THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

54yo F with Severe Insulin Resistance and Psychiatric Disease

Isabel Casimiro, MD PhD

Endorama 11-2018

Dr. Casimiro does not have any relevant financial relationships with any commercial interests.

HPI

- 54yo F with Hx of HFrEF, ischemic stroke, alcoholic pancreatitis, EtOH abuse, DVT who presented with epigastric pain x 2d
- Hx of bilateral chronic knee pain s/p corticosteroid injection 8 da
- Sitting at home and developed bloating abd pain that is waxing and waning, now at 10/10
- ROS: blurry vision, polyuria and polydipsia
- Heavy alcohol use and last drink was 3 da (told someone else it was today)
- POC BG >600
- EKG: tachycardia, no acute ischemia

PMH

- DVT
- HFrEF
- Pancreatitis, alcoholic
- EtOH abuse
- Anemia

Meds

- Eliquis 5mg bid
- Asa, 81mg
- Olanzapine 5mg bid
- Vitamin C 250mg
- Lipitor 40mg
- Chlorthalidone 25mg
- Iron 325mg
- Metoprolol 50mg
- Tramadol 50mg
- Miralax

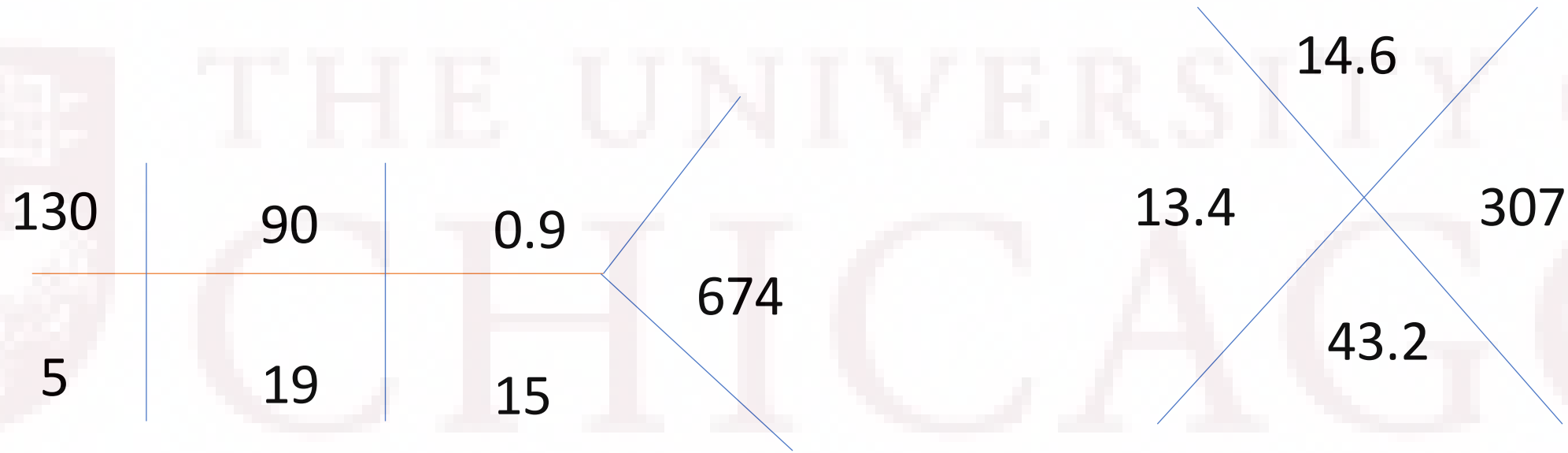
SH

- Quit smoking 7ya
- Drinks about 3 cans of beer and 2 glasses of wine daily

FH

- Heart dz & DM in mother and mat GM
- DM in mat uncle

Labs

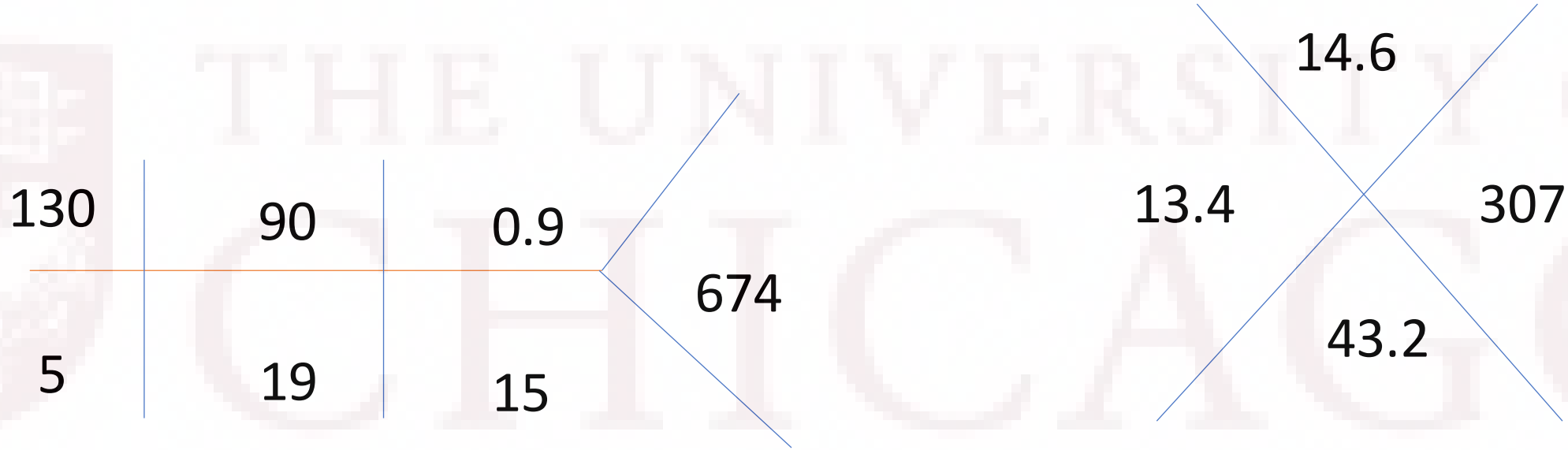


Ketones: 1.39

Protein: 8.6
Alb: 4.7
Alk phos: 128
AST: 27
ALT: 40
T bili: 0.9

Ca: 10.6
Mg: 2.1
Phos: 4.4

