ANALGESIC
ADVERSE DRUG REACTIONS

CASE STUDIES
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Conflict of Interest
Disclosure
No Conflict of Interests to Declare.

A conflict of interest is a particular financial or non-financial circumstance that might compromise, or appear to compromise, professional judgment. Anything that fits this should be included. Examples are owning stock in a company whose product is being evaluated, being a consultant or employee of a company whose product is being evaluated, etc.


Definitions
- Adverse Drug Events = injuries resulting from medication use, physical or mental harm or loss of function, including medication errors. (minor-to-life-threatening)
- Adverse drug reactions (ADRs) are previously known or newly detected side effects of drugs that may occur in the course of error-free medication use. (ISMP 2000)
- Includes allergic or idiosyncratic reactions
- Excludes withdrawal or abuse syndromes, poisoning/overdose.
- ADR = “Any response to a drug which is noxious and unintended, and which occurs at doses normally used…” (WHO 1975)
- Side effects - “an expected, well-known reaction resulting in little or no change in patient management… with intensity related to size of dose and has a predictable frequency.” (AHP 1995)
Variables in clinical drug effects

- Altered GI absorption - constipation, diarrhea, short gut
- Altered metabolism
  - Liver dz or altered metabolic enzymes (drugs/genes)
  - Reduced elimination of drug/metabolites
    - Reduced clearance = prolonged ½ life of drug
ev    - Causes - dz of kidney or liver, low cardiac output
e    - Decreased blood flow to kidney/liver)
- Patient -- Age, genetics, gender

Definitions

- Drug metabolism
- Drug elimination/clearance
- Drug-drug interactions

Drug Metabolism

- Breakdown (biotransformation)
  - Drug molecule is changed → metabolite
    - Metabolites may be active (have drug effect) or inactive
    - Drugs may travel unchanged to kidneys → excreted
  - Liver is major organ for drug metabolism
  - Small intestine-less but significant metabolism
  - Other organs-limited metabolism -- kidneys, lungs
Drug Clearance/Elimination

- **Drug Clearance** = elimination rate
  - Removal from the body of drug/metabolite
  - GI-blood to liver to bile to sm intestine
  - Kidney- filters blood into urine; unmetabolized water soluble drugs & metabolites
- **First pass** = % of ORAL med metabolized by liver or intestinal wall BEFORE reaching systemic circulation
  - Decreases amount of drug available systemically
  - Bypassed w/ intravenous route
- **“Second pass”** = drug metabolism upon return from systemic circulation to liver
  - Not bypassed w/ intravenous route
- **1/2 Life (T1/2)** = time for 50% of drug to be eliminated

Drug-drug interactions

- A change in response/effect of one drug in the presence of another drug, resulting in increase or decrease in effect of a drug at the site of action

Drug-drug interactions (Core Curriculum)

- **Types of interactions**
  - Additive effect- 2 drugs w/ similar action produce summed effect
  - Synergistic effect- 2 drugs w/ combined effect greater than either alone
  - Potentiation- 1 drug increases the effect of a second drug
  - Liver enzyme effect- Cytochrome (CYP)P450 is a family of enzymes that transform drugs into metabolites
  - Subject to competition and changes in metabolic speed of action
**Liver Enzyme Effects**

CYP450 metabolic activity can be increased or decreased by another drug, changing drug effects.

- Multiple subsets of CYP450 = different pathways
- Specific drugs use specific pathway(s)
- Inducer drugs — action of a specific enzyme metabolic pathway that increases a specific drug effect
  - Drug metabolized faster; lower plasma level, shorter duration
- Inhibitor drugs — action of a specific enzyme metabolic pathway that decreases a specific drug effect
  - Drug metabolized slower; higher plasma level, longer duration

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**J.B. Case Study**

49 y/o M w/ acute LBP w/ LLE radiculopathy

- Obese, mild HTN, Hyperlipidemia, opiate naive

**Meds**

- 2mg iv hydromorphone q4h prn (5 doses/24hr)
- NRS 8/10 relieved to 4/10; AAOx3
- Claustrophobic w/ MRIs
- Lorazepam 1mg ivp given
- Post MRI
  - easily aroused, drifts to sleep midsentence
  - Awake RR 14, O2sat 92%
  - Asleep RR 6-7 irreg, O2 sat 78% w/ 20 sec apneic periods

What happened?

