Outline

❖ Overview of diabetes and Insulin
❖ T2DM Medication
  ➢ Biguanides → Metformin
  ➢ Sulfonylureas & Meglitinides
  ➢ Thiazolidinediones
  ➢ GLP-1RA
  ➢ DPP-4 Inhibitors
  ➢ Alpha-Glucosidase Inhibitors
  ➢ SGLT2 Inhibitors
Refresher: Type II Diabetes Mellitus (T2DM)

- What is it?
  - High blood glucose levels due to a deficiency in the production or function of insulin
- CDC’s Public Health notice → “1 in 3 US Adults is at risk”
- Develops over time due to insulin resistance
  - Risk Factors: Overweight, Stress, Physical Inactivity, Genetics, Low Birth Weight, Medications
- Associated with many other conditions
  - Cardiomyopathy
  - Hypertension
  - Nerve damage (neuropathy)
  - Kidney damage (nephropathy)
When the insulin receptor binds insulin, the activated receptor phosphorylates the IRS-1 protein. IRS-1 can lead to recruitment of GRB2, activating the Ras pathway.

IRS-1 activates PI 3-kinase, which catalyzes the addition of a phosphate group to the membrane lipid PIP$_2$, thereby converting it to PIP$_3$. PTEN can convert PIP$_3$ back to PIP$_2$.

PIP$_3$ binds a protein kinase called Akt, which is activated by other protein kinases.

Akt catalyzes phosphorylation of key proteins, leading to an increase in glycogen synthase activity and recruitment of the glucose transporter, GLUT4, to the membrane.
Receptor phosphorylation capacity diminished

Tyrosine-P of IRS prevented by serine-P, which impairs IRS signaling
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Tyrosine phosphatases dephosphorylate insulin receptor, terminate signal

IRS expression reduced
Impaired activity
Receptor phosphorylation capacity diminished

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IRS expression reduced Impaired activity

Impaired insulin-stimulated activation of Akt and atypical PKC
- Glucose transporter
- PKC deficient in muscle; in liver, increases lipid synthesis
Receptor phosphorylation capacity diminished

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Tyrosine phosphatases dephosphorylate insulin receptor, terminate signal

IRS expression reduced

Impaired activity

Impaired insulin-stimulated activation of Akt and atypical PKC

- Glucose transporter
- PKC deficient in muscle; in liver, increases lipid synthesis

In liver, TRB3, a protein normally inhibited in presence of glucose, is active and inhibits and blocks Akt
How Fatty Diets Contribute to Insulin Resistance

- High Fat Diet
  - Triacylglycerols (TAGs)
    - Diacylglycerides (DAGs)
      - Activate Protein Kinase C (PKC)
        - Increased Phosphorylation of Insulin Receptor at incorrect locations
          - Autophosphorylation is not as effective
            - No recruitment of IRS-1
Type I vs. Type II Diabetes

- Type I
  - Autoimmune disorder in which immune system attacks the Beta Cells of the Pancreas, causing little or no insulin production

- Type II
  - Deficiency in the production or function of insulin
    - Abnormal insulin receptor
    - Dysfunctional insulin signaling

- Progression of Type II Diabetes (Fonseca, 2009)
  - Beta cells stimulated
  - Glucotoxicity and lipotoxicity
  - Vicious cycle
Diagnosis

- Glucose Criteria:
  - Fasting plasma glucose (WHO) ≥ 126 mg/dL
  - Non-fasting plasma glucose or symptoms of hyperglycemia ≥ 200 mg/dL
  - 2-hour plasma glucose during an oral GTT ≥ 200 mg/dL
- Hemoglobin A1C ≥ 6.5%
- WHO
  - 6% (below 42 mmol/mol) is considered non-diabetic
  - 6-6.4% (42 to 47 mmol/mol) indicates impaired fasting glucose regulation and is considered prediabetes
  - 6.5% or more (48 mmol/mol and above) indicates the presence of type 2 diabetes
Need for Many Drugs

● Therapeutic Lifestyle Changes (TLCs) Recommended
  ■ 1) Weight Control
  ■ 2) Healthy Diet
  ■ 3) Physical Activity

● TLCs are hard to implement
  ○ May also take some time
Some Terminology:

