60 mL/min/1.73 m2 or UACR ≥30 mg/g)

Maximally tolerated **ACEi/ARB**

SGLT2i with primary evidence for reducing CKD progression
- May be initiated with eGFR ≥20 mL/min/1.73 m2
- Continue until transplant or dialysis

Or

GLP-1 RA with proven CKD benefit

If A1C above target
On **SGLT2i?** Consider adding **GLP-1 RA** *(or vice versa)*

Additional therapy needed to achieve treatment goals?

† **High risk for ASCVD:** Typically age ≥55 years plus ≥2 risk factors (e.g., hypertension, obesity, smoking, dyslipidemia, albuminuria)
‡ Avoid use in patients with **heart failure**

Glucose-Lowering Efficacy

Very High:
Dulaglutide (high-dose)
Semaglutide
Tirzepatide
Insulin
Combination oral or injectable therapy

High:
GLP-1 RA *(not listed above)*
Metformin
SGLT2i
Sulfonylurea
Pioglitazone

Intermediate:
DPP-4i

Weight-Loss Efficacy

Very High:
Semaglutide
Tirzepatide

High:
Dulaglutide
Liraglutide

Intermediate:
GLP-1 RA *(not listed above)*
SGLT2i

Neutral:
DPP-4i
Metformin

Cost and Access

Consider oral options available in a generic form or at a lower cost, such as:
- Metformin
- Sulfonylurea
- Pioglitazone

Consider insulins that are available at lower cost:
- NPH or regular

Insulin analogs have lower hypoglycemia risk than human insulin (NPH or premixed)

Patient assistance programs may be available for certain brand name medications

Additional therapy needed to achieve treatment goals?

CLASS	ASCVD	HEART FAILURE	RENAL
SGLT2is**	**FDA approved CVD benefit:** • canagliflozin • empagliflozin **Neutral:** • bexagliflozin • dapagliflozin • ertugliflozin	**FDA approved HF benefit:** • dapagliflozin • empagliflozin **Evidence for HF benefit:** • canagliflozin • ertugliflozin	**FDA approved renal benefit:** • canagliflozin (DKD) • dapagliflozin (CKD) • empagliflozin (CKD) **Neutral:** • bexagliflozin • ertugliflozin
GLP-1 RAs^^	**FDA approved CVD benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ) **Neutral:** • exenatide ER • semaglutide (oral)	**Evidence for benefit in symptomatic HFpEF and obesity:** • semaglutide (SUBQ)	**Evidence for renal benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ)

FDA labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 1/2025.

** The ADA recommends sotagliflozin (SGLT1/2 inhibitor) as an option for heart failure benefit. It is not FDA-approved for glycemic management.
^^ Tirzepatide (GIP/GLP-1 RA) is under investigation for cardiorenal benefit.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD):

Consider use of a **GLP-1 RA** or **GIP/GLP-1 RA** in adults with T2DM, MASLD, and overweight/obesity for **weight loss** and potential benefit in metabolic dysfunction-associated steatohepatitis (MASH).

In adults with T2DM and biopsy-proven **MASH** (or those at high risk for clinically significant liver fibrosis), the use of pioglitazone, GLP-1 RA, or GIP/GLP-1 RA is preferred for glucose management due to potential benefits in MASH. Combination therapy (pioglitazone plus GLP-1 RA) may also be considered in these patients.

In patients with T2DM and **decompensated cirrhosis**, insulin therapy is preferred for management of hyperglycemia.

ASCVD: atherosclerotic cardiovascular disease **CKD:** chronic kidney disease **DKD:** diabetic kidney disease **EF:** ejection fraction **HFpEF:** heart failure with preserved ejection fraction **UACR:** urine albumin-creatinine ratio

pyrls
More clinical pearls at pyrls.com

Metformin (Glucophage)

- Mechanism of Action: Primarily decreases hepatic glucose production
- Avoid in CKD (<45 mls/min)
- GI side effects – give with food
  - Diarrhea
- Weight neutral to weight loss
- Low risk hypoglycemia
- B12 deficiency
- Hold during contrast administration for 48 hours

