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PRACTICAL APPROACH

DRUG INTERACTIONS IN A PALLIATIVE SETTING

DISCLOSURE STATEMENT:

I have no actual or potential conflict of interest in relation to this presentation.

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LEARNING OBJECTIVES

- **BE AWARE** OF SOME POTENTIALLY SERIOUS/FATAL DRUG INTERACTIONS IN PALLIATIVE CARE
- MAKE SAFE MEDICATION CHOICES THAT CAN POTENTIALLY **PREVENT** SIGNIFICANT/SERIOUS DRUG INTERACTIONS
- **IDENTIFY** POTENTIAL CLINICALLY RELEVANT DRUG INTERACTIONS IN PALLIATIVE PATIENT POPULATION
- **MONITOR** FOR SIGNS/SYMPTOMS OF DRUG INTERACTION EFFECTS

POTENTIAL DRUG INTERACTIONS IN PALLIATIVE CARE

- CYP450 (3A4 AND 2D6)
- QT PROLONGATION
- EXTRAPYRAMIDAL SYMPTOMS (EPS)
- SEROTONIN SYNDROME
- PHARMACODYNAMIC/ADDITIVE (ANTICHOLINERGIC/ CNS DEPRESSION)
- OTHER (IMMUNOTHERAPY, CANNABIS ETC.)

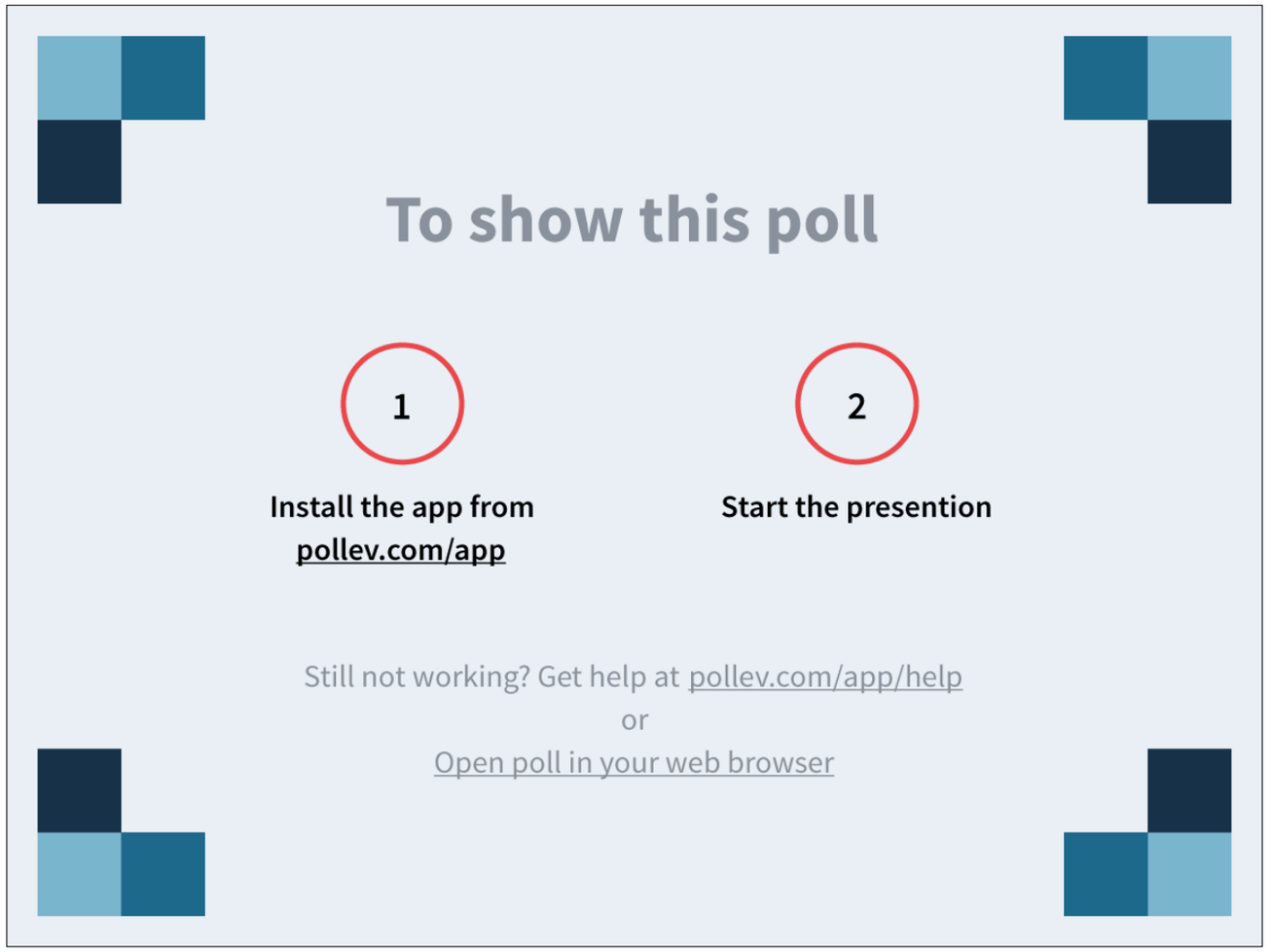
DRUG INTERACTIONS

- PHARMACOKINETIC DRUG INTERACTIONS:
  - When one drug alters the absorption, distribution, metabolism or excretion of the other drug

- PHARMACODYNAMIC DRUG INTERACTIONS:
  - When drugs influence each others effects directly. Usually occurring between drugs with similar or opposite pharmacological effects.

CYP450 INTERACTIONS: CASE

- 72 year old female with metastatic ovarian cancer.
- Diagnosis: Oral candidiasis (thrush) causing significant pain.
- Failed a 10 day treatment with nystatin and is started on fluconazole 100mg PO daily for 7 days.
- Home medications: fentanyl patch 75 mcg/hr q72h and hydromorphone for breakthrough among others.