Labs



Ketones: 1.39

A1c: 10.7% (4.8% in 2017)

Protein: 8.6
Alb: 4.7
Alk phos: 128
AST: 27
ALT: 40
T bili: 0.9

Ca: 10.6
Mg: 2.1
Phos: 4.4

Thoughts?

Thoughts?

- New diagnosis of DM
- Could there be a component of pancreatitis related insulin deficiency?
- What about her anti-psychotic?

More HPI

More HPI

- Has had pancreatitis 4x
- Since Dec of last year she has been craving sweets like cakes and donuts
- Instead of eating food she will eat “a whole cake” and a 2L soda throughout the day
- Of note, in Dec of last year she was hospitalized here for delirium/hallucinations associated with alcoholism and for alcoholic pancreatitis; she was discharged on olanzapine
- Denies current hallucinations, has not seen a Psychiatrist since that hospitalization

Physical Exam

- BP: 104/69, Pulse 108, T: 36.8 C, wt: 99.8kg/220 lbs, Ht: 162.6cm/5’4” BMI: 37.76
- Constitutional: no acute distress, obese
- HEENT: EOMI, oropharynx clear
- Neck: supple, no thyromegaly + acanthosis nigricans
- Cardiovascular: regular rate and rhythm, nml S1/S2
- Pulmonary/Chest: good respiratory effort, clear to auscultation bilaterally
- Abdomen: soft, non-tender, nondistended
- Extremities: no edema
- Neurological: alert, oriented
- Skin: warm, dry
- Psychiatric: not agitated, thought content appropriate