- Suspect drug-drug interaction
  - Not oversedated on ivp hydromorphone
  - Not oversedated on w/ opioid caused oversedation
  - Both CNS depressants
    - Additive or Synergistic effects
      - Side effects w/ concurrent use greater than response with either drug alone.
  - Suspect undiagnosed Sleep apnea
    - CNS depressants lower sleep arousal; apnea (less arousal from sleep)↓
    - THM (Take Home Message)
      - Caution w/ simultaneous use of drugs w/ same effect
      - Consider undiagnosed sleep apnea risk
**STOP BANG Questionnaire**

High risk of OSA: answering yes to three or more items

Low risk of OSA: answering yes to less than three items

1. Snoring
   - Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

2. Tired
   - Do you often feel tired, fatigued, or sleepy during daytime?

3. Observed
   - Has anyone observed you stop breathing during your sleep?

4. Blood pressure
   - Do you have or are you being treated for high blood pressure?

5. BMI
   - BMI more than 35 kg/m²?

6. Age
   - Are you over 50 yr old?

7. Neck circumference
   - Neck circumference greater than 40 cm?

8. Gender
   - Male?

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**Dizzy case**

68 y.o F - diffuse joint pain/deformity r/t RA

- Comorbid depression, HTN
- New onset dizziness, nausea after admission
- Medications: (new) TDF 25 mcg/hr, (old) sertraline (Zoloft), (old) hydrocodone, (old) doxazosin (Cardura)
- VS wnl; no orthostatic drop
- Na on admission 135; 4 days after TDF 126;
  - Endocrinologist d/c'd TDF; Na 136 in 4 days; n/v/dizziness resolved
  - Pain increased; resumed TDF; 4 days later Na 123
  - N/V & dizziness recurred

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**The Low Sodium Story**

- Multiple causes
  - Na loss - i.e. thiazide diuretics, diarrhea
  - High excess - i.e. CHF, CRF, hypotonic IVF, polydipsia
  - Neuro-hormonal - SIADH
    - Syndrome of inappropriate antidiuretic hormone (ADH) - reabsorbs water from renal tubules into blood
- Causes of SIADH
  - Many drugs - SSRIs, carbamazepine, oxcarbazepine, amitriptyline, cyclophosphamide, opioids, chemotherapy, NSAIDs, ciprofloxacin, amiodarone, oxytocin, ACE inhibitors
  - CNS disorders - (CVA, ICB/trauma, infection, transitory)
  - Diseases - pneumonia, HIV, hereditary, malignancies
The Low Sodium Story

- hyponatremia (HN)
  - Na+ is chief extracellular ion
  - SIADH causes serum dilutions
    - From serum promotes water to move extracellularly
    - Into Neural (brain), GI, muscle tissues
    - No peripheral edema w/ SIADH
  - Dizziness, nausea, vomiting, HA, anorexia, muscle cramps/weakness, diarrhea, depressed LOC, seizures
  - Cerebral edema/encephalopathy- may be fatal
  - S/S more severe w/ acute, rapid changes

Dizzy Case Study

- Patient Risk factors for HN
  - Elder, female
  - Meds – opioids & SSRI-- SIADH
    - Fentanyl subclass = synthetic piperidine opioid
      - Associated w/mild serotonergic effect
    - SSRIs- documented SIADH association alone
      - Clinically significant risk w/ combination of serotonergic SSRIs, TCAs, NSRTIs:
        - Some studies- 10 fold risk increase w/ SSRI+ diuretic+ ACE inhibitor
        - In this case fentanyl added to pre-existing SSRI

Dizzy Case Study Conclusions

- Synergy of combined SSRI & TDF caused SIADH in this patient
- Pt benefited from both medications
- Rx- salt tabs; s/s controlled
- Option- non-serotonergic opioid (i.e Morphine)
Final Words on HN

Most frequent electrolyte imbalance for inpatients
• One study: 42%; 25% on admission (can be chronic)
• Risk w/ multiple medications & elder age
• Serum < 129mEq/L earlier w/ elders
• Odds ratio for falls and fractures in elders *
  ◦ Mild cognitive impairment
  ◦ May ?? osteoporosis – induces bone resorption to mobilize Na
• Elders w/ unsteady gait and/or confusion should be checked for mild hyponatremia


Case Study - JL

50yo F chronic LBP/PLPS. Bipolar dz, hx med overuse (now meds dispensed per spouse)
• s/p fall, drowsy, falling asleep during conversation
• Stable Home meds x years
  ◦ Morphine ER 60mg q12h, tramadol 50mg tid prn, baclofen, clonazepam 1mg tid, quetiapine (seroquel) 600mg qhs
• VS 8.1-69-18 82/46, 95% sat
  ◦ urine tox = + opioids/bzd, neg ETOH;
• Abnormal labs - BUN 43/crt 2.5, Hgb 10, Hct 32.2, myoglobin 314, troponin <0.03
• Why so sleepy?