SGLT-2 Inhibitors

- Empagliflozin (Jardiance), canagliflozin (Invokana), dapagliflozin (Farxiga), bexagliflozin (Brenzavvy), ertugliflozin (Steglatro),
- Mechanism of Action: By inhibiting Sodium–glucose co-transporter 2, this results in an increase in glucose excretion through the urine
- Caution in patient with urinary infection history (drugs increase sugar to the urine which can be food for bug)
- Generally not effective for diabetes in eGFR <30 mls/min (heart failure/renal benefit proven down to 20 mls/min)
- Benefits
  - Cardioprotective effects (reduction in major CV events)
  - Renal benefit
  - Evidence of benefit in HFrEF and HFpEF (even in patients without diabetes) – dapagliflozin and empagliflozin

SGLT-2 Inhibitors

- Mild diuretic type effect – watch BP, volume depletion, dehydration risk
  - Monitor K+; hyperkalemia risk especially in patients on ACE, ARB, etc.
- Caution on bone fracture risk, euglycemic ketoacidosis
- Rare: Extremely rare association of necrotizing fasciitis of perineum, amputation
  - Conflicting evidence
- A1C lowering effect is typically less than 1 point when used as monotherapy

GLP-1 Agonists

- Liraglutide (Victoza) – once daily, exenatide (Byetta = twice daily or Bydureon = once weekly), lixisenatide (Adlyxin) – once daily, dulaglutide (Trulicity) – once weekly, semaglutide (Ozempic) – once weekly, Rybelsus once daily oral option
- Mechanism of Action: Glucagon-like peptide 1 agonists enhance glucose dependent insulin secretion, slows gastric emptying, and reduces post prandial glucagon to reduce blood sugars
- Strict administration for oral semaglutide – 30 minutes before food/beverage/medications
- Typical A1C lowering effect of 0.5-1.5 (possibly up to 1.8) when used as monotherapy

GLP-1 Agonists

- N/V is the major adverse effect - (slows GI tract - can alter absorption of some drugs)
- Promotes fullness, weight loss can be a beneficial effect
  - Semaglutide, tirzepatide have strongest weight loss and are preferred via diabetes guidelines if weight loss is a compelling indication; liraglutide also has a weight loss product
- Typically better in A1c reduction than most oral diabetes medications
- Injection and cost are potential downsides
- Rare concern with thyroid cancer and risk of pancreatitis
- Cardiovascular protection
- Avoid combining with DPP4 inhibitors (overlapping mechanism)

GIP/GLP-1 Agonist

- Tirzepatide (Mounjaro)
- Glucose-dependent insulinotropic polypeptide (GIP) receptor agonist combined GLP-1 agonist which helps promote glucose-dependent insulin secretion, reduces excessive glucagon secretion and delays gastric emptying
- ADRs similar to GLP-1 agonists
  - Nausea, vomiting, GI pain are the most common adverse effects (dose dependent)
  - Tachycardia, pancreatitis, acute renal failure potentially due to dehydration from N/V/D
  - Boxed warning due to risk of thyroid tumors
- Weekly subQ injection (2.5 mg weekly initial – may increase by 2.5 mg every 4 weeks up to a max of 15 mg
- Avoid use with DPP4 inhibitors or another GLP-1 agonist
- Preferred (in addition to semaglutide) in the diabetes guidelines for weight loss

Sulfonylureas

- Glipizide (Glucotrol), Glyburide (Glynase), Glimepiride (Amaryl)
- Mechanism of Action: Stimulate insulin release via beta cells in the pancreas
- Inexpensive
- Weight gain can be problematic in our likely already overweight diabetes population
- Careful in patients with sulfa allergy
- Elderly can be especially at risk for hypoglycemia (chlorpropamide and glyburide on Beer's list)
- Glyburide has an active metabolite that can accumulate in impaired renal function
  - Glipizide generally preferred in elderly
- Chlorpropamide can cause SIADH
  - Typically never used because of this
- Lowers A1C up to 1-2 points when used as monotherapy

DPP-4 Inhibitors

- Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta)
- Mechanism of Action: Prolongs incretin effects amongst many actions; incretin is responsible for promoting fullness, weight neutral to weight loss is common with these agents – nice advantage
- Expensive
- Sitagliptin most commonly used – be aware of dose adjustments in CKD
- More data coming out on risks with heart failure (not as concerning as pioglitazone at this point), avoid saxagliptin
- Rarely causes pancreatitis
- Not likely to cause hypoglycemia like sulfonylureas unless used with SU's or insulin
- A1C lowering effect typically less than 1 point when used as monotherapy

TZD's

- Pioglitazone (Actos)
- Mechanism of Action: bind peroxisome proliferator-activated receptor (PPAR) gamma which helps improve insulin resistance in adipose tissue
- Weight gain, edema risk, avoid in heart failure
- Hypoglycemia rare when used alone
- Possible increase in osteoporosis risk
- Inexpensive