Diabetic Management

Go to now | 7/13/2018 | 07/13/18 - 07/13/18

1 hr 2 hr 4 hr

Radiology-GMI-ED ADULT

07/12 0700 - 07/13 0659

Time:	0105	0139	0140	0239	0242	0340	0401	0406	0456	0535	
Glucose (mg/dL)	Graphs cannot display in the current view										
Accucheck											
POC Glucose		209		250		157			147		POC Glucose
Serum Glucose											
Serum Glucose	237						163				Serum Glucose
Insulin Drip											
insulin Dose (Units/hr)			7.1 U...		8.9 U...			5.5 U...			insulin Dose (Units/hr)
Insulin Dose											
insulin glargine Soln (Units)										25	insulin glargine Soln (Units)

07/13/18 - 07/13/18

Radiology-GMI-ED ADULT			CCD Adult Emergency Dept. University of Chicago						
07/12 0700 - 07/13 0659			07/13 0700 - 07/14 0659						
0406	0456	0535	0702	0723	0740	0852	0858	1145	1201
Graphs cannot display in the current view									
	147		255	253				417	
							292		
5.5 U...					0 Uni...				
						7			19
		25							

Endo Recs:

Endo Recs:

- Continue lantus 25U daily
- Increase novolog from 7U to 12U tid w meals, increase SSI from medium to high dose SSI tid cc and qhs
- “She has developed extreme insulin resistance since starting olanzapine and now has uncontrolled DM. The relationship between atypical antipsychotics such as olanzapine and the development of metabolic alterations such as development of DM and weight gain has been well established […] we would like to involve our Psychiatry colleagues to determine if Pt needs to stay on this medication or if it can be switched to another medication that is less likely to cause untoward metabolic effects.”

American Diabetes Association. Diabetes Care

Review Article | Position Statements

14. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes—2018*

American Diabetes Association

DOI: 10.2337/dc18-S014 Published 1 January 2018

Inpatient DM Management

- In the patient who is eating meals, glucose monitoring should be performed before meals. In the patient who is not eating, glucose monitoring is advised every 4–6 h
- More frequent blood glucose testing ranging from every 30 min to every 2 h is required for patients receiving intravenous insulin
- When discontinuing IV insulin, a transition protocol is associated with less morbidity and lower costs of care
- A patient with type 1 or type 2 diabetes being transitioned to outpatient subcutaneous insulin should receive subcutaneous basal insulin 2–4 h before the intravenous insulin is discontinued
- Converting to basal insulin at 60–80% of the daily infusion dose has been shown to be effective

Inpatient Glycemic Targets

- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (10.0 mmol/L)
- Once insulin therapy is started, a **target glucose range of 140–180 mg/dL** (7.8–10.0 mmol/L) is recommended for the majority of critically ill patients and noncritically ill patients.
- More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients, if this can be achieved without significant hypoglycemia.

Anti-Psychotics & DM

- Study of 307 patients with psychotic illnesses showed that clozapine and non-clozapine anti-psychotics (such as olanzapine) both caused type 2 diabetes (17% vs 18%), obesity (48% vs 54%), dyslipidemia (35% vs 38%) and hypertension (32% vs 39%) with mean treatment duration of 7.6 years, while other APDs also induced similar side-effects (Reed et al., 2014)
- Removal of olanzapine from non-clozapine group did not change results

TABLE 5. Antipsychotics Prescribed in the Non–Clozapine Group

Antipsychotic	Total
Olanzapine	51
Aripiprazole	50
Risperidone	39
Quetiapine	22
Perphenazine	19
Haloperidol	15
Haloperidol decanoate	11
Ziprasidone	8
Fluphenazine	6
Fluphenazine decanoate	6
Loxapine	3
Risperidone microspheres	3
Thiothixene	3
Paliperidone palmitate	1
Lurasidone	1

APDs Increase Rate of Hyperglycemia in Adults and Children

- European First-Episode Schizophrenia Trial reported a 20–30% incidence rate of hyperglycemia after 1 year of treatment with olanzapine, quetiapine and ziprasidone, but no significant differences between these APDs (Fleischhacker et al., 2013)
- Comparison of 28,858 APD users with 14,429 controls showed that the risk of diabetes increased 3-fold in children and adolescents treated with APDs (Bobo et al., 2013)
- The incidence of DKA is approximately 10 times higher in patients exposed to second gen antipsychotics, where most have a psychotic disorder, compared with the general population (Cohen and Correll 2009).