- **Pharmacokinetics**
  - “Pharmaco-” & “-kinetics”
  - the process by which a drug is absorbed, distributed, metabolized and eliminated by the body

- **Pharmacodynamics**
  - “Pharmaco-” & “-dynamics”
  - the interactions of a drug and the receptors responsible for its action in the body
Insulin
Insulin

- Type I and eventually, T2DM
- Often given with other medications (e.g. metformin)
- Basal insulin initially $\rightarrow$ low, continuous dose
- Bolus insulin $\rightarrow$ rapid-acting
- Sustained improvements compared to other agents
- Side effects/Disadvantages:
  - Weight gain
  - Hypoglycaemia
  - Fluid retention
  - Need for self-monitoring
- Others: inhaled insulin, insulin injections
Insulin

- Different types of injectable insulin depending on when individual wants it to act
- Adherence is very important

Biguanides: Metformin
Biguanides

Biguanide:

- a colorless solid that dissolves in water to give highly basic solution that slowly hydrolyzes to ammonia and urea
- "biguanidine" refers specifically to a class of drugs that function as oral antihyperglycemic drugs used for diabetes mellitus or prediabetes treatment

Metformin

- An asymmetric dimethylbiguanide
- the only one of its class that is still on the market and the only biguanide available in clinical practice
Metformin Origins

❖ Originates from the French Lilac flower (Galega officinalis)
❖ It is an herb that has been used for centuries in folk medicine
❖ Metformin was first described by Emil Werner and James Bell in 1922
❖ Received approval for by the US Federal Drug Administration (FDA) for T2DM in 1994!
❖ Glucophage “Glucose Eater” was the first to hit the market in the US
❖ Metformin is now believed be the world's most widely prescribed antidiabetic medication
Metformin

❖ **What is it?**
Oral antihyperglycemic agent

❖ **What does it do?**
Improves glucose tolerance, lowering both basal and postprandial plasma glucose

❖ **First line agent!**
Recommended early initiation as 1st line of defense for monotherapy and combination therapy for patients with T2DM

❖ **Advantages?**
Unlike sulfonylureas, Metformin does not cause hyperinsulinemia (excess levels of insulin in circulation)

➢ It does not cause insulin secretion
Metformin

- Low risk of hypoglycemia (low blood sugar)
- Low chances of weight gain
- Reduces mortality rates by decreasing hepatic glucose synthesis
- Sensitizes peripheral tissues to insulin by:
  - Activating insulin receptor expression
  - Enhancing tyrosine kinase activity
- Reduces risk of T2DM related complications
- Can also aid in the prevention of CVD by activating the PPAR-α pathway
  - PPARs: ligand-activated transcription factor involved in the regulation of a variety of processes
  - PPARα: expressed in the kidneys, liver, heart, muscle, adipose tissue among others
Metformin

Pharmacodynamics:
- Reduces fasting plasma glucose by 2-4 mmol/L and HbA1c by 1-2%
- Reduces diabetes endpoint by 21%
- Reduces diabetes related death by 30%
- Reduces myocardial infarction by 33%
- May reduce risk of breast and pancreatic cancer with patients with T2DM

Pharmacokinetics:
- Oral bioavailability: 40-60%
- Plasma half life: 4-9 hours
  ➢ Peak action after ~3 hours
- Absorbed by organic cation transporters and remains unmetabolized in the body
- Widely distributed to the intestines, liver and kidney
- Primary route of elimination is through the kidney (urine)

The recommended starting dosage of metformin is 500 mg twice daily. The maximum dosage for children age 10 to 16 is 2000 mg, and for adults age 17 and older is 2550 mg.
Metformin

Side effects:

❖ Predominantly GI issues
  ➢ Abdominal discomfort/disturbances
  ➢ Diarrhea
  ➢ Nausea
  ➢ Dyspepsia (impaired digestion)
    ■ 30% of patients

❖ About 10% of patients can not tolerate the drug

❖ Some cases may develop lactic acidosis

Contraindications:

❖ NOT to be given to patients with
  ➢ Chronic kidney disease (CKD)
  ➢ Liver disease
  ➢ Conditions predisposing individuals to hypoxia or reduced tissue perfusion
  ➢ Renal deficiency (Glomerular Filtration Rate: <30mL/min)
    ■ Must assess renal function prior to starting metformin
Mechanism of Action

