Conflict of Interest Disclosure

- Author’s Conflict of Interest
- June Oliver- No conflict of interest

Guiding Principles

- Clinical changes in S&S require thorough eval
  - Are changes serious or life threatening?
  - What is the likely cause?
  - What is the appropriate treatment?
- Pitfalls
  - Jumping to conclusions based on personal bias or incomplete information
  - Once a conclusion is reached, further investigation often stops
Guiding Principles
- Opiophobia still exists
  - Easy target; knee jerk reaction for some
- Employ reasoned, inclusive evaluation
  - Consider opioid side effects
    - Most resolve w/ regular use/stable dose
  - Consider other medication effects
  - Consider medical etiologies, metabolic imbalances
  - Consider TIMING of new therapies/derangements with onset of S&S
    - Consider uncontrolled pain is risk factor for delirium
- Ask Yourself “What else could cause this?”
  - Before & After you form a conclusion

Psychotic Case Study
- 58 y/o M w/ Multiple Myeloma & bony mets
- NRS 3-4/10 scapula, T-spine
- Meds
  - Fentanyl patch (TDF) 100mcg/hr, hydromorphone 8-10 mg po prn
    - Stable dose x 4 wks
  - Prednisone Rx started 4 days ago
- Last 48 hrs, increasing agitation, hallucinations, confusion
- Cause?
- What else do you want to know about pt?

Potential Causes
- Pharmacologic, metabolic, metastatic, infectious
  - VS: 98.3-78-18 140/72
  - Brain MRI: neg/ wnl
  - Lytes: Na 136, K 3.9, Ca 9.6, Bili 1.1, BUN/crt 12/1; LFTs ok, WBC 6, H&H 11/34
  - No other new medications
- PCP requests decrease TDF to 50mcg/hr and po hydromorphone to 4mg prn
- What’s new?
  - Only steroid Rx
Steroid-induced psychosis

- Known since 1950’s
  - Uncertain Incidence – 5.7% (1983); 30-50% in rheumatologic Rx (2010).
- Onset
  - S&S usually 3-4 days of steroid start
  - can occur anytime, including during taper or after stopped
- Steroid Psych S&S vary
  - subtle mood changes - memory deficits - psychosis
  - of those w/S&S – mania 35%; depression 28%; psychosis 24%.
- Risk factors
  - Dose - Prednisone equivalent of 40mg/day
  - Female gender, elder age
  - Prior psych illness NOT a clear risk factor

Rx Options

- Steroid taper - preferred
- If unable to taper or S/S persist
  - Antipsychotic meds - neuroleptics-phenothiazines
    - Olanzapine (Zyprexa) risperidone (Risperdal),
    - Quetiapine (Seroquel), haloperidol (Haldol),
    - chlorpromazine (Thorazine)
  - TCAs worsen psych S&S
- Patient Outcome
  - Steroid taper – resolution of S&S w/ same opioids and continued pain control

Psychotic Case Study

Sleepy Case Study

- 72 y/o F w/ lung Ca & bony mets
- NRS 5/10 spine, RLE, abd.
- Analgesia: TDF 75 mcg/hr & MSIR 15 prn - stable use x 2 weeks
- 2-3 days – more drowsy, nausea, weak, pain moderate
- PCP requesting decrease in opioids
- Cause?
- What more do you want to know about the pt?
Sleepy Case Study - con’t

- **Potential Causes**
  - Pharmacologic
    - Opioids, BZDs, anti-emetics, AEDs, TCAs, antihistamines
  - CNS process, malignant metastases, infection
  - Metabolic - lytes, ammonia, BUN, Bili

- Check most recent changes for likely cause
  - No new meds
  - VS, CBC wnl, Na 135, K 3.8, Ca 12.9, (norm 8.5-10.5)
  - Bun/crt 10/1.5, LFTs ok

Side Effect Analysis

- Who’s to blame? Opioids vs Calcium!
  - Opioid dose stable x 2 wks
  - Opioid side effects decrease w/ continued use
    - Most common @ start of Rx and w/ dose change
  - Sedation precedes opioid respiratory depression
    - If overdosed ⟷ over sedated, pain typically minimal
  - This pt= VSS, RR 16, pain mod
  - Hypercalcemia
    - S&S - confusion, decreased LOC, N/V, BP, polyuria
    - S&S w/ calcium above 12 mg/dL

