



Case Studies: Pain, Migraine, Neuropathy

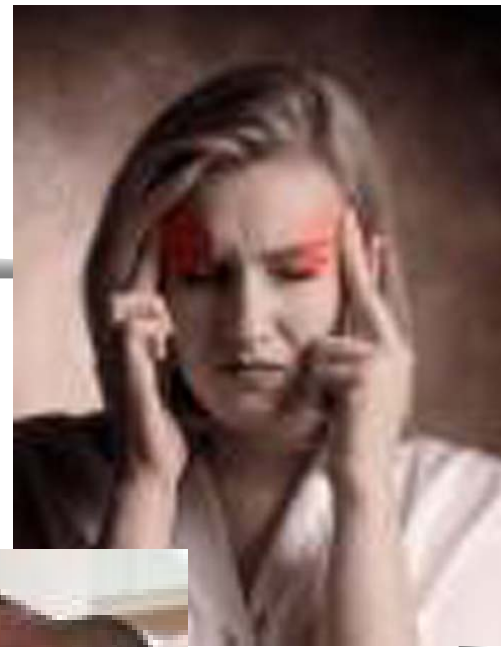
Gwen McMillin, PhD

Outline

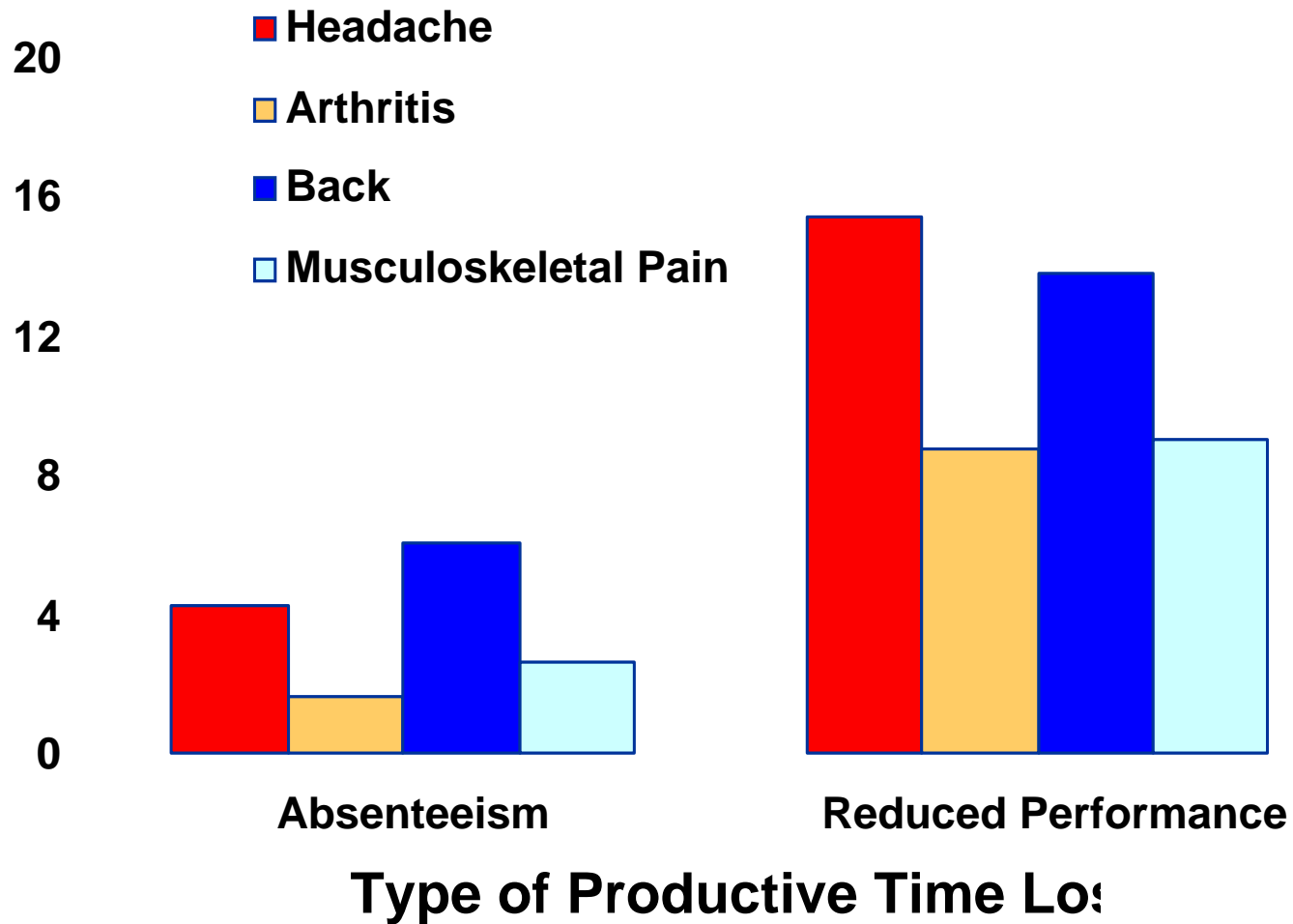
- Review of need for pain management services and personalized care
- Opportunities for the laboratory to support and improve patient care
 - Drug screening and/or monitoring?
 - PGx?
 - Biomarkers?
- Cases
- Discussion