Drugs drug interactions?
• Additive effect? (opioid & BZD & psych med)
  ◦ PTA- Stable meds w/o ADRs so why now w/ ADR?
• Liver enzyme interactions? None known and why now?
• Altered Clearance?
  ◦ Clinical alterations? Yes w/ acute kidney injury (AKI)
  ◦ ED- narcan given w/ alertness & anxiety
  ◦ Admitting dx medication overuse/abuse
  ◦ Morphine w/ active metabolites renally cleared
  ◦ Metabolites accumulate w/ clinical effect plus parent drug effect
  ◦ 4x of intermittent AKI w/ similar s/s
Morphine
- 95% metabolized in liver by glucuronidation
- 3 active metabolites
  - M3G (inactive analgesic), M6G and normorphine
  - Recirculated by liver for days in healthy individuals
  - Add analgesia & neurotoxic/neuroexcitatory effects
  - Metabolites last longer than parent drug — especially in renal impairment leading to oversedation, hypotension, bradycardia, resp depression, urinary retention, myoclonus, etc.

JL Case Study Outcome
- Morphine ER d/c’d;
  - Keep clonazepam 0.5mg tid, quetiapine 500mg qhs
  - Started oxycodone ER 30mg q12h
  - 24 hr later more alert; mildly drowsy
  - BUN 33/crt 1.4
  - Pain mod
  - Added lumbar medial branch nerve block w/ RFA w/ further improvement
  - THM
    - Ask what is most recent change? (altered renal clearance)
    - Don’t assume hx of med overuse/abuse explains all new s/s

Case Study – A.N.
- 86 y/o F
  - Admit w/ new Left Thoracic HZ & severe pain
  - PMH- LBP/PLPS, severe OP, RA (chronic steroids), hx multiple fxs, episodic CKD
  - 8/22- Transforaminal thoracic epidural steroid (TESI)
    - Continued thoracic pain- now both left & right sides
    - 8/27- Rib Xrays showed acute fx ribs 3-4-6-7-8
    - Refused further intervention of intercostal nerve blocks- states rough handling during TESI!
AN. Clinical Course
• 8/21 - AAOx3; severe burning
  • BUN/Crt 52/1.2, LFTs wnl
  • Meds: gabapentin 300 mg tid (used PTA)
  • methadone 2.5 mg q12h (new)
  • amitriptyline (Elavil) 25 mg bid (new)
• 8/26 - AAOx3; pain severe w/ movement mod/hi at rest;
  • BUN/Crt 65/1.8
  • Methadone 5 mg q12h: gaba same @ 300 mg tid
• 8/28 - unresponsive episodes, VSS, twitching
  • BUN/crt 80/2.3
  • What happened?

What happened?
• Sedation, unresponsiveness, twitching, VSS
• Marked Sedation (all can cause)
  • VSS - so opioids less likely cause
• What's old?
  • Tolerates gabapentin dose PTA w/o side effects
• What's new?
  • Methadone-started 8/20; increased 8/26; s/s noted 8/28
  • TCA (amitriptyline) - started 8/21; no s/s x 1 week
• Worsening AKI --

What happened?
• Decreased renal function – lower drug clearance
• Methadone
  • Metabolized in liver
  • Steady plasma levels 3-5 days
• Amitriptyline
  • Metabolized in liver; T1/2 = 10-26 hr
• Gabapentin
  • Excreted unchanged from kidney
  • Not metabolized in liver
  • Accumulates in renal failure
  • Known for twitching and sedation w/o VS changes
A.N. Case Study Outcome

- 8/28- held gaba & ami; held p.m. methadone
- 8/29- j methadone to 2.5mg q12h
  - Pt refused further methadone; pain mod
  - Twitching present but less
  - Still drowsy; BUN/crt 69/1.8
- 9/2- AAOx3, pain low/mod, no twitching
  - Hydrocodone/acetaminophen 10/325 2-3 tab/day
  - Amitriptyline 10mg qhs
  - No gabapentin x 5days ; BUN/crt 25/0.8

Conclusions

- Multiple factors as possible contributors
- Likely dominant factor AKI & gabapentin
- 7 days post TESI had less HZ type pain
  - Rib pain briefly severe w/ position changes
  - Able to participate slowly w/ Therapy
- Severe Osteoporosis pts
  - Need very gentle position changes to avoid new fx's!