Calcium Conclusion

- After Rx ⟷ Ca norm, S&S resolved
  - IVF, biphosphonates

- Opiophobia
  - Opioids often viewed w/ suspicion & distrust
  - “Jumping to conclusions” w/o exploring other possibilities
  - Reasoned evaluation of side effects
    - Consider opioid side effects AND....
    - Ask “What else could cause this?”
**Sleepy Case Study #2**

- 63 y.o F w/ hx PAD (bypass x2), acquired hemolytic anemia, hx leukocytosis & thrombocytosis, personality disorder, R BKA w/nonhealing/infected stump wound;
  - debridement/graft on 5/5.
- AAOx3 pre-op and post-op
- By 5/9 drowsy, slurred speech
- By 5/10 disoriented, hallucinating (sees circus performers), restless.

**Medications**

- Chronic & current –
  - Amitriptyline (Elavil) 25 qhs
  - Pregabalin (Lyrica) 50 tid,
  - Duloxetine (Cymbalta) 60 qd,
  - Fentanyl patch 25 mcg/hr
  - Clopidogrel (Plavix), lorazepam (Ativan) 0.5mg po qd, trazadone 150 mg qhs, lactulose
- New post-op
  - 5/4 hydromorphone PCA (on 5/6 used 14.8mg/24hr)
  - 5/6 IV Abx q6h
  - 5/7 - diphenhydramine (Benadryl) 25 mg po q6h ATC-
    hx possible allergy to PCN??

**Labs & VS**

- VS
  - 5/8 Tmax 99.7- HR 98-RR 18. BP 105/66 - 152/76; 97% O2 sat
  - 5/10 = 97.7- 81-18. BP 120/60, 98 % on 2L/NC
- 5/3 wound C&S = acinetobacter
- Chem- wnl 5/3
  - 5/10 = Na 141, K 3.9, Cl 107, Co2 29, Bun/crt 8/0.4, glucose 99, Tot protein 5.8
- CBC – 5/3 @ baseline abnormal
  - 5/3 = WBC 19.7- Hgb 7.6, Hct 26.3, Pt 954
  - 5/8 = WBC 9.6- Hgb 7- Hct 23.7- Ptt 868
Who's to blame?

- VS changes/hypoxia- stable
- CNS event- no motor/sensory deficits
- Metabolic- + abnormalities in CBC
- Infectious- + wound C&S
- Post anesthetic effect- had surgery
- Psychiatric- has psych diagnosis
- Medications- multiple meds

Who's to blame? (A closer look)

- Metabolic-- + abnormalities-
  - CBC chronic/stable; chemistry wnl
- Infectious- + wound C&S
  - no systemic sepsis
- Post anesthetic effect- had surgery-
  - no AMS x 1st 4 days post op
- Psychiatric- has psych diagnosis
  - baseline w/o hallucinations/ sedation
- Medications-
  - multiple meds

Who's to blame?

- Multiple medications- closer look!
  - No change in clearance (renal/liver)
  - What’s old
    - Opioids, amitriptyline, duloxetine, trazodone
  - What’s new?
    - PCA, ampicillin/sulbactam (Unasyn),
      diphenhydramine (Benadryl)
  - Consider- opioid tolerant, AMS uncommon w/ Abx
  - Diphenhydramine (Benadryl)- started 5/7; 9 doses by 5/9; 13 doses by 5/10.
  - Drowsy on 5/9; hallucinating by 5/10
**Treatment**
- d/c diphenhydramine (Benadryl) on 5/10
- Decrease PCA to 0.2 mg q10min (mild pain)
- 5/11- Mentally clear/hallucinations gone
  - PCA use 5.5 mg/24 hr
  - Other meds same

Hey, let’s stop the diphenhydramine!!!

**Anticholinergic side effects**
- Acetylcholine = neurotransmitter supporting parasympathetic/cholinergic actions
- Necessary for brain/thought processing
- > 600 drugs w/ anticholinergic (AC) effects
  - atropine, scopolamine, antihistamines (diphenhydramine),
    TCAs (amitriptyline), sleep aids (doxylamine),
    antispasmodics (oxybutynin, cyclobenzaprine),
    Parkinson’s meds (benztropine), neuroleptics
    (chlorpromazine), etc………..