Pain

- 1 in 3 Americans will experience chronic pain in his or her lifetime
- Over 50 million Americans suffer from chronic pain
- Societal burden of pain in the USA is estimated at > \$100 billion annually



Lost productivity due to pain

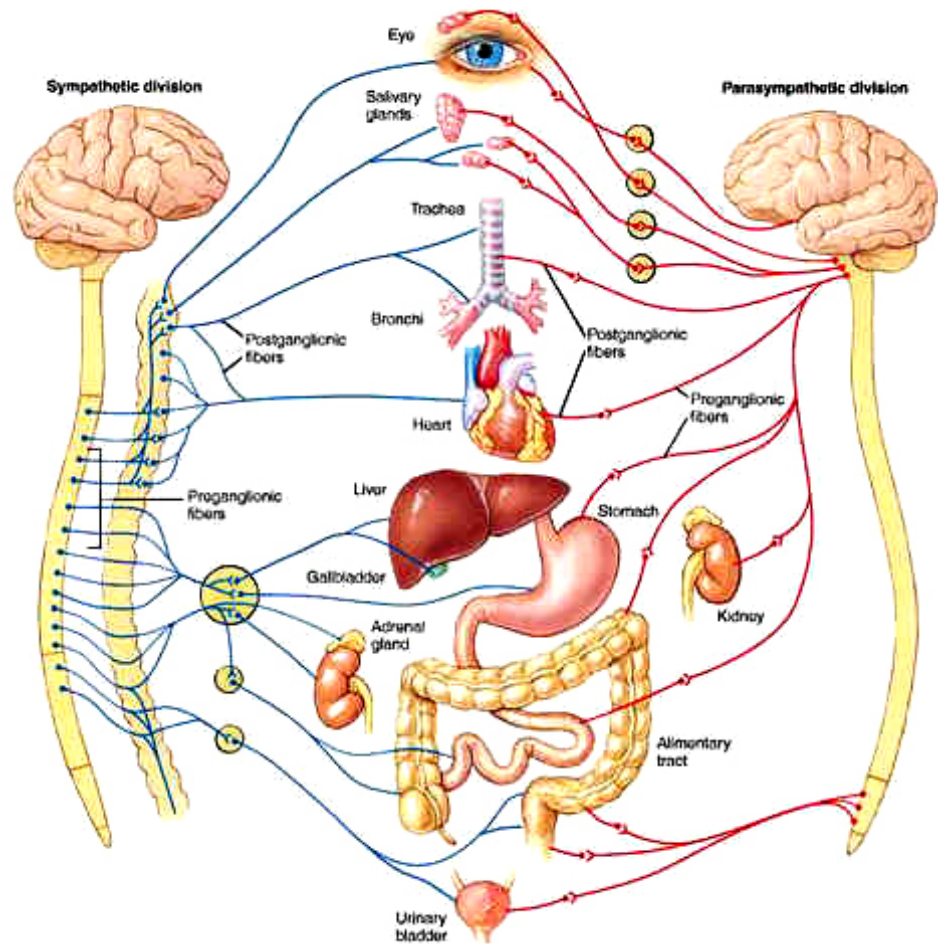


Be pain free!!!!