Clinically, fluconazole can increase the dose of fentanyl by _____?
https://www.polleverywhere.com/multiple_choice_polls/ZnwjEWxziyaZtcF

CYP450 INTERACTIONS

- INHIBITORS:
  - STRONG: 5 FOLD INCREASE IN PLASMA AUC OR 80% DECREASE IN CLEARANCE = 200-300% “INCREASE IN DOSE”
  - MODERATE: 2 FOLD INCREASE OR 50-80% DECREASE = 50-100% “INCREASE IN DOSE”
  - 3A4: CLARITHROMYCIN, FLUCONAZOLE, VERAPAMIL/ DILTIAZEM, ERYTHROMYCIN
  - 2D6: BUPROPION, FLUOXETINE, PAROXETINE, SERTRALINE, METHADONE, HALOPERIDOL, DULOXETINE

FLOCKHART TABLE

Fluconazole = moderate inhibitor

- Need to be thinking could this patient tolerate a 50-100% dose increase at this time?
- Doesn’t mean can’t give fluconazole at all - just need to be aware, monitor or perhaps adjust the dose fentanyl
- Dose related
- Worse case - patient dependant chose alternative however most azoles are moderate CYP inhibitors

***tamoxifen is metabolized by CYP2D6 to active metabolites therefore 2D6 inhibitors (strong i.e. paroxetine, fluoxetine) may reduce its efficacy - some studies have shown decrease progression free survival, more recurrences etc. -> the clinical relevance is a debatable topic.

(Aubert RE, Stanek EJ, Yao J, Teagarden JR, Subar M, Epstein RS, Skaar TC, Desta Z, Flockhart DA. 2009Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors J Clin Oncol 2718sCRA508) -**Patients receiving TAM + a CYP2D6 inhibitor had a 2-year BrCa recurrence rate of 13.9% versus 7.5% in patients receiving TAM alone (HR 1.92, 95% CI 1.33–2.76, p < 0.001).**

Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, Paszat LF) - **absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine (an irreversible inhibitor of CYP2D6) were associated with 24%, 54%, and 91% increases in the risk of death from breast cancer, respectively (P<0.05 for each comparison. We estimate that use of paroxetine for 41% of tamoxifen treatment (the median overlap in our sample) would result in one additional breast cancer death within five years of cessation of tamoxifen for every 19.7 (95% confidence interval 12.5 to 46.3) patients so treated; the risk with more extensive overlap would be greater.**

(The impact of CYP2D6-predicted phenotype on tamoxifen treatment outcome in patients with metastatic breast cancer A Lammers, R H J Mathijssen, T van Gelder, M J Bijl, A-J M de Graan, C Seynaeve, M A van Fessem, E M Berns, A G Vulto, R H N van Schaik Br J Cancer. 2010 Sep 7; 103(6): 765–771) -**Co-administration of CYP2D6 inhibitors alone was also associated with a worse OS (HR=3.55; P=0.002; 95% CI: 1.59-7.96) and TTP (HR=2.97; P=0.008; 95% CI: 1.33-6.67) compared with patients without CYP2D6 inhibitors.**

CYP450 INTERACTIONS

- INDUCERS:
  - 3A4: PHENOBARBITAL, PHENYTOIN, ST JOHN'S WORT
- SUBSTRATES:
  - 3A4: FENTANYL, METHADONE, OXYCODONE, MIDAZOLAM, HALOPERIDOL, DEXAMETHASONE, TRAMADOL, ONDANSETRON
  - 2D6: HALOPERIDOL, TRAMADOL, *CODEINE, *TAMOXIFEN, *GENETIC POLYMORPHISMS

Pro drugs:
-Tamoxifen is metabolized by CYP2D6 to active metabolites therefore 2D6 inhibitors (strong i.e. paroxetine, fluoxetine) may reduce its efficacy - some studies have shown decrease progression free survival, more recurrences etc. -> the clinical relevance is a debatable topic.
-codeine -> morphine; tramadol -> active metabolites (CYP2D6 inhibition decreases analgesia i.e. fluoxetine)
Genetic polymorphisms: 75 different variants of 2D6 gene that convey wide range of different activity from no activity to ultra rapid metabolism (poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs)).
*A higher incidence of adverse events has also been reported in PMs that receive neuroleptics.
- Morphine and hydromorphone are substrates of UGT2B7 (glucuronidation) therefore not really much CYP interactions
Pregabalin and gabapentin - no CYP interactions