Muscarinic acetylcholine receptor blockade
- Peripheral- smooth muscle (GI,GU,bronchial, cardiac),
  salivary/sweat glands, ciliary body of eye
- CNS– anxiety, agitation, dysarthria, confusion, visual hallucinations, bizarre behavior, delirium, psychosis,
  paranoia, coma, and seizures.

Hallucinations often ”Alice in Wonderland-like” or
”Lilliputian type,” - people appear to become larger and smaller
- may appear to grab invisible objects in air
Anticholinergic Side Effects

- Pt's w/Dementia & Elderly at risk
  - Decreased cholinergic reserve
  - Acetylcholine –lower production, less receptors
  - Decreased drug clearance
  - 2-3x more AC reactions than gen population
  - AC mental status changes typically w/ more abrupt onset than other causes
- Beers criteria for inappropriate geriatric meds
  - 1st generation antihistamines (diphenhydramine) r/t anticholinergic effects and decreased clearance
  - Strong recommendation to avoid use except w/ severe allergic reaction Rx.

Dizzy case #1

- 80 y/o F admitted tripped over suitcase w/ pubic rami fx.
  - PMH- arthritis, HTN, PUD
  - VS- 98.3-80-24 BP 148/58 O2sat 98% (stand 117/48)
- Meds:
  - 8/11 ketoralac (toradol) 15mg ivp x1, simvistatin, quinopril, HCTZ
  - 8/12 hydrocodone 5/325 (4 tab/24 hr)
  - 8/13 add TDF 12mcg/hr as can’t ambulate w/ pain

Case #1 –con’t.

<table>
<thead>
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<th></th>
<th>Na</th>
<th>K</th>
<th>Bun</th>
<th>Cr</th>
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<td>159</td>
<td>7.4</td>
<td>8.6</td>
<td>24.6</td>
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</table>

- 8/10 (admission)- no dizziness/n/v
- 8/13 – c/o dizziness, mild nausea, occ emesis
- 8/14 -PCP suggest lower opioids r/t dizziness and n/v
Case #1 (con’t.)

- Possible causes- dizziness/n/v
  - Meds- Opioids, other meds
  - VS- orthostatic, HTN, deconditioning
  - Neuro process – possible TIA, CVA
  - Metabolic- dehydration, electrolyte imbalance

- Time of onset symptoms
  - 8/13- before TDF started; but hydrocodone in use
  - 8/13 Lytes- low Na that was wnl on admission
    - Why? Hemoconcentration / dehydration & diuretics

The Low Sodium Story

- Multiple causes
  - Na loss- i.e. thiazide diuretics, diarrhea (hypovolemic)
  - H2O excess- i.e. CHF, CRF, hypotonic IVF, polydipsia (hypervolemic)
  - Neuro-hormonal- SIADH (euvolemic)
    - 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, craniotomy)
  - Diseases- pneumonia, HIV, hereditary, malignancies

The Low Sodium Story

- S/S hyponatremia (HN)
  - Na+ is chief extracellular ion
  - SIADH causes serum dilutions
    - Promotes water to move intracellularly
    - Into Neural, 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

Listen to this…

I am very important because…
**Case Study #1 (con't.)**

- **Case Study - Patient risk factors for HN**
  - Thiazide diuretics
  - ACE inhibitor effect (save K and lose Na)
  - Possible medication induced SIADH
  - Risk increased with:
    - Concurrent use of drugs w/ potential HN effect
    - 10 fold risk increase w/ SSRI + diuretic + ACE inhibitor
    - Elderly, females

- **Outcome**
  - Stopped HCTZ on 8/12
  - Lowered quinopril from 40 bid to 20 bid on 8/13; skipped a.m. dose 8/14
  - 8/15: Na 131, no n/v/dizziness; ambulating w/ mild pain on same analgesics