Types of pain

- Nociceptive
- Neuropathic
- Psychogenic
- Idiopathic



Tools for pain management

- Drugs
- Non-medicinal
 - Exercise
 - Diet
 - Massage
 - Hypnosis
 - Biofeedback
 - Accupuncture
 - TENS
- Surgery



Management of pain

- Multidisciplinary Teams
 - MDs
 - PharmD
 - Physical therapy
 - Psychology
 - Other
- Creative, personalized
- Compliance



Excerpts from the Pain Management Center Medication Agreement, UUHSC

Opioid medications will be prescribed for you only by your Pain Clinic doctor.

You agree not to ask for opioid medications from any other doctor

You agree to provide regular samples for drug screens. Positive tests for any illegal substances will result in your discharge from this clinic and referral elsewhere for substance abuse evaluation and management.

You must take opioids only as directed. Federal law prohibits giving this medication to anyone else.....

If I do not follow these guidelines my doctor may taper and stop my opioids and refer me elsewhere for care.

Patient signature: _____ Witness Signature _____ Date _____

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Questions from the lab



- What type of specimen?
- Conditions of collection and storage?
- What drugs are anticipated?
- What “illegal” drugs should be detected?
- Should these specimens/results be handled in a forensic manner?

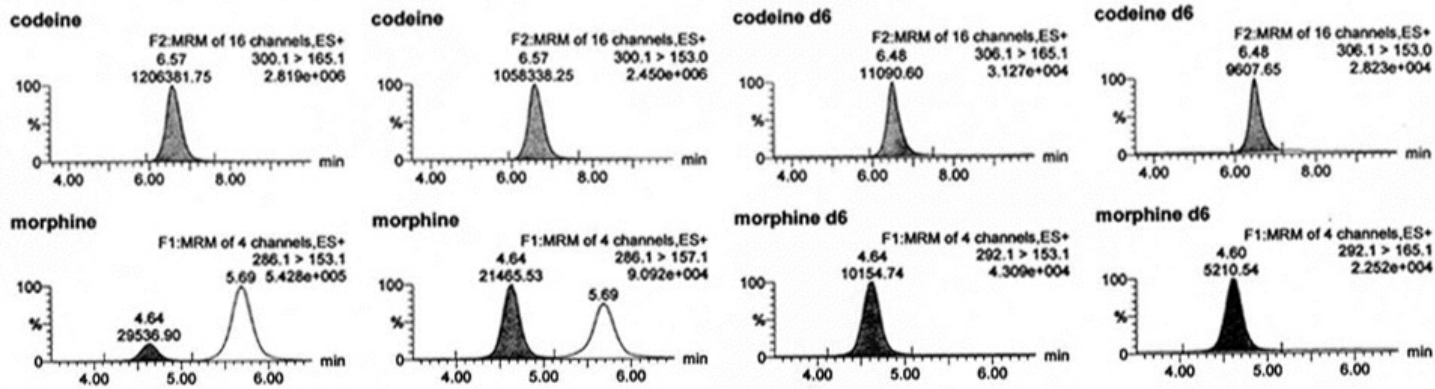
Urine drug screens



- Vary in drugs detected
- Vary in definition of positivity
 - ED vs employment testing vs medical
- Vary in performance characteristics
- For medical purposes, are not treated with chain of custody and therefore may not be good “evidence”

Laboratory support

- Drug screens (and confirmations)



- Therapeutic drug monitoring
- Pharmacogenetic testing
- Biomarkers

Drug testing options today

- Marijuana metabolites
- Cocaine metabolites
- Phencyclidine
- Amphetamines
- Opiates
 - Codeine
 - Morphine
 - Hydromorphone
 - Hydrocodone
 - Oxycodone
- Barbiturates
- Benzodiazepines

- Methadone
- Propoxyphene
- Fentanyl
- Meperidine
- Tramadol

- Triptans
- Antidepressants
- Antiepileptic drugs
- β -Blockers
- Other...