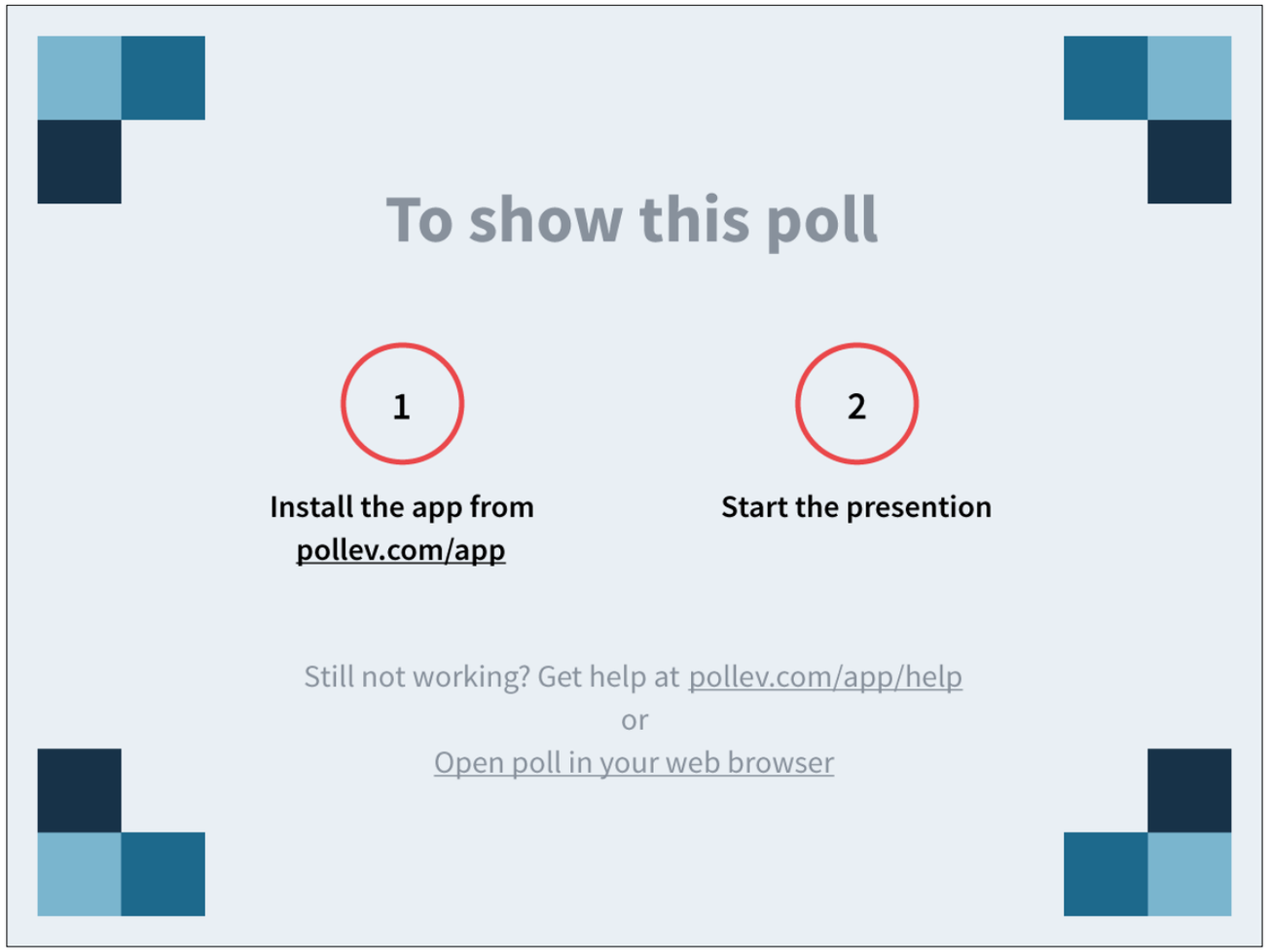
CYP450 INTERACTIONS: CASE WRAP UP

- CONTINUE FLUCONAZOLE AS ORDERED AND CURRENT FENTANYL PATCH DOSE, *BEING AWARE* OF POTENTIAL DRUG INTERACTION
- *MONITOR* FOR POTENTIAL INCREASED EFFECTS OF FENTANYL (SEDATION, CONFUSION, OPIOID NEUROTOXICITY ETC.)

Different story potentially if fluconazole dose was 400 mg (for fungemia or esophageal candidiasis) - would potentially change opioid (especially if pain not stable) to immediate release opioid or continue fentanyl patch (especially if at home) and monitor closely still.

QT PROLONGATION: CASE

- 78 year old female with metastatic lung cancer on methadone 15 mg PO q8h with hydromorphone for breakthrough.
- Other medications include citalopram 30 mg PO daily and clonazepam HS for longstanding depression and anxiety.
- Recently admitted with pneumonia, she was started on moxifloxacin.
- Patient had an ECG that resulted with a QTc = 543



When should you considering adjusting medication(s)?
https://www.polleverywhere.com/multiple_choice_polls/zCDgSG7iyE3PRgt

QT PROLONGATION

- RISK FACTORS:
  - **MODIFIABLE**: ELECTROLYTE DISTURBANCES, > 1 QT PROLONGING MEDICATION, CYP INHIBITORS, EXCESSIVE DOSES
  - **NON-MODIFIABLE**: FEMALE, CV DISEASE, >65 YEARS, LIVER OR KIDNEY IMPAIRMENT

QT prolongation lead to TdP which can decompensate further to ventricular fibrillation leading to sudden cardiac death.
[Pathophys: early afterdepolarizations (EAD's) and prolonged nonuniform repolarization that could initiate and perpetuate torsades de pointes]
[CV disease: HF, CAD, bradycardia]
-TdP is highly dependent on the presence of risk factors, and drug-induced TdP is an extremely rare event in patients without any risk factors. [Over 90% of patients who develop TdP have at least one risk factor and 71% have two or more risk factor.]
-each 10-ms increase in QTc interval contributes approximately a 5% to 7% exponential increase in risk for TdP in these patients.

QT PROLONGATION

- **DEFINITE RISK:** METHADONE, METHOTRIMEPRAZINE, HALOPERIDOL, CHLORPROMAZINE, DOMPERIDONE, CITALOPRAM, ONDANSETRON, ESCITALOPRAM, AZITHROMYCIN, CIPROFLOXACIN, MOXIFLOXACIN, LEVOFLOXACIN, FLUCONAZOLE
- **POSSIBLE:** CLOZAPINE, MIRTAZAPINE, RISPERIDONE, VENLAFAXINE, TRAMADOL
- **RISK WHEN USED WITH CONCOMITANT QT DRUGS/EXCESSIVE DOSE**: QUETIAPINE, TCA'S, METOCLOPRAMIDE, DIPHENHYDRAMINE

HTTPS://CREDIBLEMEDS.ORG/HEALTHCARE-PROVIDERS/DRUG-LIST/

CREDIBLE MEDS MOBILE APP

Woosley, RL, Heise, CW and Romero, KA, www.CredibleMeds.org, QTdrugs List, [Accessed: May 2018], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