**HA & Nausea Case Study**

- **5/10 - 70 y.o F admitted w/ severe facial pain, abd pain, n/v, worsened HA x 1 month; VSS**
  - Hx - PHN (HZ 7 yr prior), IBS, migraines
  - 5/11 Stellate Ganglion Block - facial pain mild/mod
  - 5/11 GI Consult - EGD neg; MRI abd neg; restrict fluids
- **Meds**
  - 5/11 - NS IVF, topiramate 25 mg bid, pregabalin 50 mg tid, carbamazepine 200mg q6h, hydrocodone q4h prn,

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<th>Na</th>
<th>K</th>
<th>Bun</th>
<th>Cre</th>
<th>Egr</th>
<th>Glu</th>
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- **5/12 - d/c home on esomeprazole; abd & facial pain mod; no n/v**
- **5/14 - readmit w/ abd pain, n/v x 1 day, HA and severe R facial pain**
  - CT abd neg
  - VS - 98-69-20; 135/63; 99% sat RA
- **Meds**
  - Hydromorphone 1 mg ivp q4h prn; methadone 2.5mg q12h
  - Carbamazepine 200 mg tid, ondansetron 8mg iv q8h, dicyclomine 20 mg tid, sumatriptan pm, esomeprazole, topiramide, pregabalin same
HA & Nausea Case Study

- Labs
  - 5/14: Na 124, K 3.9, Bun 9, Cre 0.5, Glu 95, WBC 4.5, Hgb Hb 12/35, Platelets 35, Lipase 97, LFT wnl
  - 5/15: Na 125, K 3.9, Bun 8, Cre 0.5, Glu 95, Carbamazepine level 7.7 (4-12 norm)

- 5/16- Repeat Stellate ganglion block; fluid restrict; NS ivf
- 5/17- Decrease carbamazepine to 200 mg bid
- 5/18- HA & facial pain low/mod; abd pain mod/high; c/o weakness

### Labs

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<tr>
<th>Date</th>
<th>Na</th>
<th>K</th>
<th>Bun</th>
<th>Cre</th>
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<tr>
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<td>125</td>
<td>3.9</td>
<td>8</td>
<td>0.5</td>
<td>95</td>
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5/19- mild Abd pain, mild HA; facial pain mild.

- Home on same meds
- Conclusion
  - SIADH r/t carbamazepine at non-toxic levels
  - Risk factors- age, female, medications
  - 24-48 hr after decrease dose s/s reduced
  - Likely HN PTA w/ delayed onset of SIADH as on carbamazepine for 1 year

Dizzy case #2

- 68 y.o F - diffuse joint pain/deformity r/t RA
  - Comorbid depression, HTN
  - New onset dizziness, nausea
- Meds: (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;
- Pain increased; resumed TDF; 4 days later Na 123
**Dizzy case #3**

- Patient risk factors for HN
  - Meds – opioids & SSRI – SIADH

- Conclusion
  - TDF causing or contributing to SIADH
  - SSRI could also contribute in combination effect
  - Pt benefited from both
  - Rx- salt tabs; s/s controlled

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**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
    - S/S when < 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

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**“Seeing Things” Case Study**

- 75 y/o M w/ DM, CKD on HD, Legally Blind, CHF, COPD, PAD, L foot gangrene
  - 4/30- L transmetatarsal amputation
  - stump & phantom pain 6-8/10
  - AAOx3 w/hallucinations at intervals

- Meds:
  - Enalapril, carvedilol, insulin, clopidogrel, furosemide, spironolactone, MS 3mg iv q4h ATC &1mg q2h pm (20 mg /24h)
  - 5/5 Pain 5x –r/o morphine accumulation in CRF
    - Change to TDF 25 mcg/hr, pregabalin 50 mg post HD, hydromorphone 1mg ivp q3h prn, duloxetine 20mg

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*Ayus JC. Is chronic hyponatremia a novel risk factor for hip fracture in the elderly?. Nephrol Dial Transplant 2012 Oct; Vol 27*
“Seeing Things” Case Study

- VS- 99.1-73-18 ; BP 160/66; 100% o2 sat on RA
- Other: BNP 145, Hgb A1C 7.7,
- Pain- improved control at mod level now
- Hallucinations continue at intervals; sees animals, children, objects in pictures moving.
  - Aware it is not real