Metformin enters the cell via hOCT1 (expression in intestine)

Interacts with mitochondria decreasing complex 1 activity

Decrease ATP production → Decreasing the ratio of ATP to AMP

Activation of AMPK
IRS1/2 activation

PI3K binds to IRS phosphorylates PIP2→ PIP3

Activation of PDK1/2 which phosphorylates PKB

In skeletal muscle: PKB induces translocation of GLUT4 into the membrane

In the liver: PKB reduces glucose production, increases lactate production

Reduction in gluconeogenesis: Less ATP → Less cAMP and less G6Pase FBpase which are enzymes in gluconeogenesis
Metformin Recap

❖ First line of defense
❖ Metformin is an oral diabetes medicine that helps control blood sugar levels
❖ Metformin is used to improve blood sugar control in people with type 2 diabetes and is sometimes used in combination with other medications
❖ Metformin’s effects are mediated by AMPK, which is a liver enzyme important in insulin signaling
❖ AMPK activation is required for metformin’s inhibitory effect on glucose production in the liver
❖ AMPK also causes GLUT4 to deploy into the plasma membrane for insulin-independent glucose uptake in skeletal muscle
❖ For an overall reduction of blood sugar
Sulfonylureas

&

Meglitinides
Sulfonylureas & Meglitinides

- **Sulfonylureas**
  - Developed as variants of sulfonamides (antibiotic) after they were reported to cause hypoglycemia
  - 1st generation
    - Tolbutamide, Chlorpropamide
  - 2nd generation → greater potency, lower dose needed
    - Glibenclamide, Gliclazide, Glipizide, Glimepiride
  - Taken once daily
  - Oral medication
  - Increase insulin secretion

- **Meglitinides**
  - Two main types:
    - Nateglinide & repaglinide
  - Taken with meals
  - Oral medication
  - Increase insulin secretion
Normal Insulin Release

1. Glucose uptake by GLUT2
2. Metabolism
3. ATP:ADP increase
4. K<sub>ATP</sub>-channel closure
5. PM depolarization
6. Ca<sup>2+</sup> influx through VDCC
7. [Ca<sup>2+</sup>]<sub>i</sub> increase
8. Insulin granule exocytosis

PM: Plasma membrane
Mechanism of Action

- Both sulfonylureas & meglitinides stimulate β cell insulin release
- BUT sulfonylureas & meglitinides bind to different parts of the ATP-sensitive potassium channel → meglitinides have a more rapid onset and shorter duration of action
## Pharmacokinetics

<table>
<thead>
<tr>
<th>Sulfonylureas</th>
<th>Meglitinides</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High bioavailability</td>
<td>- Repaglinide half life of 1h → makes it suitable for patients with poor renal function</td>
</tr>
<tr>
<td>- Metabolized in the liver, forms active and inactive metabolites that are eliminated along with unchanged drug through urine and bile</td>
<td>- Insulin response to repaglinide last 4-6h</td>
</tr>
<tr>
<td>- Half life &lt;10h for some, &gt;24h for others</td>
<td>- Nateglinide slightly faster onset &amp; shorter duration of action (3-5h)</td>
</tr>
<tr>
<td></td>
<td>- Both metabolized in the liver, producing inactive metabolites that are mostly excreted in the urine</td>
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### Pharmacodynamics

<table>
<thead>
<tr>
<th>Sulfonylureas</th>
<th>Meglitinides</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Higher failure rates as a monotherapy than metformin or rosiglitazone</td>
<td>• Well suited to patients with irregular meal patterns or to elderly at risk of hypoglycemia</td>
</tr>
<tr>
<td>• Can be used a first line treatment option in patients who are intolerant of metformin</td>
<td>• Usually used in combo with metformin, insulin or a thiazolidinedione</td>
</tr>
<tr>
<td>• Can be used in combination with other glucose lowering medication except meglitinides</td>
<td>• Can be used as monotherapy</td>
</tr>
<tr>
<td></td>
<td>• Randomized controlled trials found that greater reduction of HbA1c and FPG with repaglinide than nateglinide</td>
</tr>
</tbody>
</table>
How does it help with treating T2DM?