APDs and increased risk of DKA

- Systematic review of current studies regarding antipsychotic-associated DKA from Danish adverse drug event (ADE) reports (Polcwiartek et al., 2016)
- DKA occurred in 15 males (62.5 %) and nine females (37.5 %)
- Nine patients (37.5 %) were confirmedly diagnosed with T1DM following DKA resolution

Table 2
Overall comparison of antipsychotic-associated DKA with type 1 etiology, sorted by SGA ($n = 25$) [a]

SGA	DKA, *n* (%)	Confirmed T1DM, *n* (%)	SCZ or SZA, *n* (%)	M:F ratio	Mean age ± SD (range), years	Median time to DKA (IQR), months	Dose range, mg/day (*n*)
Aripiprazole	6 (24)	1 (16.7)	3 (50)	4:2	32.3 ± 15.8 (15–55)	5 (3–12)	10–30 (3)
Clozapine	3 (12)	1 (33.3)	3 (100)	3:0	39.7 ± 6.5 (33–46)	1 (0.53 –1.25)	500–550 (2)
Olanzapine	9 (36)	2 (22.2)	5 (55.6)	5:4	36.9 ± 9.4 (22–48)	6 (3.5–18)	5–30 (8)
Quetiapine	1 (4)	0	0	0:1	41	1.1	400
Risperidone	6 (24)	5 (83.3)	3 (50)	4:2	30.2 ± 15.5 (6–46)	5 (1.1–6)	0.5–8

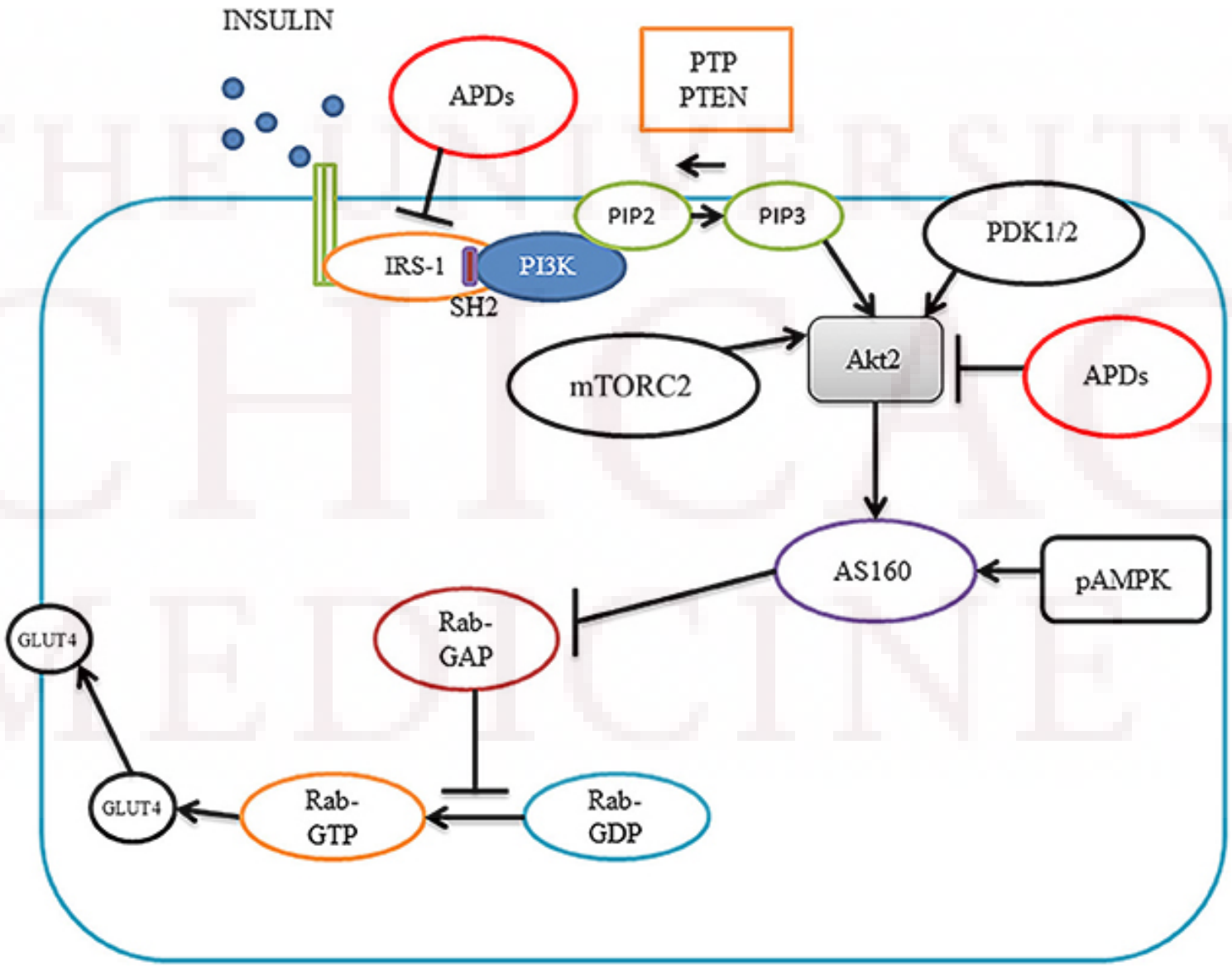
How do APDs increase insulin resistance?