QTc>500 = 2-3 fold increase risk torsades de pointe
[Also want to adjust potentially if have an increase in QTc > 60 ms]
It is dose related -> Want to look for drug interactions and potentially adjust doses/stop altogether.
QTc 450-500 = monitor closely
Technically for men: >470 is prolonged and for women: >480 is prolonged
Credible meds: university based and federally funded (US) Centre for education and research on therapeutics (under FDA contract safe use initiative).
Methadone: [Increases QTc ~10 ms for every 50 mg PO, can cause bradycardia]
->TdP usually with doses >100mg/day however has been reported with doses 29 mg/day
Haldol increased risk with IV and dose related (usually >30 mg)

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QT PROLONGATION

- HOSPITAL RISK SCORE
  - LOW RISK: 0-6 POINTS
  - MODERATE RISK: 7-10 POINTS
  - HIGH RISK: 11-21 POINTS
- MODIFIED COMMUNITY RISK SCORE: (NOT VALIDATED SCORING TOOL)
  - LOW RISK: <7
  - MODERATE TO HIGH RISK: ≥7

Tisdale JE et al. Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients. Circ Cardiovasc Qual Outcomes. 2013 Jul; 6(4): 479–487.

See one pager for table.

-a risk score predicting the development of QTc interval prolongation was developed using easily obtainable clinical variables that are independent risk factors for prolonged QTc interval in hospitalized patients in cardiac care units.

[Hospital: Age ≥ 68 (1); female (1); loop diuretic (1); serum K ≤3.5 (2); QTc ≥450 (2); acute MI (2); ≥ 2 QTc prolonging drugs (3); sepsis (3); heart failure (3); 1 QTc prolonging drug (3)

community: female (1); age >65 (1); loop diuretic (1); heart failure (3); family history (3); ≥ QTc prolonging drugs (3)]

All independent predictors of QTc prolongation

-The risk score effectively distinguished hospitalized patients at moderate or high risk for QTc interval prolongation from those at low risk.

-Using the risk score stratification of low (score < 7), moderate (score 7–10) and high (score ≥ 11), the incidence of QTc interval prolongation in the low, moderate and high groups was 15%, 37% and 73%, respectively

****

- In patients who developed QTc interval prolongation, laboratory values at the time of first occurrence of QTc interval prolongation, active diagnoses, and past medical history were used in the analysis.
- Unpaired Student's t-test was used to compare continuous variables, assuming equal or unequal variances between the groups, and Chi-Square or Fisher's Exact test, as appropriate, was used for categorical variables.

-Significant continuous variables were dichotomized based on the results of the univariate analysis. Dichotomized variables were compared using the Chi square or Fisher's Exact test as appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were determined for each variable.

-In order to arrive at a risk score for QTc interval prolongation, the sum of all points was calculated for each patient. In order to determine cut-off points for low, moderate and high risk of QTc interval prolongation, patients were stratified by total point scores and the proportion of patients with QTc interval prolongation was examined for each point score.