- In insulin resistance, cells do not respond properly to insulin → cannot be easily absorb glucose from bloodstream → beta cells increase levels of insulin to help glucose enter the cells.
- Sulfonylureas & meglitinides basically mimic insulin resistance state → overload of insulin to help with glucose uptake.
What can result from these drugs?

- **Sulfonylureas**
  - Hypoglycemia & weight gain
  - Studies suggested that sulfonylureas associated with less benefit against CD in patients with T2D than metformin
  - RCTs show no increase in cardiovascular mortality/morbidity

- **Meglitinides**:
  - Hypoglycemia & weight gain
  - No association between meglitinides & cardiovascular disease/risk
What can result from these drugs?

- Meglitinides and sulfonylureas are NOT a long term solution!
  - Studies in patients with T2D have shown that the efficacy usually declines after 6-12 months of sulfonylurea treatment
  - Overloading of insulin production worsens insulin resistance in the long run
  - Experiments done by Ketterer et al. suggest that insulin resistance in the body affects insulin levels in the brain & could prevent insulin from getting in to the brain → metabolic rate and hunger signals → obesity
    - We see weight gain as a side effect of the drugs
Thiazolidinediones
Thiazolidinediones (TZDs)

Mode of action:

- are peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists
  
  - PPAR-γ expressed in *adipose tissue*, liver, skeletal muscle
  
  - activates genes involved in *insulin sensitivity* (e.g., glucose and lipid metabolism)
  
  - differentiation of adipocytes: reduces circulating levels of FFAs
  
  - implicated in improvement of β-cell function
TZDs continued

- Onset is gradual, taking 2-3 month for max effect per individual

- Efficacy: reduces HbA1c by 0.7-1.6% as a monotherapy or combination

- Use: restricted due to cardiovascular risk, **weight gain**, and fractures
  
  - Weight gain is subcutaneous
  
  - Visceral fat is reduced or unaltered
Free Fatty Acids (FFAs)

Under normal functioning:

Insulin → IR binding → suppresses HSL → regulates FFAs in blood
FFAs and T2D

Under insulin resistance:

Insulin $\rightarrow$ IR binding $\rightarrow$ decrease suppression HSL $\rightarrow$ hydrolysis of TG $\rightarrow$ glycerol and FFAs in the blood $\rightarrow$ taken up by the liver $\rightarrow$ synthesizes more FFAs

FFAs reduce insulin sensitivity by inhibiting insulin-mediated glucose uptake
Randle/Glucose-Fatty Acid Cycle

Competition between sources to be used as energy by the body

- In a **fasting state** body will activate lipolysis and use fatty acids

- In a **fed state** will use glucose

- Mediated by Malonyl-CoA: signals glucose utilization & regulates FA oxidation

- In **insulin resistance**:
  
  Inability to metabolize glucose leads to too much FFA oxidation

  With TZDs there is more use of glucose usage as energy source and restricting the use of FFAs for hepatic gluconeogenesis
Thiazolidinedione

Liver
(Direct activation of PPARγ?)

Adipose

Activation of PPARγ

Muscle
(Direct activation of PPARγ?)

Modification of gene expression/transcription

↓ Lipolysis
↓ Free fatty acids

↓ TNF-α
↓ Leptin
↑ Adiponectin

Improved insulin sensitivity

↓ Plasma FFA
reset glucose-fatty acid (Randle) cycle

↓ Hyperglycaemia
GLP-1RA drug
Incretins

● Incretins: Inc = increase; in = protein
  ○ hormones to enhance insulin secretion.
  ○ decrease glucagon which decreases glucose
    ■ Goal of treating diabetes
  ○ 2 main hormones:
    ■ Glucose-dependent insulinotropic peptide (GIP)
      ● Released from K-cells in duodanum
      ● GIP levels in T2D: ability of beta cells to produce an insulin response are substantially reduced
    ■ glucagon-like peptide-1 (GLP-1)
      ● Released from L-cells in the ileum and colon
        ○ After a meal GLP-1 levels are reduced in T2D. Insulin regulating effect on beta cell function are compromised
Absorbed glucose in circulation stimulates insulin secretion by pancreatic beta cells.