- Unclear, but there are three molecular mechanisms that may explain APD-induced diabetes:
  - (1) insulin resistance due to the direct effect of APDs
  - (2) APD-caused insulin resistance through increased appetite & obesity
  - (3) APD-induced β-cell dysfunction and apoptosis

Insulin resistance due to the direct effect of APDs

- As many as 20–50% of APD treated patients are obese and have diabetes, but APD-induced insulin resistance can be independent of weight gain and increased food intake as well
- APDs have been shown to inhibit Akt activity and thus cause insulin resistance in muscle cells (Engl et al., 2005)
  - Muscle is the main site for glucose utilization and represents 80% of glucose consumption
- Olanzapine diminished insulin-induced IRS-1 phosphorylation and abolished insulininduced pPI3K, pAkt, and pGSK-3, while amisulpride, which does not cause diabetes, did not result in the above changes, indicating the importance of the insulin pathway in APDinduced diabetes (Engl et al., 2005)

Figure 1. Insulin signaling pathways and antipsychotic effects.

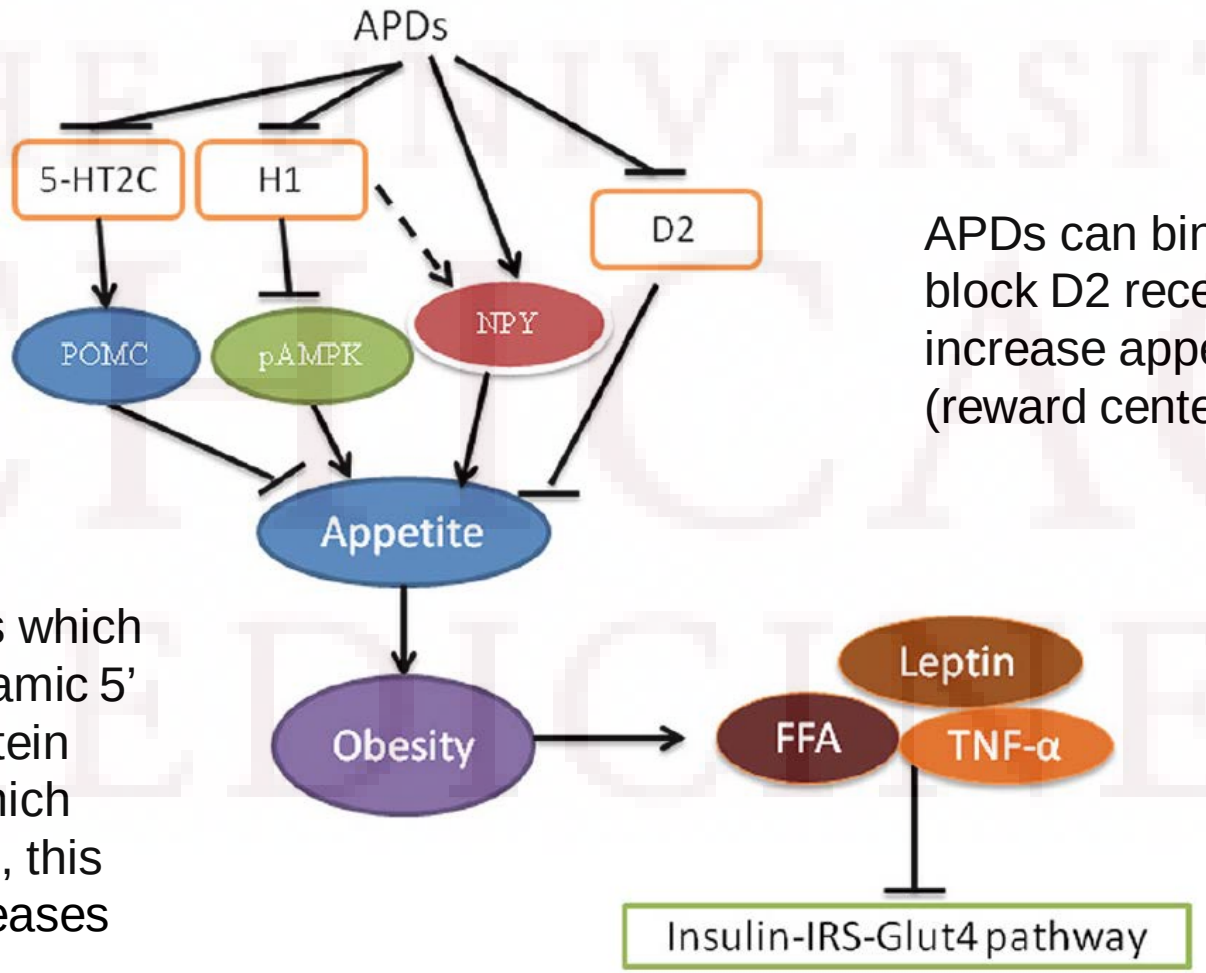


APD-caused insulin resistance through obesity

- APD-induced insulin resistance and diabetes are associated the increased weight gain, BMI and intra-abdominal adiposity, particularly in patients with chronic APD treatment (Bou Khalil, 2012; Manu et al., 2012)
- In rodent models male rats are repeatedly reported less sensitive to APD-induced weight gain than females
- APDs cause rapid weight gain (stage 1) followed by a steady weight gain for about 1 year (stage 2) to reach a plateau and then a stage (stage 3) for maintaining heavy weight
  - APDs block serotonin 5-HT2C, histamine H1, and dopamine D2 receptors to increase appetite and thus increase food intake, leading to obesity

FIGURE 2 | Antipsychotics cause insulin resistance via obesity.