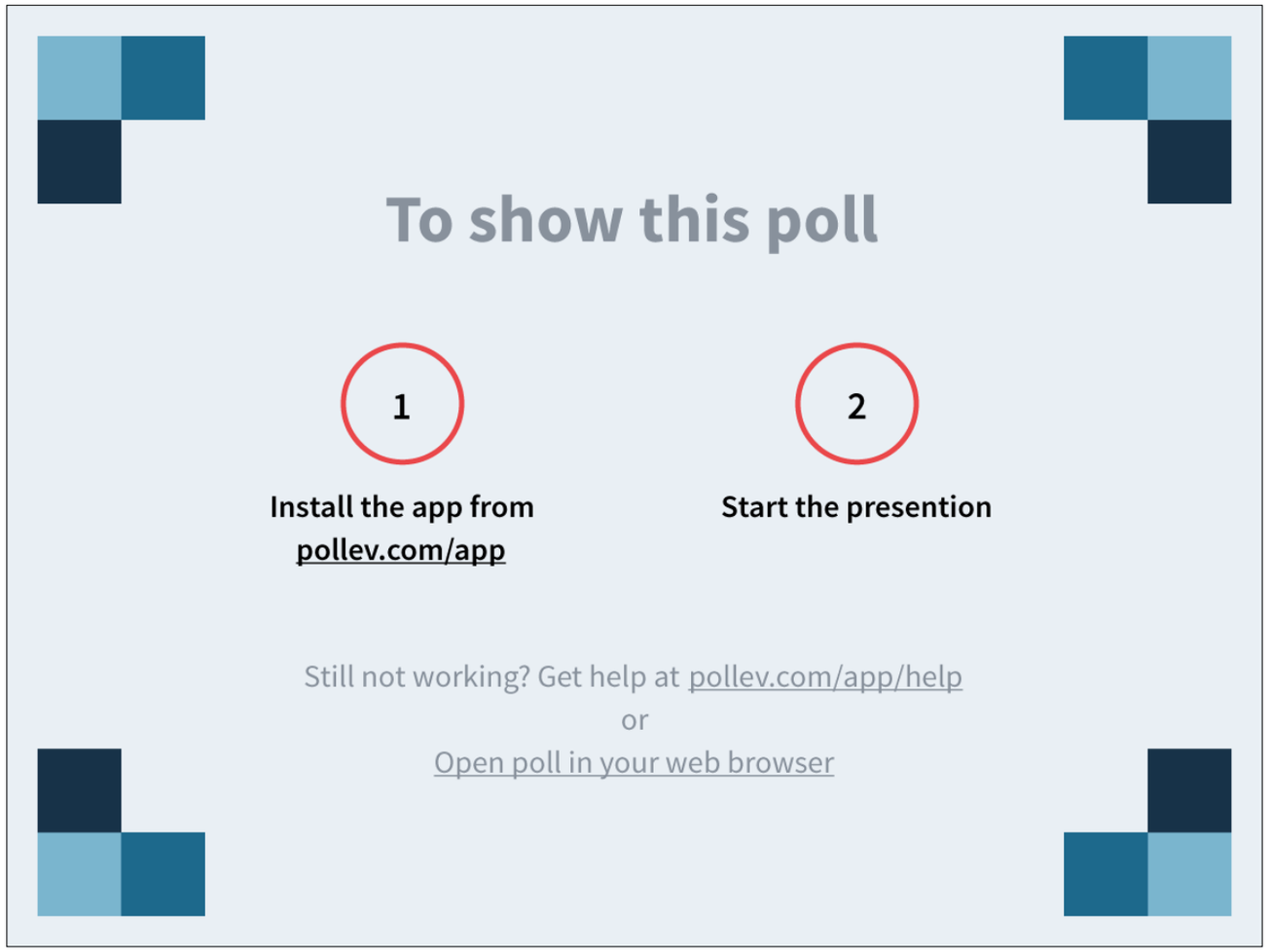
QT PROLONGATION: CASE WRAP UP

- *DISCONTINUE* MOXIFLOXACIN. START AMOXI-CLAV 875/125MG PO BID. (IF PENICILLIN ALLERGY: DOXYCYCLINE 100MG PO BID)
- DEPENDING ON BASELINE ECG AND PATIENT'S CURRENT MENTAL HEALTH STATUS, DISCUSS WITH PATIENT POTENTIALLY *DECREASING* CITALOPRAM TO MAX RECOMMENDED DOSE IN ADULTS >65= 20MG DAILY.
- *MONITOR* FOR NEW PALPITATIONS, FAINTING, NEW CHEST PAIN, NEW/ACUTELY INCREASED DYSPNEA, DIZZINESS, NAUSEA

Potential Alternative antibiotics:
CAP: Doxycyline, amoxi-clav
AE COPD: above or cefuroxime
Complete ECG at baseline (prior to starting methadone), within 30 days of initiation or dose changes then annually (more frequently if QT is prolonged or patient having syncope).

EXTRAPYRAMIDAL SYMPTOMS (EPS): CASE

- 82 year old male with metastatic bladder cancer recently admitted for refractory nausea and vomiting.
- Patient was started on metoclopramide 10 mg SC QID and haloperidol 1 mg SC q4h PRN.
- Bloodwork revealed reduced kidney function with eGFR ~ 25 ml/min (baseline is usually 40's).
- After a 3 days of being admitted the patient started becoming restless and fidgety, crossing and uncrossing legs repetitively and continuously hitting his hands on his legs becoming more and more distressed and anxious.



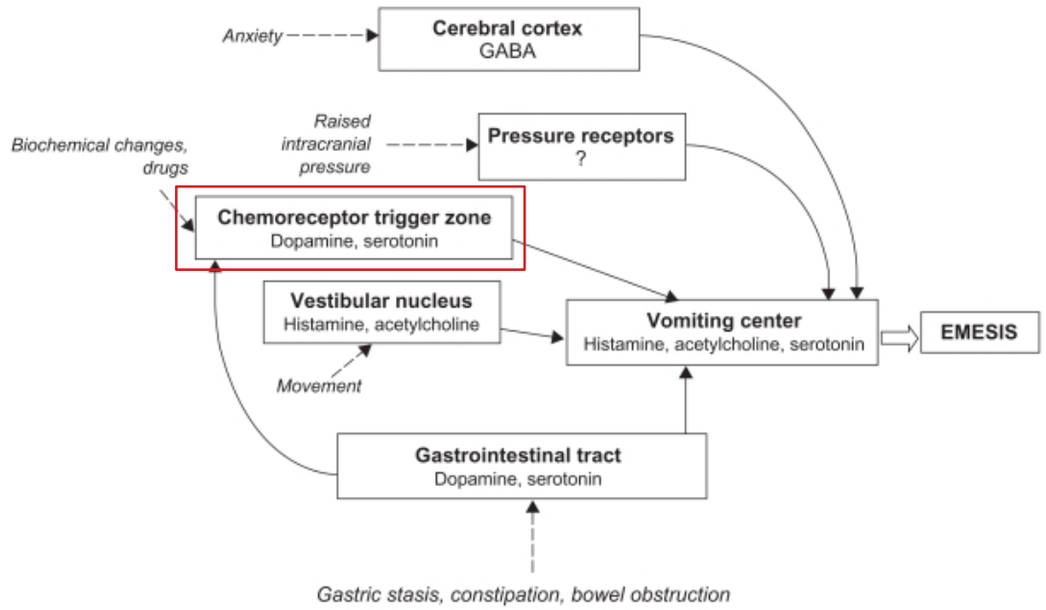
Which of these antiemetics has the highest risk of EPS?
https://www.polleverywhere.com/multiple_choice_polls/NmdeShvj4YtnHYr

EXTRAPYRAMIDAL SYMPTOMS (EPS)

- D2 antagonism:
  - >70% D2 receptor occupancy is correlated with antipsychotic efficacy
  - >80% receptor occupancy causes movement disorders
- Acute and chronic EPS:
  - Acute dystonia (painful muscle spasms): hours to days
  - Parkinsonism (tremor, cogwheel rigidity): 1 week
  - Akathisia (restlessness, urge to move): week 1 - 8
  - Tardive dyskinesia (lip smacking, choleric movements): months to years

Small window between therapeutic effects of antipsychotics and toxicity
Some cases akathisia has happened within 15 minutes of IV administration
New onset anxiety - consider akathisia
Akathisia vs delirium or both

EXTRAPYRAMIDAL SYMPTOMS (EPS)



Glare et al. Treating nausea and committing in palliative care: a review. Clinical interventions in aging. 2011: 6; 243-259.

Mechanisms of nausea: A lot of the causes of nausea in this patient population originate from dopamine receptors (why maxeran and haldol are first line medications) however comes with EPS risk (too much dopamine antagonism). Often require more than one medication that acts at dopamine receptors.

