DRUG-INDUCED DISEASE

- Definition:
  - The unintended effect of a drug that results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and/or to require hospitalization
- In other words, medications used to treat one disease can increase a patient's risk for another.
- Adverse reactions can develop into diagnosable diseases of their own.
  - Elevated BP → hypertension
  - Elevated blood glucose → diabetes
- Post-market drug surveillance and pharmacovigilance is needed to detect and evaluate previously unreported <u>adverse reactions</u>.
  - Need to differentiate adverse reactions (blanket statement) from drug-induced disease.

ATYPICAL ANTIPSYCHOTICS: WEIGHT GAIN, DYSLIPIDEMIA, DIABETES

- Indicated for schizophrenia but is associated with metabolic symptoms

- Dyslipidemia in the form of hypertriglyceridemia (TG > 150 mg/dL) occurs more frequently in patients on therapy with atypical antipsychotics.

- Patients experiencing antipsychotic-induced weight gain, elevated cholesterol and elevated blood glucose have been shown to be at increased risk for type 2 diabetes.
  - Each drug has a unique spectrum

1. Sadibašić B, Macić-džanković A, Šabić A, Torlak B, Lastrić G, Ćustović A. The incidence of dyslipidemia (hypertriglyceridemia and hypercholesterolemia) in patients treated with the new generation of antipsychotic drugs compared to conventional therapy. Med Glas (Zenica). 2014;11(2):350-5.
2. Tisdale J, Miller D. *Drug-induced Diseases: Prevention, Detection, and Management.* 2005.

ATYPICAL ANTIPSYCHOTICS – ADVERSE EFFECTS→ DRUG-INDUCED DISEASE

Table	Adverse effects of atypical antipsychotic treatments				
Drug	EPS	Hyperprolactinemia	Weight gain	Sedation	Other
Clozapine	Absent	Absent	High frequency	High frequency	Agranulocytosis, seizures, hyperlipidemia, hyperglycemia
Risperidone	Low frequency	Frequent	Low frequency	Infrequent	
Olanzapine	Rare	Rare	High frequency	High frequency	Hyperlipidemia, hyperglycemia
Quetiapine	Absent	Absent	Infrequent	High frequency	
Ziprasidone	Rare	Rare	Absent	Low frequency	QTc interval prolongation
Aripiprazole	Rare	Absent	Rare	Infrequent	

EPS, extrapyramidal symptoms.

CLAIMS DATA

- Includes:
    - Patient age and gender
    - Physician ID
    - Date and location of procedures/services provided
    - ICD-10 coding (diagnosis), CPT coding (procedures), amount paid or allowed limit
    - Medications prescribed, when prescribed, dose and days supplied
- Advantages of claims data:
    - Assessing medication compliance
    - Good reflection of tests, procedures, and services provided
- Many important elements of a patient's record are not captured in bills.

CLAIMS DATA VS. ELECTRONIC MEDICAL RECORDS DATA

Comparison: Claims Data vs. EMR Data		
	Claims Data	**EMR Data**
Scope of Data	Broad: Captures information from all doctors/providers caring for a patient	Limited: Captures only the portion of care provided by doctors using the EMR
Scope of Patients	Insured patients only	All patients (including uninsured)
Prescription Data	An accurate record of all prescriptions that were filled including dates of refills	Contains only that a physician prescribed a drug but not whether or not it was filled/refilled
Non Prescription Drugs	Not present	Present
Data Richness	Limited: diagnosis, procedures	Rich: lab results, vital signs, patient surveys, habits (smoking, etc), problem list, etc.

DRUG-INDUCED DISEASE IN CLAIMS DATA: AN ALGORITHM

- Does the ICD coding (diagnosis) indicate the existence of a drug-induced disease?

- Are there prescribed medications capable of inducing a disease state?

- Is there a diagnosis for the drug-inducible disease sometime after medication initiation? Is time of diagnosis consistent with the time to disease onset?

- Are there medications later prescribed that treat the drug-induced disease? Is the timing between the medications consistent with drug-induced disease diagnosis?

- Is there a dose-dependent relationship between the causative drug and disease?

- Are there similarities between individuals that develop the drug-induced disease?
  - Age and gender
  - Tests, labs, and procedures shared by affected individuals (CPT codes)
  - Location of procedures

ATYPICAL ANTIPSYCHOTIC-INDUCED TYPE 2 DIABETES MELLITUS

- Weight gain as an adverse effect → Type 2 Diabetes Mellitus

- Metabolic disorder characterized by high blood sugar, insulin resistance, and lack of insulin, with long-term complications such as heart disease and kidney failure.