Decrease POMC via inhibition of 5-HT2C receptors & directily increase NPY



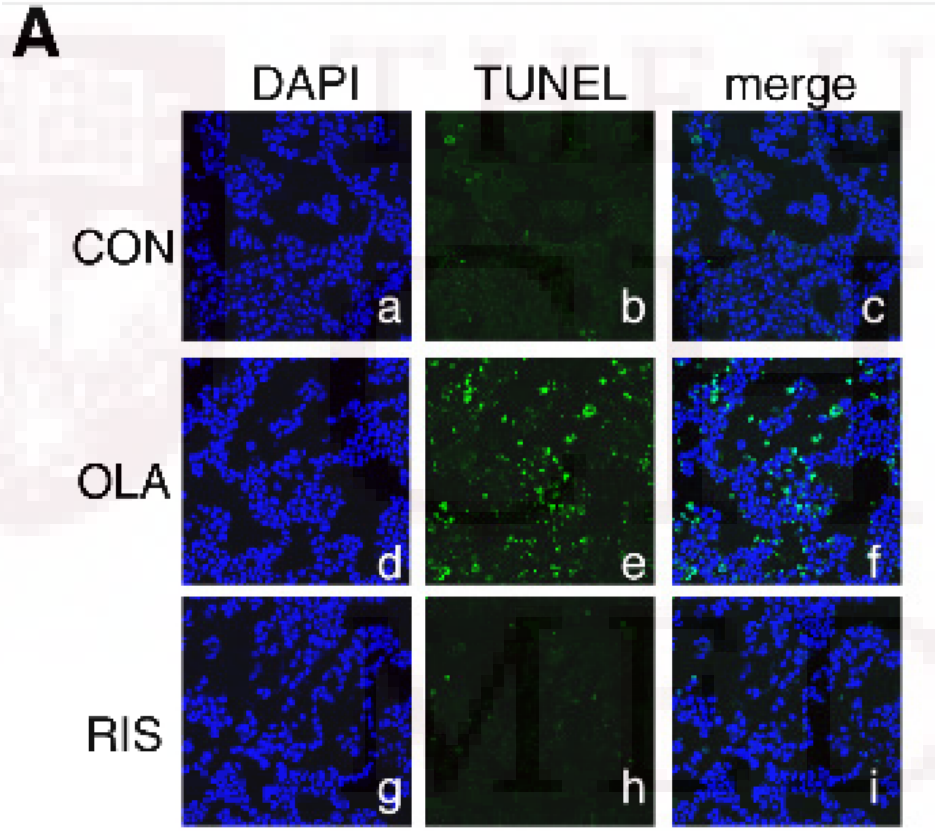
APDs can bind and block D2 receptors to increase appetite (reward center)