LW Case Study

- 61 y/o M; hx ETOH abuse, acute LBP/RLE pain,
  - fungal infection great toe (mild toe pain)
  - MRI - L5-S1 discitis/osteomyelitis; sm disc extrusion
  - AAOx3; VSS: Pain severe & limiting activity; opiate naive.
- Rx
  - IV, Abx, topical ketoconazole to toe infection
  - 4/9- start TDF 25mcg & gabapentin 300mg tid, hydromorphone (HM) 1mg ivp q4h prn
  - 4/13 - Pain severe;
    - TDF 50 mcg/hr, gabapentin 600id, HM 1mg ivp q3hr
    - NRS decreased to 4/10 w/ ambulation tolerance
LW Case Study

7 days later (4/20) - severe LBP/RLE

- Awake; eyes closed; furrowed brow
- VSS;
- MRI w/ fluid/disc impinging S1 nerve root
- Rx - gabap 800 H5 & 600 bid,
  - add amitriptyline (Elavil) 10mg HS,
  - hydromorphone 4mg po q4h prn,
  - Continue same TDF 50

4/20 Eyes closed, awake Severe wnl Bun/crt 14/0.9
- gabap & stelv d/c’d by PCP (received 3 doses gab 600, no stelv)
- VSS; falls asleep midsentence, hand tremors; pain lw,
  - TDF 25 mcg/hr
- Confused, drowsy, awakens spontaneously; pain mod
  - VSS sleeping RR 5/min & 14 awake; Bun 27
  - Rx - d/c TDF 25, keep HM 4mg po (x 1/2hr used)
- Less drowsy; still drifts to sleep or “stares”; pain mild
  - Oriented to time; RR 8 asleep & 16 awake
  - BUN/crt 20/1.1
- Drowsy, drifts to sleep, confused, pain mod
  - No opioids used / 24 hr
  - BUN/crt: 12/0.8, LFTs mild elevation

<table>
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<tr>
<th>Mental</th>
<th>Pain</th>
<th>VS</th>
<th>Lab</th>
<th>Rx</th>
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<tr>
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<tr>
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<td>None drawn</td>
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<tr>
<td>4/22</td>
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<td>mid tremors</td>
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<td>RR 9 asleep &amp; 14 awake</td>
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<tr>
<td>4/24</td>
<td>Confused, Confused</td>
<td>Mild</td>
<td>RR 6 asleep &amp; 16 awake</td>
<td>BuN/crt 20/1.1</td>
</tr>
</tbody>
</table>
| 4/27     | Drowsy, drifts asleep, Confused | mild | RR 6 asleep & 16 awake | BuN/crt 12/0.8 Ammonia 5%  (o) 11-47
  - mid/LFTs up | No opioids 24 hr TDF off x 48 hr |
What Happened?
• Drowsiness, AMS w/ fall in RR
  • RR improved w/o opioids
  • AMS remained altered
• Impaired hepatic clearance of opioids
  • Kidney clearance unimpaired
  • Improved RR w/o long acting opioid (TDF)
• Hepatic encephalopathy remained longer
  • Ammonia and LFTs elevated
  • Eventually AAOx3 w/ prn HM only and mod pain

Hepatic Encephalopathy
• Decreased clearance of cerebral toxins
• Ammonia = protein metabolite from bowel
  • Detoxified in liver to water soluble form for renal excretion (BUN)
  • Liver impairment allows ammonia into blood & CNS
• S/S vary
  • Minor-impaired concentration, mild or episodic drowsiness, tremors, slurred speech
  • Major- marked confusion to profound coma

Hepatic Encephalopathy
• Why Now? (No ETOH for weeks)
  • Multiple possible precipitants
    • i.e. Infection, constipation, diuretics, renal failure, medications
  • Consider drug induced liver injury (DILI)
    • Idiosyncratic-genetic aberrant drug metabolism causing hepatocyte necrosis
    • Onset weeks to months after drug use
    • Some common drugs- amiodarone, diclofenac, isoniazid, disulfiram, ketoconazole, valproate.
    • Most recover w/ removal of drug
T.S. Case Study

55 y/o M w/ DM, obesity, OSA
- Infected knee prosthesis and TKA revision.
  - PTA- 100mg hydrocodone/day
- POD #1 pain severe 6-9/10 & tingling
  - 15 mg po oxycodone/12hr (5/325 tabs)
  - 1mg ivp hydromorphone/12hr
  - 30mg hydrocodone/12
  - 30mg ivp ketorolac/12hr
- Abx- cefazolin (Ancef)
  - Rifampin 300mg bid added POD #2 for joint salvage
  - Highly penetrable to all body tissues

T.S. Case Study

POD #3 pain mod x2.5hr @rest; 8/10 activity pain
- Meds
  - Gabapentin 600mg tid
  - Hydromorphone 6mg po q4hr prn (30 mg/24 hr)
  - Baclofen 10mg tid
- Why pain hard to control?
  - Opioid tolerance PTA
  - Drug-drug interaction w/ rifampin
    - Historically used for TB; expanding use w/ HIV related infections and intra-articular staph infections