EXTRAPYRAMIDAL SYMPTOMS (EPS)

Table 5 Receptor affinities for selected antipsychotics (derived from Procyshyn et al. [92] Howard et al. [93], and Lal et al. [94])

Drug	D_2 blockade[a]	5-HT_{1A} blockade	5-HT_{2A} blockade	α_1 blockade[b]	α_2 blockade	H_1 blockade[c]	M_1 blockade[d]
Haloperidol	+++++	+	+++	+++	+	+	+
Levomepromazine (methotrimeprazine)	+++	?	++++	+++++	++	+++++	++
Chlorpromazine	++++	+	++++	++++	++	+++	+++
Olanzapine	+++	+	++++	+++	++	++++	++++
Quetiapine	++	++[e]	+++	+++	+++	+++	++
Risperidone	++++	++	+++++	++++	++	+++	–
Aripiprazole	+++++[e]	++++[e]	++++	+++	+++	+++	–

Table 4 Receptor site affinities of commonly used antiemetics[2,54,142]

Drug	Dopamine antagonist	Histamine antagonist	Acetylcholine (muscarinic) antagonist	Serotonin type 2 antagonist	Serotonin type 3 antagonist	Serotonin type 4 agonist
Chlorpromazine						
Cisapride						
Cyclizine						
Domperidone						
Haloperidol						
Hyoscine						
Levomepromazine						
Metoclopramide						
Ondansetron						
Prochlorperazine						
Promethazine						

Notes: Black, high affinity for receptor; dark gray, moderate affinity; light gray, low affinity; white, no known affinity.

Glare et al. Treating nausea and committing in palliative care: a review. Clinical interventions in aging. 2011: 6; 243-259.
Bush, SH et al. Clinical assessment and management of delirium in the palliative care setting. Drugs 2017: 77; 1623-1643

Higher affinity = higher EPS risk

Tables showing affinity for dopamine receptors among antipsychotics (top table) and antiemetics (bottom table)

Further research from studies (kinetic) showed metoclopramide D2 affinity very close to methotrimeprazine and prochloperazine and possibly a higher affinity. Haloperidol is highest affinity.

EXTRAPYRAMIDAL SYMPTOMS (EPS)

- Antiemetics:

Haloperidol>>metoclopramide>prochlorperazine>chlorpromazine>methotrimeprazine

- Antipsychotics:

Atypical: Risperidone>olanzapine>quetiapine>clozapine

Typical: Haloperidol>chlorpromazine>methotrimeprazine

Metoclopramide EPS incidence shows as high as 25% and is dose and duration related (>30mg/day, >12 weeks) also related to age and renal function (crcl<40%, elderly)

EXTRAPYRAMIDAL SYMPTOMS (EPS)

- Prevention:
  - Avoid chronic use if possible
  - Avoid in patients with risk factors (parkinsons, previous EPS, reduced renal function)
  - Avoid combining D2 antagonists
  - Use lowest effective dose
- Treatment:
  - Stop offending agent if possible
  - Benzodiazepines
  - Diphenhydramine 25-50 mg IV
  - Benztropine 1-2 mg IV

Pretreatment with diphenhydramine will prevent the acute extrapyramidal symptoms with high-dose metoclopramide but may block the peripheral prokinetic effects

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EXTRAPYRAMIDAL SYMPTOMS (EPS): CASE WRAP UP

- Stop metoclopramide and haloperidol.
- Start ondansetron 4-8mg SC q8h + PRN
- Consider low dose dexamethasone
- Consider benzodiazepine to manage akathisia symptoms if +++distressing to patient

- At a later time may be able to try renally adjusted metoclopramide (5 mg q6h) or full dose if patient's AKI resolves (EPS risk increases with pt's underlying risks (AKI, age), dose, IV, duration.) Avoid combining D2 antagonists.
- If patient became even more restless/agitated/distressed (even after metoclopramide stopped) consider benzodiazepine short term to help treat akathisia (increased sedation however and potential increase confusion/delirium)
- Ensure bowels being appropriately managed as ondansetron has higher constipation incidence

SEROTONIN SYNDROME: CASE

- 78 year old female with metastatic ovarian cancer has severe neuropathic pain as well as underlying depression.
- Medications: methadone 12 mg PO q8h plus duloxetine 90 mg PO daily and mirtazapine 30 mg PO HS.
- She was recently started on amitriptyline 25mg PO HS for pain and on-going insomnia.
- 3 days after starting amitriptyline she started complaining of generalized body aches, developed a mild tremor with myoclonus, became diaphoretic and was shivering. Vitals showed she was afebrile but a slight increase in blood pressure and heart rate. WBC was normal.

Blood cultures ruled out infection

SEROTONIN SYNDROME

- Mild: diarrhea, tremor, incoordination
- Moderate: Agitation, hyperreflexia, diaphoresis
- Life threatening: Delirium, rigidity, hyperthermia (rhabdomyolysis, renal failure, seizures, disseminated intravascular coagulation)
- Consider other differential diagnoses: Neuroleptic malignant syndrome, opioid induced neurotoxicity, EPS, anticholinergic toxicity

A spectrum of disease/symptoms reflecting degree of serotonergic activity.
Triad symptoms: altered mental status (agitation, restlessness, disorientation/confusion) + neuromuscular abnormalities (tremors, Clonus, hyperreflexia, rigidity) + autonomic hyperactivity (hypertension, tachycardia, hyperthermia, dry mucous membranes, shivering)
Usually develops over 24 hours of an increased dose, the addition of a serotonergic agent or over dosing.
NMS: usually develops over days to weeks; involves more sluggish neuromuscular responses (bradyreflexia) myoclonus is more rare, resolution takes usually over 9 days
Anticholinergic: muscular tone and reflexes usually normal
Other deliriums: difference is neuromuscular activation in SS
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Findings: bilateral babinski signs, ocular clonus (slow continuous horizontal eye movements), inducible muscle clonus, dilated pupils, deep tendon hyperreflexia
Can diagnose using Hunter Toxicity Criteria Decision Rules (84% sensitive and 97% specific: Must have been taking a serotonergic agent and meet one of the following:
- spontaneous clonus
- Inducible clonus PLUS agitation or diaphoresis
- Ocular clones PLUS agitation or diaphoresis
- Tremor PLUS hyperreflexia
- Hypertonia PLUS temperature >38 C PLUS ocular clonus or inducible clonus