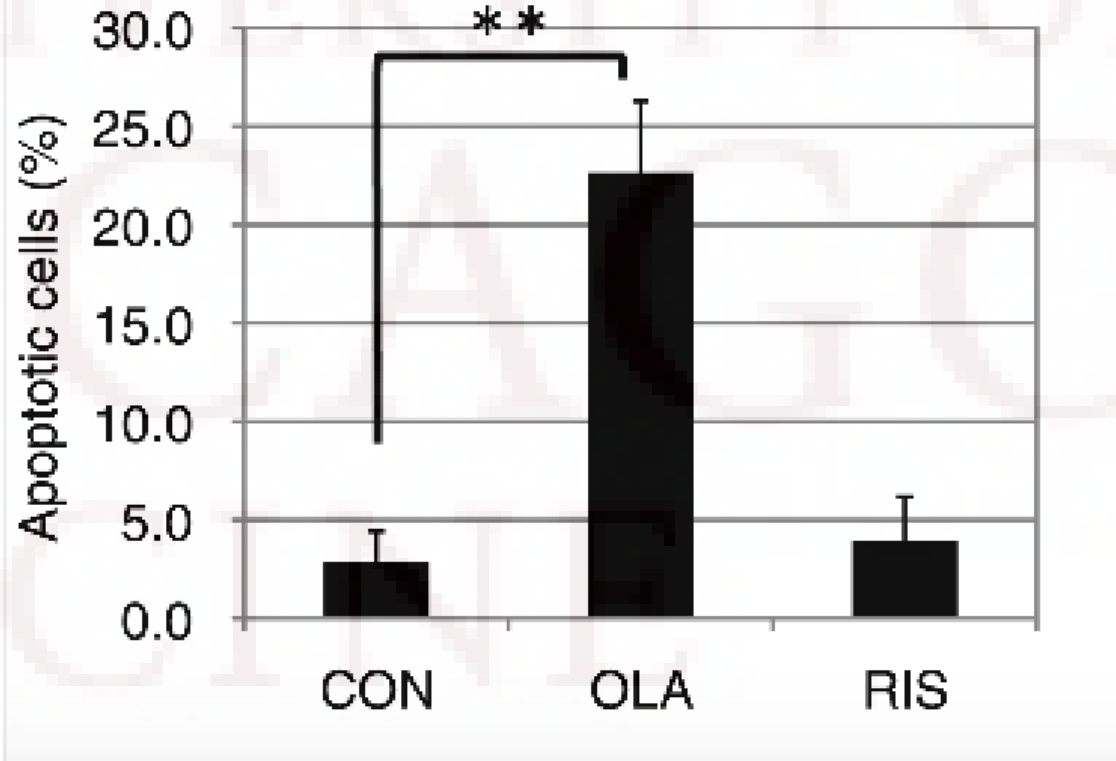
Block H1 receptors which activates hypothalamic 5' AMP activated protein kinase (AMPK), which stimulates appetite, this also indirectly increases NPY