Rifampin
- Potent inducer of several CYP 450 enzymes
  - Most potent induction CYP3A4 and CYP2B6
  - Likely Modest induction CYP2D6 (clinical studies)
  - Weak induction CYP1A2
- Pathway characteristics
  - 3A4 pathway strongly inducible
  - 2B6 minimally inducible
- Decreases concentration of most opioids
- Area under the curve (AUC)=graph of plasma concentration x time
  - Shows drug exposure to patient


**Rifampin and Opioids**

Oxycodone – excellent documentation
- CYP3A4 major substrate (metabolic pathway)
- >86% w/ po and 53% iv
  - Decreased oral bioavailability from 69% to 21%

Morphine – excellent documentation
- 96% Metabolized by glucuronidation enzymes; <4% CYP enzymes
- Unclear mechanism; possible intestinal wall induction (P-glycoprotein) & increased GI excretion
- Plasma level decreased approx 66%; loss of analgesic effect

Methadone – excellent documentation
- CYP3A4 major substrate
- 33-68% drop in plasma levels
- Demonstrated withdrawal s/s in methadone maintenance Rx

Fentanyl – fair documentation
- 3A4 substrate
- TDF - needed increase from 23mcg/hr to 104mcg/hr to maintain same analgesia w/ 300mg rifampin/day
  - Oral transmucosal - less clinical effect likely (peak concentration same)

Hydrocodone – fair documentation
- CYP3A4 substrate
- Moderate drop/loss of analgesia

Codeine
- 10% substrate of CYP2D6 to morphine
- Moderate loss of analgesia

Hydromorphone
- Involvement of CYP not established & 95% metabolized to glucuronide
- Appears less affected - but less research (Micromedex 2015)

**T.S. Case Study Outcome**

A hydromorphone 16mg qd
- Hydromorphone 4mg po q4hr

- Caution
  - Home on Abx
  - Rifampin d/c d opioid effect may markedly increase
  - Concurrent OSA adds risk of overdose
  - Close monitoring as outpatient
MG Case Study

50 y/o F w/ Lung Ca w/ brachial plexopathy
Severe chest burning pain w/ sensory deficits

Meds
- Poor relief w/ TDF 100mcg/hr & PCA hydromorphone
- Started methadone 15mg q12h- mod pain in 24 hr
- Gabapentin 600mg tid
- Oxycodone 10mg q6pm
- Amitriptyline 25 mg qhs

1 week later very drowsy, arousable but drifts to sleep, not eating, fell in BR; VSS w/ RR 14
- BUN/cre 32/0.8; H&H 8.9/28.6; LDH & alk phos stable elevated; AST/ALT/BILI wnl

What changed? & What's new?

- Mild BUN; crt wnl
- Altered clearance?
  - crt better indicator of renal function, so less likely cause
  - Gabapentin stable dose
  - LFTs- stable

- Drug drug interaction?
  - Additive effects?
    - Less likely - Stable meds and no ADR x 1 week w/ stable labs
  - Enzyme effects?
    - CYP450 affects methadone, amitriptyline, oxycodone

CYP450 Effects

- Methadone
  - Substrate of CYP2B6 & CYP3A4 (major)
  - Inhibits CYP2D6 (mod)
- Amitriptyline
  - Substrate CYP2D6 (major)
- Oxycodone
  - Substrate CYP3A4 (major) and CYP2D6 (minor)
### CYP Overlaps & Interactions

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<th>CYP 2D6</th>
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No interactions likely if competitive inhibition increase oxy effect unlikely, weak effect.
Inhibition of antidepressive increase sedation.

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### MG Case Study Outcomes

- Held antidepressive
- Continued methadone, oxy, gaba
- AAox3 in 36 hr after last dose
- Possible additive effects of sedating meds plus CYP enzyme interaction
- THM
  - Methadone susceptible to many drug interactions via CYP 450 system
  - Know which drugs use CYP450
  - Ask your pharmacist for help!!!
Review & Conclusions

Understand ADR mechanisms
- Altered clearance - liver, kidney
- Drug-drug interactions
  - Additive/synergistic
  - Liver enzyme interactions

Ask Questions
- What’s new, Why now, What else is possible?
- The answer you get depends on the question you ask!

Proper diagnosis of ADR provides effective solutions
- Prevent patient harm
- Prevent unnecessary opioid decreases & pain
- Prevent inaccurate patient suspicion of opioid abuse
- Promote safe and effective pain management.

References