Alpha-glucosidase inhibitors

- Acarbose, miglitol
- Prevent breakdown of complex sugars in the gut
- GI side effects
- GI SE's and frequent dosing make these medications seldom used
- If patient has hypoglycemic episode, you MUST use simple sugars (i.e. glucose tablets)
  - Complex sugars may not be broken down due to the drugs MOA
- Hypoglycemia risk typically not an issue if used alone

Glinides

- Repaglinide
- Stimulates insulin release
- Hypoglycemia
- Weight gain risk
- Needs to be dosed with meals
- Frequent dosing can be a downside

Max A1C Lowering

- Metformin 1-2
- GLP1 – 1.5-1.8
- SGLT2 – 1
- SU 1-2
- DPP4 - 0.8
- TZD – 0.8

Insulin

- Sliding Scale
  - Short term use
- Long Acting
  - Targets fasting
- Rapid Acting
  - Targets post-prandial
- Diet Changes

Long Acting

- Glargine (Lantus, Basaglar, Toujeo), detemir (Levemir), degludec (Tresiba)
- Fasting blood sugars
  - Will bring down all blood sugars (lasts all day)
- Weight gain, hypoglycemia
- Degludec has a much longer duration of action than detemir/glargine; be careful with increasing dose to quickly as it will take longer to get to steady state (“ultra-long acting”)
  - May have to wait longer before increasing (up to 5-7 days versus 2-3 days for glargine/detemir)
- Typically target about 10% increases in dose for patients not at goal

Intermediate Acting Insulin

- Intermediate Acting Insulin
  - NPH
  - Rarely used due to use of long acting
  - May seen in;
    - Cost concerns
    - Refractory patients
    - Been on it a long time
  - May be used in combination with rapid acting insulin and dosed twice daily for those who have difficulty with basal/bolus regimens

Short Acting

- Short acting
  - Regular insulin (Humulin R, Novolin R)
  - Typically given before the meal, rapid acting easier to manage
  - Can be a challenge in cognitively impaired elderly patients who may not remember to eat or decide not to eat following dose of insulin
  - Available without a prescription
  - Cheaper

Rapid Acting

- Rapid acting
  - Insulin aspart (Novolog), lispro (Humalog), glulisine (Apidra)
  - Give with meals or just prior
  - Useful in preventing/bringing down post-prandial blood sugars (those big spikes following meals)
  - Can be used just once or twice daily in Type 2
  - Sliding scale is not ideal management

Blood Glucose Targets

- Postprandial
  - Rapid acting insulin
  - Sulfonylureas
  - DPP-4
  - GLP-1
  - Glinides
  - Alpha-glucosidase inhibitors
- Preprandial/fasting
  - Long acting insulins
  - Metformin
  - TZDs
- Both
  - SGLT-2

Type 1 Diabetes

- Insulin therapy
- Insulin pumps preferred
  - Allows for potential tighter control and more flexibility with meals
  - Guidelines recommend
  - Automated, closed loop CGM/Pump
- If basal/bolus method used, rapid acting injections necessary for meals
- Frequent blood sugar checking necessary
- Initial dose requirements can vary but 0.5-1 units/kg in divided doses (for those using basal/bolus method) may be appropriate starting place
- Insulin requirements are often less in Type 1 than Type 2 diabetes

500 Rule

- Estimation of insulin to carb ratio – 500 rule
  - Used to help a patient determine how much insulin to use based upon carbohydrate intake
  - Take 500 divided by the total daily dose of insulin
  - Resulting fraction is the approximate rapid acting insulin to carb ratio for that patient
  - I.e. – patient takes a total daily dose of insulin of 30 units: 500/30 = 17/1 (carbs/unit of insulin)
  - *Use rule of 450 for regular insulin

1800 Rule

- Insulin correction factor – 1800 rule
  - Estimates amount of blood sugar lowering effect per unit of insulin
  - Divide 1800 by the total daily dose of insulin
  - I.e. – patient takes a total daily dose of insulin of 60 units: 1800/60 = 30; 1 unit of rapid acting insulin would bring down the blood sugar by 30 mg/dL
  - This can be applied if the patient needs extra blood sugar lowering above and beyond the requirements for the anticipated meal/snack intake
  - *Use rule of 1500 for regular insulin