PGx and biomarkers for pain

■ PGx

- PK: CYPs, UGTs, MDR1, OAT1, etc.
- PD: OPRM1, 5-HTT, NMDA, $\alpha_2\delta-1$ etc.

■ Biomarkers

- Five proteins (2.9-8.2 kDa) elevated in CSF from rats subjected to inflammatory pain model
Gineste et al. *Drugs* 2003;63:23-9
- CRP and severity of acute sciatic pain
Sturmer et al. *Ann Rheum Dis* 2005;64:921-5
- Cytokines (IL-2, 4, 6, 8, 10, 12, etc.)
- Oxidative stress markers (vitamins A, C, E, β -carotene, lipid peroxides, coenzyme Q10, GSH, TBARS, SOD, etc.)

So how can we help?

Collaborate!

- Testing options and services -- LAB
- Utility of results -- CLINIC
- Outcome studies -- LAB + CLINIC

Case #1

Adapted from Galer et al. *Pain* 49 (1992):87-91

- 46 yr old white female
- Hx of T12-L1 paraplegia resulting from trauma 12 yrs earlier
- chronic lower back and flank pain
- Otherwise healthy
- Failed medications
 - Oxycodone/APAP (Percocet) to 90 mg/day of oxycodone
 - Morphine (MS Contin), to 300 mg/day (oral)
 - Adjuvant meds from many drug classes
- Adverse effects
 - Sedation
 - Anxiety

Case #1 (cont.)

- Pain clinic therapy:
 - Methadone, 10 mg every 4 hrs
 - Controlled 60% of pain with minimal sedation or other side effects for 1 yr +
- Opportunities for more personalized therapy?
 - Individual variability in opioid response
 - Fair chance for adjuvant meds?



Discussion

Possibilities

■ Genotyping

- PK genes: CYP2D6, others?
 - PM variants are associated with higher concentrations, greater effects of methadone
 - Although morphine failed in this patient, still useful to know for PK expectations and also for other meds
- PD genes: OPRM1
 - A118G, G794A, and T802C variants have reduced receptor binding and signaling with morphine
 - Intronic variants of OPRM1 and exonic variants of OPRD1 are associated with dependency

Clin Pharmacokinet 43(2004): 983-1013

Possibilities (cont.)

■ Drug monitoring

- Good candidate for determining patient-specific reference concentration for methadone?
- Jannetto et al. (submitted 2005) found good correlation of oxycodone C_{ss} with pain relief but not with tramadol, methadone, or hydrocodone
- Contribution to adjuvant drugs not known

Case #2

From Dr Nancy Brotanow

- 42 yr old white female
- Hx of severe back pain following discectomy for a herniated disc and radiculopathy
- Lumbar fusion performed but severe pain persisted
- Presents one year after lumbar fusion
- Medications
 - Oxycodone (OxyContin)
 - 100 mg/d
 - Gabapentin (Neurontin)
 - 1800 escalating up to 3600 mg/d
 - Tizanidine (Zanaflex)
 - 6 mg/day

Case #2 (cont.)

■ Pain clinic therapy:

- Non-drug therapy
 - Biofeedback
 - Massage
- 6 mo post
 - Wean off oxycodone and tizanidine
- 1 - 2 yrs post
 - Wean off gabapentin
 - 2700 mg/d
 - 1800 mg/d
 - 900 mg/d

■ Maintenance

- Escalate gabapentin with flare-ups
- Massage

■ Opportunities for more personalized therapy?

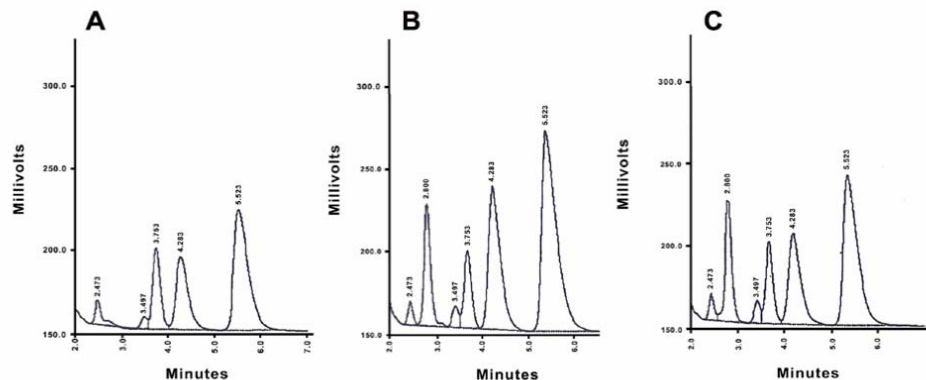
- Time required for control
- Absorption of gabapentin



Discussion

Gabapentin TDM!!!