- Criteria for Diagnosis of Diabetes:
  - Fasting Plasma Glucose (FPG) ≥ 126 mg/dL or higher on two separate tests
  - Plasma glucose ≥ 200 mg/dL after two hours after consuming 75 g glucose
  - A1C ≥ 6.5%

IDENTIFYING ATYPICAL ANTIPSYCHOTIC-INDUCED TYPE 2 DIABETES MELLITUS (1)

- <u>ICD-10 coding</u> – many codes for Drug-induced diabetes

- <u>Diagnostic Procedures</u>
  - Blood sugar tests
    - Fasting blood sugar test
    - Oral glucose tolerance test

- <u>Treatment</u>
  - 1st line medication is <u>metformin monotherapy</u> unless contraindicated
  - Glucometers, diabetic test strips, control solution

Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naïve schizophrenia patients. Neuropsychopharmacology. 2010;35(9):1997-2004.

IDENTIFYING ATYPICAL ANTIPSYCHOTIC-INDUCED TYPE 2 DIABETES MELLITUS (2)

- Retrospective cohort study (Schizophrenia patients from Denmark, 1997-2007)

- Most <u>causative medications</u>: Olanzapine (25%) > Clozapine (11.7%)

- Age at first antipsychotic prescription was 34.1 years.

- <u>Age of onset</u> of type 2 diabetes was 40.4-43.1 years.

- <u>Median time to onset</u> after first antipsychotic prescription was 3.9 years. Therefore we can check for diabetes medications (e.g. metformin) at around the 4 year mark, assuming comprehensive long-term electronic health and/or medical records.

- Females were associated with an increased diabetes risk.

- Discontinuers of olanzapine had no increased risk compared to patients that never received olanzapine.

1. Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naïve schizophrenia patients. Neuropsychopharmacology. 2010;35(9):1997-2004.

IDENTIFYING ATYPICAL ANTIPSYCHOTIC-INDUCED TYPE 2 DIABETES MELLITUS (3)

- Dose dependent relationships:

  - Olanzapine seemed to have dose related adverse metabolic effects on glucose and lipid metabolism.

  - No association between clozapine daily dose (mg/day) and weight gain.

  - No association between clozapine daily dose (mg/day) and the development of diabetes or nonconfirmed diabetes.

1. Cohen D, Correll CU (2009). Second-generation antipsychotic associated diabetes mellitus and diabetic ketoacidosis: mechanisms, predictors, and screening need. J Clin Psychiatry 70: 765–766.
2. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. Am J Psychiatry. 2000;157(6):975-81.

ATYPICAL ANTIPSYCHOTIC-INDUCED ACUTE PANCREATITIS

- Hypertriglyceridemia (TG ≥ 500) as an adverse effect → Acute pancreatitis

- Life-threatening emergency characterized by sudden inflammation and severe pain

- Caused by intrapancreatic activation of digestive enzymes (proteases), leading to self-digestion of the pancreas
  - Elevated serum pancreatic enzymes
    - Amylase (normal 60-180 units/L, >450 units/L indicative of damage)
    - Lipase (normal 5-160 U/L, >400 U/L indicative of damage)

- Can potentially cause harm to other vital organs (heart, lungs, kidneys), bleeding into the gland, infection, cyst formation and death

- Most people with acute pancreatitis recover completely with proper treatment.

IDENTIFYING ATYPICAL ANTIPSYCHOTIC-INDUCED ACUTE PANCREATITIS

- ICD-10 coding: K85.3 for Drug induced acute pancreatitis

- Pharmacovigilance study of pooled, spontaneously reported adverse events

- Most causative medications: Clozapine (40%) > Olanzapine (33%) > Risperidone (16%)

- Procedures: Diagnosis - blood levels of amylase and lipase
  - Other tests: secretin stimulation test, glucose tolerance test, imaging (ultrasound, CT, MRI), biopsy, endoscopic retrograde cholangiopancreatography
  - Treatments: pain medications, IV fluids, surgery in severe cases

- Time to onset (diagnosis) in most cases occurred within 6 months after the start of therapy.

- No significant correlation between daily dose and the time to diagnosis.

- Mean age ~ 39 ± 14 (but not age restricted) with slight male predominance.

- Location: Hospital emergency room

Koller EA, Cross JT, Doraiswamy PM, Malozowski SN. Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. Pharmacotherapy. 2003;23(9):1123-30.

SUMMARY

- Medications used to treat one disease can induce another, and this needs to be differentiated from normal disease since taking away the underlying causative medication is essential to relieving drug-induced disease.

- Claims data uniquely provides patterns that are consistent with trends in drug-induced disease, allowing for the identification of drug-induced disease even in the absence of traditional clinical data such as vital signs and lab values.

- Using claims data, we can identify drug-induced diabetes and pancreatitis associated with certain atypical antipsychotics.

QUESTIONS?