Glucose in lumen of intestine stimulates secretion of incretins, which enhance glucose-dependent insulin secretion.
Mechanism of action: GLP-1RA’s activate on pancreatic Beta cells to increase nutrient-induced insulin secretion

- Food ingestion
- GLP-1RA combines to the GLP-1 receptor and transducing cAMP (secondary messenger)
  - (1) targeting PKA (Protein Kinase A) substrate phosphorylation and glucose-stimulated insulin secretion (independent stimulation of insulin exocytosis)
  - (2) sent to EPAC2 (major isoform of EPAC that is expressed in islets) which is expressed in the brain (neuroendocrine and endocrine tissues). It is involved in diverse cellular functions in tissues.
  - (3) transduced through the activation of RAP1 that plays a key role in controlling the Calcium dependent exocytosis in Beta cells and in other types of cells.
GLP-1RA’s con’t

- Adverse effects
  - Nausea
    - Can be terminated by 4-8 weeks by increasing the dose
  - Hypoglycemia
    - Risk is low unless it is combined with insulin or sulfonylureas
  - Possible association between GLP-1RAs and the risk of pancreatitis and pancreatic cancer has received much attention but there is no causal link yet to date.
GLP-1RA beneficial for treating T2DM

- Inhibiting glucagon secretion
- Reducing blood pressure and total cholesterol (LDL cholesterol and triglycerides)
- Delays stomach emptying which can help spread glucose absorption that will restrict hyperglycemia.
- Increase number of beta cells by aiding growth and inhibiting apoptosis.
GLP-1RA facts

- Administered by subcutaneous injection
- Efficacy
  - Exenatide
    - $T_{\text{max}}$: ~2hr
    - Half-life: 3-4hr
    - Elimination: through renal by glomerular filtration (formation of urine) and proteolytic degradation
  - Liraglutide
    - $T_{\text{max}}$: ~9-12hr
    - Half-life: 10-15hr
  - Lixisenatide
    - $T_{\text{max}}$: 1-2hr
    - Half-life: 2-4hr
    - Main affect on the meal right after injection
  - Albiglutide
    - $T_{\text{max}}$: 3-5 days
    - Half-life: 6-7 days
  - Dulaglutide
    - $T_{\text{max}}$: 12-72hr and Half-life: 4 weeks (stable levels after 2 weeks)
  - Not recommended to be given to patients who have severe renal disease
DPP-4 Inhibitors
Dipeptidyl peptidase 4 (DPP-4) inhibitors

Mechanism of Action:

- Inhibitors cause increases in GLP-1 and GIP which are rapidly degraded by DPP-4
  
  - GLP-1 causes reduction in glucagon secretion and involved in insulin biogenesis
  
  - GIP reduces gastric acid secretion and implicated in adipogenesis & β-cell proliferation
  
  - both are implicated in insulin response/secrection after eating
Food Intake

Release of active GLP-1 and GIP in response to an increased concentration of glucose in the digestive tract lumen.

DPP-4 rapidly degrades incretins (within few minutes).

DPP-4 Inhibitor blocks incretin degradation.

Key:
- GLP-1
- GIP
- Inactive Incretins

DPP-4

Incretins stimulate insulin secretion

Potentiates Incretin Effect + Insulin release – Glucagon release

Incretin Effect + Insulin release – Glucagon release

GI Tract
DPP-4 inhibitors continued

- Usually given as mono, dual, or triple therapy (with insulin, metformin, or TZDs)

- Efficacy:
  - Produces 77-99% of DPP-4 inhibition
  - Reduces FPG (fasting plasma glucose)
    - less than 126mg/dl
  - HbA1c 0.5-0.8% reduction

- Use: weight neutral, no CVD risk increase, low hypoglycemia risk
Alpha-Glucosidase Inhibitors
Alpha-Glucosidase inhibitors

- Prevents breakdown of carbohydrates
  - Blunting postprandial rise in glucose levels
- Mechanism of action: Inhibition of enzymes needed to digest carbohydrates
- Independent of insulin
- Long Term Effects: Small decrease in hemoglobin A1c levels
Breakdown of Carbohydrates