- Absorption is saturable
- Elimination reduced by renal impairment
- Therapeutic ranges suggested
 - 15-30 mg/L for chronic pain
 - 2-10 mg/L for seizures



Possibilities

- Genotyping
 - PK genes: not metabolized or protein bound
 - PD genes: mechanism of action not clear
 - Mouse strain-dependent effects in pain models (nociceptive) suggest heritability of pain response to gabapentin and pregabalin
Chesler et al. Pain 106 (2003):325-35
 - VSCC $\alpha_2\delta$ -1 or $\alpha_2\delta$ -2 are possible targets
- Biomarkers?

Case #3

Adapted from Sumpton and Moulin. *Ann Pharmacother* 35 (2001):557-9

- 39 yr old white female
- Hx of chronic neuropathic back pain
- Otherwise healthy
- Failed medications
 - Amitriptyline
 - Desipramine
 - Imipramine
- Anticholinergic side effects limit dosing despite ~50% relief from pain

Case #3 (cont.)

- Pain clinic therapy:
 - Venlafaxine (Effexor XR), 75 mg/day
 - Comparable pain relief to TCAs but no adverse effects

- Need for personalized therapy
 - Balance efficacy with side effects
 - Variable dosing with TCAs



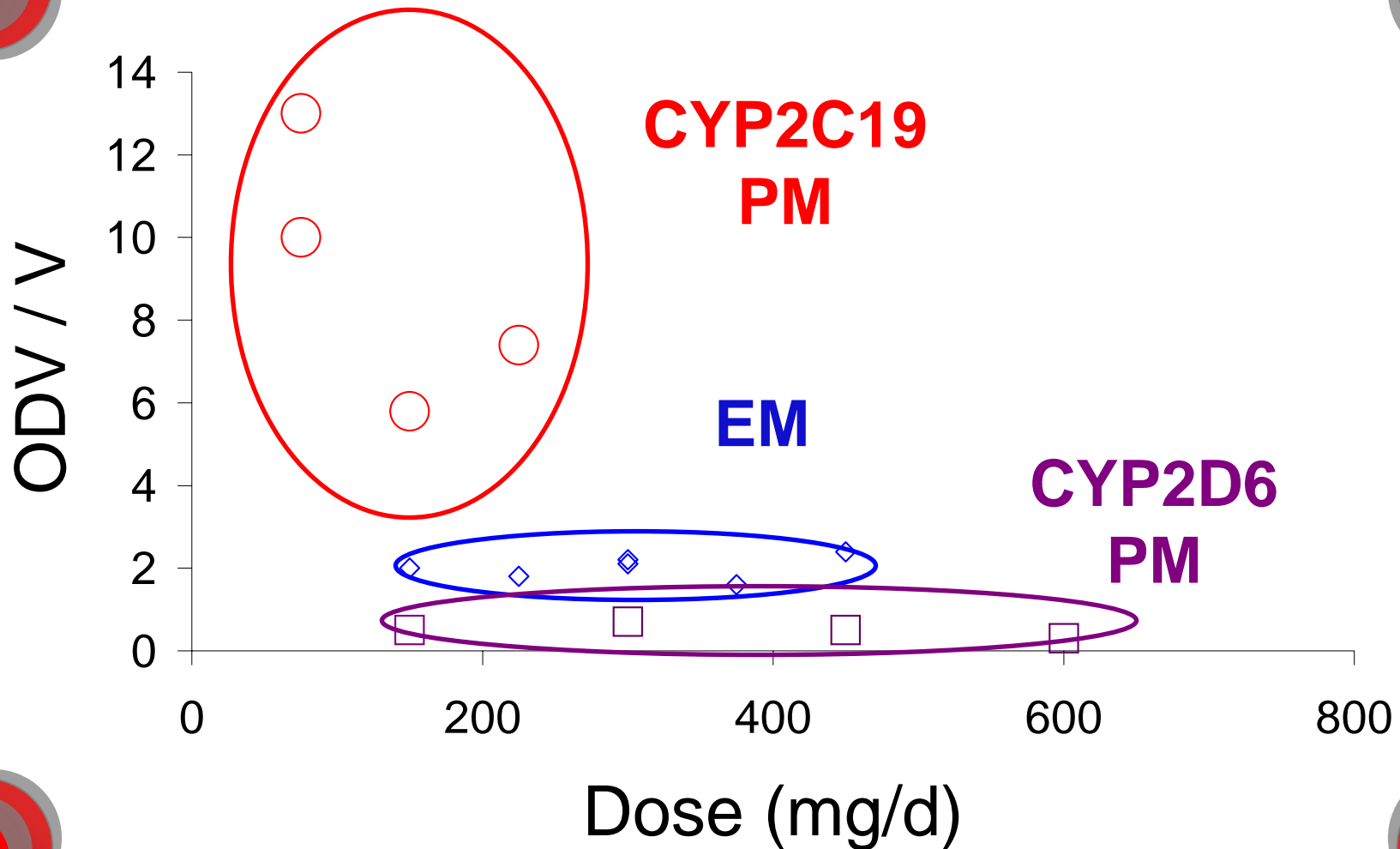
Discussion

Possibilities

■ Genotyping

- PK genes: CYP2D6, CYP2C19, CYP2C9
 - TCAs are in general activated by CYP2C19 and are inactivated by CYP2D6
 - Venlafaxine is activated by CYP2D6 and inactivated by CYP2C19 or CYP2C9
 - Genotype-based dosing guidelines are published
- PD genes
 - Efficacy: noradrenergic and serotonergic system genes
 - Toxicity: muscarinic-cholinergic, histaminic, adrenergic system genes

Venlafaxine genotype-phenotype correlations



Possibilities (cont.)

- Drug monitoring

- Monitor venlafaxine concentrations
- Monitor TCA concentrations