APD-induced β-cell dysfunction and apoptosis

- Studies of olanzapine-induced insulin resistance in canine models no expected b-cell compensation for olanzapine-induced insulin resistance (compared to HFD) (Ader et al., 2005; Bergman and Ader, 2005)
- Acute treatment with clozapine and olanzapine at the dosages of 10 and 3 mg/kg respectively produced insulin resistance evidenced by decreased glucose infusion, increased hepatic glucose production and decreased peripheral glucose utilization
- Clozapine and olanzapine also decreased b-cell insulin secretion under hyperglycaemic clamp
- APDs have also been linked to an increase in apoptosis of β- cells, leading to lower mass and thus decreased insulin secretion. Ozasa et al. demonstrated that APDs can act directly on b-cells to cause apoptosis (Ozasa et al., 2013)

Effect of olanzapine and risperidone on a hamster pancreatic β cell line





(Ozasa et al., 2013)

Patient Course

Diabetic Management

Go to now | 7/16/2018 | 07/16/18 - 07/17/18

T3SW

Time:	07/16 0700 - 07/17 0659			07/17 0700 - 07/18 0659						
	2015	0036	0443	0818	0839	0840	1529	1535	1819	1831
Glucose (mg/dL)	Graphs cannot display in the current view									
Accucheck										
POC Glucose		233		204			151		149	
Serum Glucose										
Serum Glucose			196							
Insulin Dose										
insulin aspart (Units)	22				20	2		20		20
insulin glargine Soln (Units)					45					

- Psych recommended changing olanzapine to 0.5mg Haldol Qd
- Discharged on 45U lantus Qd, and nov 20U tid w meals, high SSI
- " It is unclear if patient has a primary psychotic illness vs substance-related symptoms. Patient is currently being treated with very small dose of haldol which would not be expected to make much of a difference if patient had primary psych issue
  - Dx: Delirium due to medical condition vs. Underlying neurocognitive d/o"

Continued Pt Course

- No show to Endo or Psych appointments, appears to have gone to PCP appt (community)
- Re-admitted 2 months later after “running out of insulin”
  - A1c now 12.2% (from 10.7%)
- After BGs came down with insulin (40U L and 20U N) in the ED she wanted to go home and reported “Walgreens now had her medications”
- 1 week later re-presented with abd pain -> EtOH induced pancreatitis (went to 2 birthday parties and indulged with EtOH)
  - Discharged with 50U lantus, Nov 20U tid cc, high SSI and PCP f/u; still on haldol

Conclusions

- ADA inpatient glycemic targets: 140–180 mg/dL; 110–140 mg/dL, may be appropriate for selected patients if hypoglycemia can be avoided
- Chronic administration of APDs is known to cause diabetes, which has been demonstrated in both epidemiological investigations in patients and in animal studies
- Higher risk of DKA has been seen with using APDs, and may uncover Pts who have T1DM or LADA
- Antipsychotics may induce insulin resistance, glucose dysregulation, and even type 2 diabetes mellitus independent of weight gain and adiposity
- APDs have been shown to inhibit Akt activity in the insulin pathway and thus cause insulin resistance in muscle cells
- APDs can increase appetite and food intake, as well as delay satiety signaling
- APDs have also been shown to cause β-cell dysfunction and apoptosis

Objectives

- To review inpatient blood sugar management guidelines
- To discuss the relationship between insulin resistance and anti-psychotic agents

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