SEROTONIN SYNDROME

- Medications with definite risk:
  - MAOI's
  - All SSRI's (paroxetine, sertraline, citalopram, including St John's Wort)
  - SNRI's (venlafaxine, duloxetine)
  - TCA's (imipramine, clomipramine, amitriptyline)
  - Opioids (methadone, fentanyl, meperidine, tramadol, dextromethorphan)
  - Lithium

Opioids = weak SSRI's (moreso with interactions I.e. MAOI's)
Dose related
Some SSRI's with longer half life (fluoxetine) can precipitate the syndrome even if discontinued for up to 6 weeks (along with irreversible MAOI's - can cause symptoms to persist for days to weeks potentially.
Monitor for drug interactions precipitating SS (pharmacokinetic and pharmacologic)
i.e. linezolid + SSRI = linezolid is reversible, nonselective inhibitor of monamine oxidase (Several cases of serotonin syndrome in patients taking linezolid and SSRIs have been reported, including two reports with sertraline, one with paroxetine, four with citalopram, and two with fluoxetine)

SEROTONIN SYNDROME

- Medications not considered a risk (rare):
  - Mirtazapine
  - Trazodone
  - Bupropion
  - Opioids (morphine, oxycodone, hydromorphone, codeine)
  - Methylphenidate
  - Cyclobenzaprine
  - Antipsychotics

Reported to cause serotonin syndrome in case reports (often in combination with SSRI's etc.) but likely do NOT have enough serotonergic activity to contribute.
Ketamine may have antidepressant-like effects involving a serotonin-dependant mechanism - some studies done in animals, not well studied.

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SEROTONIN SYNDROME: CASE WRAP UP

- **Discontinue offending serotonergic agents plus supportive care.**
- Stop amitriptyline.
- Start weaning/tapering duloxetine and mirtazapine.
- Consider benzodiazepines for treatment/sedation if symptoms persist or worsen.
- Once recovered and showing no signs of serotonin syndrome, if pain still uncontrolled can consider adjuvant gabapentin or pregabalin.
- For insomnia can consider melatonin or low dose zopiclone (3.75 mg) however monitor closely for any confusion/delirium.
- For severe depression consider restarting antidepressant with low serotonin syndrome risk (trazodone, mirtazapine, bupropion) in collaboration with specialist. Quetiapine is another option as an adjuvant for underlying depression + insomnia. Continue monitoring (serotonin syndrome, QT prolongation etc.)

Mild serotonin syndrome can develop into severe life threatening.
Mild = removing the offending agents and supportive care can resolve symptoms within 24 hours.
Moderate = may require benzodiazepines and possibly serotonin antagonist (cyproheptadine) and cardiac monitoring in hospital
Severe = as above but possible ICU admission (ventiliation/intubation, sedation etc)
For tapering of chronic pain or antidepressants may warrant discussion with specialists (psychiatrist, palliative/pain specialists, pharmacists)
Restarting causative agents needs to be risk vs benefit and case by case. If patient has complete resolution (usually within 24 hours for mild) this can be trialled with close monitoring.
Duloxetine: max dose with clinical benefit 60mg daily. Doses up to 120 mg were studied however didn’t show any increased benefit.
Mirtazapine doesn’t have as high risk serotonin syndrome - however in combination with others can help in precipitating SS.
Ensure patient is not taking any NHP’s
Higher incidence of SS in those with end stage renal disease on SSRI’s

PHARMACODYNAMIC/ADDITIVE: CASE

- 78 year old male with metastatic gastric cancer and history of malignant bowel obstruction.
- Past medical history of CKD (CrCl baseline ~30's).
- Current medications: Hydromorphone, hyoscine and metoclopramide.
- He started experiencing severe nausea with reflux/vomiting and burning pain in his esophagus. He was started on dimenhydrinate 25-50 mg SC q6h + ranitidine 50 mg SC q8h.
- Within a day he start having increased confusion and hallucinations and became agitated/restless.

PHARMACODYNAMIC/ADDITIVE: ANTICHOLINERGIC

- Anticholinergic Effects:
  - Dry mouth
  - Blurred vision
  - Constipation
  - Urinary retention
  - Delirium

PHARMACODYNAMIC/ADDITIVE: ANTICHOLINERGIC

- Beers Criteria list of strong anticholinergic drugs:
  - Antihistamines (dimenhydrinate, diphenhydramine, ranitidine)
  - Skeletal muscle relaxants (cyclobenzaprine)
  - Antidepressants (TCA's, doxepin >6mg, paroxetine)
  - Antipsychotics (methotrimeprazine, loxapine, olanzapine, chlorpromazine)
  - Antispasmodics/antisecretory (atropine, scopolamine, hyoscine)
  - Urinary incontinence (oxybutynin, solifenacin)

PHARMACODYNAMIC/ADDITIVE: ANTICHOLINERGIC

- Other factors that can potentiate the interaction:
  - Dose related
  - Patient factors
    - Renal or liver dysfunction

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PHARMACODYNAMIC/ADDITIVE: CASE WRAP UP

- Discontinue dimenhydrinate
- Decrease ranitidine to 50mg sc q24h based on eGFR
- Consider dexamethasone 4-6 mg sc daily
- Consider antacid product (i.e. almagel) PO q6h PRN
- Consider adjusting doses of other medications based on kidney function (metoclopramide)
- If bowel obstruction confirmed, consult with palliative specialist (discontinue metoclopramide and start low dose haloperidol)

Need to rule out MBO and assess cause of acute nausea/vomiting (i.e. constipation)
If MBO - discontinue motility agents (start dex and octreotide)
If no MBO dex still beneficial for pain and nausea
Dimenhydrinate effective for nausea caused by movement disorders/vertigo not this case (see mechanisms slide)