- Concentrations of total TCAs are correlated with response to neuropathic pain. TDM of TCAs reduced the risk of toxicity in patients treated for neuropathic pain.

Rasmussen et al. Ther Drug Monit 26(2004):352-60.

Case #4

From Dr Nancy Brotanow

- 45 yr old white male executive
- Hx of severe, often daily migraines since age 20
- Otherwise healthy
- Years of failed therapy via internist, allergist, neurologist
- Failed medications
 - Propranolol (Inderal)
 - Sumatriptan (Imitrex)
 - NSAIDS
 - Short-acting opiates

Case #4 (cont.)

■ Pain clinic therapy:

- 1st regimen
 - Gabapentin (Neurontin)
 - Citalopram (Celexa)
 - Mood changes, dizziness
- 2nd regimen ~ 1 yr
 - Topiramate (Topamax)
 - Paroxetine (Paxil) - for 1 mo
 - PRN: Eletriptan (Relpax), Celecoxib (Celebrex), Tramadol (Ultram)
 - Rescue if persistent: Oxycodone/APAP (Percocet)
- Non-drug therapy @ ~ 9 mo
 - Biofeedback
 - Lifestyle changes
 - Relaxation
- 1 yr into therapy: kidney stone
- 3rd regimen
 - Oxcarbazepine (Trileptal) to replace topiramate
- 19 months into therapy
 - Wean off meds
 - Rescue with eletriptan



Discussion

Possibilities

- Biomarkers
 - May have assisted in diagnosing cause of pain?
- Genotyping
 - PK genes: panel of CYPs
 - PD genes: panel of receptor genes
- Drug monitoring
 - Support drug and dosing selections
 - Identify and manage drug-drug interactions
 - Determine patient-specific therapeutic range?

Opportunities

- Better communication RE drug screens
- More TDM
- Development of therapeutic ranges and other interpretive data?
- PGx utility?
- Identification/characterization of biomarkers?
- Outcome studies

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