Poly-saccharide $\rightarrow$ Di, oligo-saccharide $\rightarrow$ Mono-saccharide
1. Starch ingested by mouth
Ingestion

- Breakdown of starch (polysaccharide)
- Salivary Amylase coats starch
  - Salivary amylase catalyzes hydrolysis of starch molecule
1. Starch ingested by mouth
1. Starch ingested by mouth

2. Starch reaches stomach
Stomach

- Amylase inactivated by stomach acid
- Only partially hydrolyzed into shorter polysaccharides or oligosaccharides
- Mixes contents around and sends to small intestine
1. Starch ingested by mouth
2. Starch reaches stomach
1. Starch ingested by mouth

2. Starch reaches stomach

3. Starch reaches lumen of small intestine
Small Intestine

- Starch reaches small intestine in partially hydrolyzed form
- Pancreas begins to secrete alpha-amylase at duodenum
  - Further breaks down starch
- Enterocytes
  - Cells of small of small intestine
  - Also Called “absorptive cells”
  - Contain Brush Border Enzymes
    - Located on microvilli
- SGLT found on enterocytes
  - GLUT2 Transporter to be absorbed into bloodstream
Folds
Villi
Mucosa
Submucosa
Muscularis
Serosa

Epithelial cell
Lacteal
Mucus producing cell
Arteriole
Venule
Lymph vessel
Brush border enzymes
Alpha-Glucosidase Inhibitors: Side Effects

- Flatulence
  - Fermentation of unabsorbed carbohydrates in large bowel
- Diarrhea
  - Disaccharides -> more solutes in lumen of GI system -> more water in GI system due to osmotic forces
- Abdominal Discomfort
- No effect on lipids or blood pressure
- No weight gain or loss
- Many patients stop treatment due to adverse effects
SGLT2 Inhibitors
SGLT2 inhibitors

- Prevents retention of glucose
- SGLT2 inhibitors block proteins -> less glucose in the blood
- Glucosuria
  - More glucose gets excreted through the urine
- Efficacy dependent on filtration quality of kidneys
  - Taken by those who are unable to tolerate metformin
Glucose Reabsorption

- SGLT1: Collecting duct
- SGLT2: S1 segment of proximal tubule
- Distal S2/S3 segment of proximal tubule

~90% reabsorption
~10% reabsorption

No glucose
Sodium Glucose Transporters (SGLT2)

- Main function = Glucose Retention
- Located in proximal tubule of nephron
  - Functional unit of kidney
- Transfers sodium down its concentration gradient
- Insulin Independent
- ATP & Na dependent
SGLT2 Inhibitors
Side Effects

Advantages

● Weight Loss
  ○ Glucosuria
● Drop in blood pressure
  ○ Glucose in proximal tubule pulls in water -> release water & sugar
● Low incidence of hypoglycemia
● May be used as a monotherapy

Disadvantages

● Urinary tract infections
● Genital mycotic infections
  ○ Yeast infections
● Dehydration
  ○ Releasing sugar and water outside of body
Summary:

Hypoglycemic Western Medicine

- **LIVE**: Glucose Production
  - Biguanide, Thiazolidinediones
- **INTESTINE**: Glucose Absorption
  - alpha-glucosidase inhibitor
- **PANCREAS**: Insulin secretion
  - Meglitinides, Sulfonylureas, Phenylalanine derivatives, Insulin
- **ADIPOSE TISSUE**: Peripheral Glucose uptake
  - Biguanide, Thiazolidinediones
- **MUSCLE**: More glucose leave blood into tissue

Less glucose into blood → Increase insulin secretion → Restore normal glucose level in blood
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Definitions for pharmacokinetics and pharmacodynamics courtesy of Prof. Pineda cogs 174 lecture 7 (FA 17)


Scenario #1

- A 50 y/o male has gastrointestinal problems and HbA1c levels of 7%.
- Which drug should he take?
Scenario #2

- A 45 y/o female diagnosed with Type II Diabetes has been taking metformin for about one month. Her HbA1c levels have only decreased from 7% to 6.8%.
- Which drug should she take in addition to metformin?

- More than one drug can be prescribed at a time. Side effects need to be managed.