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<td>11.2</td>
<td>34.8</td>
<td>203</td>
<td>10.1</td>
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- 5/10- analgesics d/c’d by PCP r/t hallucinations
  - Pt fell trying to hit a hallucination; bruised rib
  - Start tramadol & acetaminophen- pain became severe/lancinating
- 5/15- hallucinations cont./variable frequency
  - psychology consult- depression; adjustment disorder; hallucinations not related to psych dx
- 5/16- Left AKA
  - Good postop pain control w/ epidural; pregabalin 50 mg after HD, duloxetine 20 qd, naproxen 500 qd
  - VSS, Chem & CBC at stable baseline
  - Hallucinations continue- irregular episodes

Possible causes of AMS (hallucinations)

- What’s new?
- Initial consideration-MS accumulation in CEF
- Meds- opioids, AEDs (no BZDs or Anticholinergics)
- Psychiatric- depression; not psychotic
- Metabolic derangements- no major abnormalities
- Any difference in AMS w/ change in pain meds?
  - NO!
- Neurology consult
  - Pt admits unreported hallucinations x 2 months
  - Charles Bonnet Syndrome likely
Charles Bonnet syndrome

- Also called visual release hallucinations
  - Visual hallucinations in mentally healthy pts w/ vision loss
  - Not well recognized by clinicians
    - Often misdiagnosed as psychosis, dementia
    - Often unreported by pts - distressing
  - Incidence
    - Occur in all age groups including children
    - Most are elderly (avg 70-85 y/o)
    - 11-15% of older pts w/ impaired vision admit when asked; most never told MD.

Pathophysiology

- Visual acuity or visual field loss from any cause
  - Macular degeneration, glaucoma, DM retinopathy, CVA
  - NOT w/ congenital blindness
  - Reported in visual deprivation experiments
- Denervation Hypersensitivity from visual sensory loss
  - leads to disinhibition of visual cortex areas in brain
    - These areas fire spontaneously
    - More likely w/ binocular dz
- Chronic visual decline at least 1 yr before S/S occur
  - Can occur w/ acute vision loss within few hours
- Auditory hallucinations similar w/ hearing loss

Clinical Presentation

- Variable forms
  - Simple - Lines, light flashes, geometric shapes
    - More common
  - Complex - People, animals, scenes
- No emotional impact; Recognized as not real
- No associated auditory or other sensory hallucinations
- Occur more often w/ eyes open than closed
- Variable duration - 1 minute to continuous
- Variable frequency
**Prognosis & Rx**
- Often resolve if vision can be corrected
  - Cataract removal
- Rule out other causes
  - Epilepsy, migraine, Parkinsons, delirium, drug intoxication, psychiatric dz, narcolepsy
- Techniques to help suppress hallucinations
  - REM & Change of visual focal point
  - Eye closure
  - Increased visual stimuli (lighting)
  - Reduce social deprivation

**Pharmacologic Rx**
- Meds- **may** be helpful
  - Atypical antipsychotics - Low dose olanzapine, quetiapine,
  - Cholinesterase inhibitors – donepezil
  - Antiepileptics- carbamazepine, clonazepam, valproate, gabapentin –(anecdotal reports)
  - Few case reports- cisapride, venlafaxine

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**Patient Outcome**
- Transferred to Rehab w/ pain adequately controlled;
  - Fentanyl patch 50 mcg/hr, pregabalin 50 mg M-W-F, duloxetine 30 mg qd, hydromorphone 4 mg po q4h prn
- Visual hallucinations continued but caused no concern for patient or healthcare team.
Conclusions

AMS w/ multiple possible causes
- Opioids
- Anticholinergic side effects
  - diphenhydramine, etc………
- Steroid psychosis
- Hypercalemic sedation
- Hyponatremia
  - Multiple meds: diuretics, SSRI, carbamazepine, opioids
  - Drug combinations raise risk
  - Elder age raises risk of s/s
- Visual release hallucinations
  - Mentally healthy pts w/ visual loss

Conclusions

Effective pain management requires comprehensive critical thinking considering medical and pain etiologies
- Ask “What’s new & what’s old” w/ new S/S
  - Medications
  - Metabolic/electrolyte changes
  - Medical comorbidities
  - Psychiatric conditions
- Ask “What ELSE could be the cause?”
- Avoid unnecessary suffering when opioids are incorrectly blamed.

REFERENCES

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