Sick Day – Type 1 Diabetes

- Illness can lead to hormone (epinephrine and cortisol) production and an increase blood sugar
  - Risk of diabetic ketoacidosis for type 1 patients
- Can be complicated by diet changes (i.e. nausea/vomiting) – decreased medications/insulin may be necessary if inadequate oral intake
  - Risk of hypoglycemia
- Increase blood sugar checking/CGM monitoring

Sick Day – Type 1 Diabetes

- Check for ketones in the urine
  - Monitor ketones if glucose >240 mg/dL or vomiting per ADA
- Consider small insulin boluses throughout the day as needed based upon blood sugar reading
  - 5-10% of total daily dose
- Persistent vomiting and hypoglycemia
  - May need to go to ED or hospital

Medical Procedures and Insulin

- Minimize fasting period if possible
  - Schedule patients with planned procedures as early in the morning as possible
- Insulin can be administered during and after procedure
- IV Dextrose can be given during
- Prior to procedure, checking blood sugar more frequently is appropriate (1-2 hours or signs of hypoglycemia)

Thyroid Disorders

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Hypothyroidism - Diagnosis

- Elevated TSH and low T4
- Can mimic some signs/symptoms of depression
  - TSH should be considered a differential diagnosis in patients who are experiencing signs/symptoms of depression
- Normal TSH 0.5-6 (can vary depending upon the lab)
  - Hypothyroidism typically noted by an elevated TSH
  - Subclinical hypothyroidism involves abnormal TSH (usually slightly elevated) with no to minimal clinical symptoms of hypothyroidism
  - Low T4 and normal TSH possible, but less common
- Symptoms
  - Lethargy, cold, weight gain, constipation, hair loss, dry skin, lack of energy

Levothyroxine

- Synthetic form of T4 which gets converted to T3 in the body
- Binding interactions
  - Consistency with administration
- Follow up – 6 weeks to 3 months
- If switching between generic/brand preparations, extra monitoring is appropriate (i.e. check labs 6-8 weeks following the switch)

Adverse Effects and Dosing

- Adverse effects are signs of hyperthyroidism
  - Insomnia, anxiety, tremor, tachycardia, weight loss, increased appetite
  - Prolonged suppressed TSH can lead to osteoporosis
- Usual starting dose 25-50 mcg/day
- Dosing requirements may increase 30-50% in pregnant patients

Desiccated Thyroid

- Desiccated Thyroid (porcine – derived from pigs) “Armour Thyroid”
  - Combination of T3 and T4
  - T3 has most physiological activity
  - Conversion is approximately 60 mg to 100 mcg of levothyroxine
- Guidelines do not recommend use
- Generally not required for most hypothyroidism patients but may be considered for those who fail levothyroxine therapy or have had thyroidectomy

Drugs That Can Impact Thyroid Function

- Amiodarone
  - Hyperthyroid or Hypothyroid
- Lithium
- Rifampin
- GLP-1 agonist
  - Thyroid cancer

Levothyroxine Interactions

- Binding interactions
  - Calcium
  - Cholestyramine
  - Sucralfate
  - Iron
- Enzyme Inducers
  - Phenobarbital
  - Carbamazepine

Hyperthyroidism

- A common type of hyperthyroidism is Graves' disease
- Your body is "amped up"
- Anxiety, tremor, increased pulse/arrhythmias
- Weight loss
- Osteoporosis
- Always warm, sensitive to heat
- Bulging eyes – Graves Ophthalmology
- Typically noted by a suppressed TSH (below normal TSH)

Hyperthyroidism

- “Thionamides”
- Methimazole (Tapazole)
  - Inhibits thyroid synthesis by interfering with oxidation of iodine; this is done via inhibition of the peroxidase enzyme
  - Typically will take a little while to work
  - Longer duration of action than PTU (once daily)
- Propylthiouracil (PTU)
  - Similar mechanism to methimazole
  - May be more beneficial than methimazole in the short-term, life-threatening situation
  - Generally avoid unless methimazole is not tolerable or emergency, life-threatening clinical situation
  - Higher incidence of liver problems than methimazole (boxed warning)

Thyroid Storm

- Symptoms
  - Tachycardia
  - Anxiety
  - Agitation
  - Psychosis
  - Elevated temp

- Acute management of thyroid storm – Beta blockers
  - Propranolol is most commonly used, but beta-1 selective can be considered in patients with severe respiratory disease
  - Helps with tachycardia, anxiety, and palpitations
- Corticosteroids (IV hydrocortisone)– considered in life-threatening, acute situation
- Antithyroid medication
  - I.e. PTU/Methimazole