IDENTIFYING DRUG-INDUCED DISEASE FROM CLAIMS:
SECOND GENERATION ANTIPSYCHOTICS

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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 \(\rightarrow\) hypertension
  • Elevated blood glucose \(\rightarrow\) diabetes

• Post-market drug surveillance and pharmacovigilance is needed to detect and evaluate previously unreported adverse reactions.
  • 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.

### ATYPICAL ANTIPSYCHOTICS – ADVERSE EFFECTS ➔ DRUG-INDUCED DISEASE

<table>
<thead>
<tr>
<th>Drug</th>
<th>EPS</th>
<th>Hyperprolactinemia</th>
<th>Weight gain</th>
<th>Sedation</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Absent</td>
<td>Absent</td>
<td>High frequency</td>
<td>High frequency</td>
<td>Agranulocytosis, seizures, hyperlipidemia, hyperglycemia</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Low frequency</td>
<td>Frequent</td>
<td>Low frequency</td>
<td>Infrequent</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Rare</td>
<td>Rare</td>
<td>High frequency</td>
<td>High frequency</td>
<td>Hyperlipidemia, hyperglycemia</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Absent</td>
<td>Absent</td>
<td>Infrequent</td>
<td>High frequency</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Rare</td>
<td>Rare</td>
<td>Absent</td>
<td>Low frequency</td>
<td>QTc interval prolongation</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Rare</td>
<td>Absent</td>
<td>Rare</td>
<td>Infrequent</td>
<td></td>
</tr>
</tbody>
</table>

**Table**: Adverse effects of atypical antipsychotic treatments

### References

- [www.psychiatrictimes.com/schizophrenia/atypical-antipsychedotics-treatment-schizophrenia-spectrum-disorders](http://www.psychiatrictimes.com/schizophrenia/atypical-antipsychedotics-treatment-schizophrenia-spectrum-disorders)
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

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

- **ICD-10 coding** – many codes for Drug-induced diabetes

- **Diagnostic Procedures**
  - Blood sugar tests
    - Fasting blood sugar test
    - Oral glucose tolerance test

- **Treatment**
  - 1st line medication is **metformin monotherapy** unless contraindicated
  - Glucometers, diabetic test strips, control solution

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

- Retrospective cohort study (Schizophrenia patients from Denmark, 1997-2007)
- Most causative medications: Olanzapine (25%) > Clozapine (11.7%)
- Age at first antipsychotic prescription was 34.1 years.
- Age of onset of type 2 diabetes was 40.4-43.1 years.
- Median time to onset 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.

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.

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.

http://www.healthline.com/health/amylase-and-lipase-tests#Overview1
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

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?