PHARMACODYNAMIC/ADDITIVE: CNS DEPRESSION

- CNS depressants can cause cognitive impairment, decreased level of consciousness and/or confusion
  - Benzodiazepines
  - Opioids
  - Non-benzo hypnotics (z-drugs)
  - Antipsychotics
  - Anticonvulsants (gabapentin)

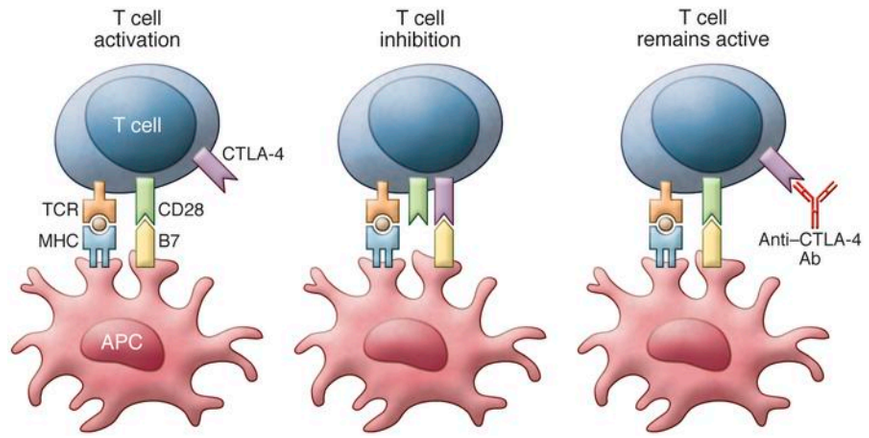
Need to also monitor for withdrawal reactions (delirium, agitation, restlessness)

August 2018: Pregabalin and the Risk for Opioid-Related Death: A Nested Case–Control Study - NSAID + opioid was control; only observational; not sure relation to gabapentin - future studies?

DRUG INTERACTIONS: OTHER

- GI bleed/ulcer: Dexamethasone +/- NSAID +/- blood thinners (give ranitidine or PPI)
- Warfarin + ___fill in the blank___
- Disease-Drug interactions:
  - Parkinsons dx + EPS medications (antiemetics of choice = domperidone, ondansetron)
  - CKD (moderate-severe) + anticholinergic medications + others (metoclopramide, morphine etc.)

DRUG INTERACTIONS: OTHER (IMMUNOTHERAPY)



J Clin Invest DOI: 10.1172/JCI80012

- Immunotherapy: Check-point Inhibitors (ipilimumab, nivolumab and pemboliuzumab) are monoclonal antibodies that are now becoming standards of care in several advanced solid cancers.

-Two types of immunotherapy have emerged as particularly effective over the past decade: immune-cell-targeted monoclonal antibody (mAb) therapy and adoptive cellular therapy (ACT).
-mAbs can either trigger the immune system by targeting tumour cells (causing cell death etc,) or act on cells of the immune system to respond to the tumour cell.
-Checkpoint blockade is a method by which T-cell function is stimulated with mAbs that block their inhibitory receptors
-Ipilimumab= CTLA-4 inhibitor
-Nivolumab and pembolizumab = PD-1 Inhibitors
J Clin Invest. 2015;125(9):3377-3383. https://doi.org/10.1172/JCI80012.
Figure 1: T cell activation requires costimulation through TCR and CD28.
Binding of B7 to CTLA-4 inhibits T cell function. Anti–CTLA-4 antibodies block CTLA-4 binding and prevent inhibition of T cell function. This figure is adapted from Clinical Therapeutics.

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DRUG INTERACTIONS: OTHER (IMMUNOTHERAPY)

- Dexamethasone: Commonly prescribed for analgesia, anti-inflammatory and antiemetic properties for symptom management in advanced disease.
- Theoretical interaction/hypothesis: Steroids antagonize the effect of the immunotherapy treatment, decreasing efficacy.
- Clinical studies are limited. The enhanced expression of PD-1 and CTLA-4 by dexamethasone has been shown in a controlled cellular environment but has not been clearly established in a clinical environment.

-A lot of the clinical studies done with immunotherapy excluded patients on corticosteroids.
-Dexamethasone/prednisone also prescribed as first line for immune related adverse events.
-Dex suppresses the immune response (going against the check point inhibitors mechanisms of action) - Some studies show dex has an effect on PD-1 and CTLA-4, enhancing the expression of both thereby suppressing the function of T cells.
-Risk vs Benefit for each patient.

DRUG INTERACTIONS: OTHER (CANNABIS)

- Cannabis: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the main psychoactive component of cannabis.
- THC is metabolized by CYP 3A4, 2C9 and 2C19
- THC is a 1A2 inducer
- CBD shown to inhibit CYP 3A4
- **Pharmacologic interactions** (most clinically significant): THC and CBD with CNS depressant drugs such as sedative hypnotics (benzodiazepaines) and alcohol.
- **Pharmacokinetic**: THC/CBD levels could be increased by 3A4, 2C9 and 2C19 inhibitors and decreased by inducers.
- **Pharmacokinetic:** THC could increase levels of drugs metabolized by CYP 1A2 and CBD could increase levels of drugs metabolized by CYP3A4

More than 65% of cannabis is excreted in the feces and approximately 20% is excreted in urine. Most of the cannabis (80-90%) is excreted within 5 days as hydroxylated and carboxylated metabolites
THC is metabolized in the liver by microsomal hydroxylation and oxidation catalyzed by enzymes of cytochrome P450 (CYP) complex
Increase THC/CBD: fluoxetine, omeprazole, macrocodes, diltiazem, verapamil
Decrease THC: phenytoin, st john's wort, rifampin
THC increase: amitriptyline, theophylline
CBD decrease: One study showed elevated clobazam levels in children 2015 Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy

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QUESTIONS OR COMMENTS?

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