PART II: PHARMACOLOGIC TREATMENT OF PAIN

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DECEMBER 20, 2018

TREATMENT ALGORITHM

- PHARMACOLOGIC TREATMENT
  - ACETAMINOPHEN
  - NSAIDS
  - NEUROPATHIC MEDICATIONS
  - MUSCLE RELAXANTS
  - TOPICAL AGENTS
  - OPIOIDS

ACETAMINOPHEN

- ANALGESIC AND ANTIPYRETIC
- MECHANISM OF ACTION POORLY UNDERSTOOD
  - BLOCKS PROSTAGLANDIN SYNTHETASE IN CNS, NOT PERIPHERALLY
  - LACKS PERIPHERAL ANTI-INFLAMMATORY EFFECTS
  - LACKS PLATELET, GI, BONE, RENAL EFFECTS

FIRST-LINE TREATMENT FOR PAIN IN THE ELDERLY

MAXIMUM 3000MG/DAY

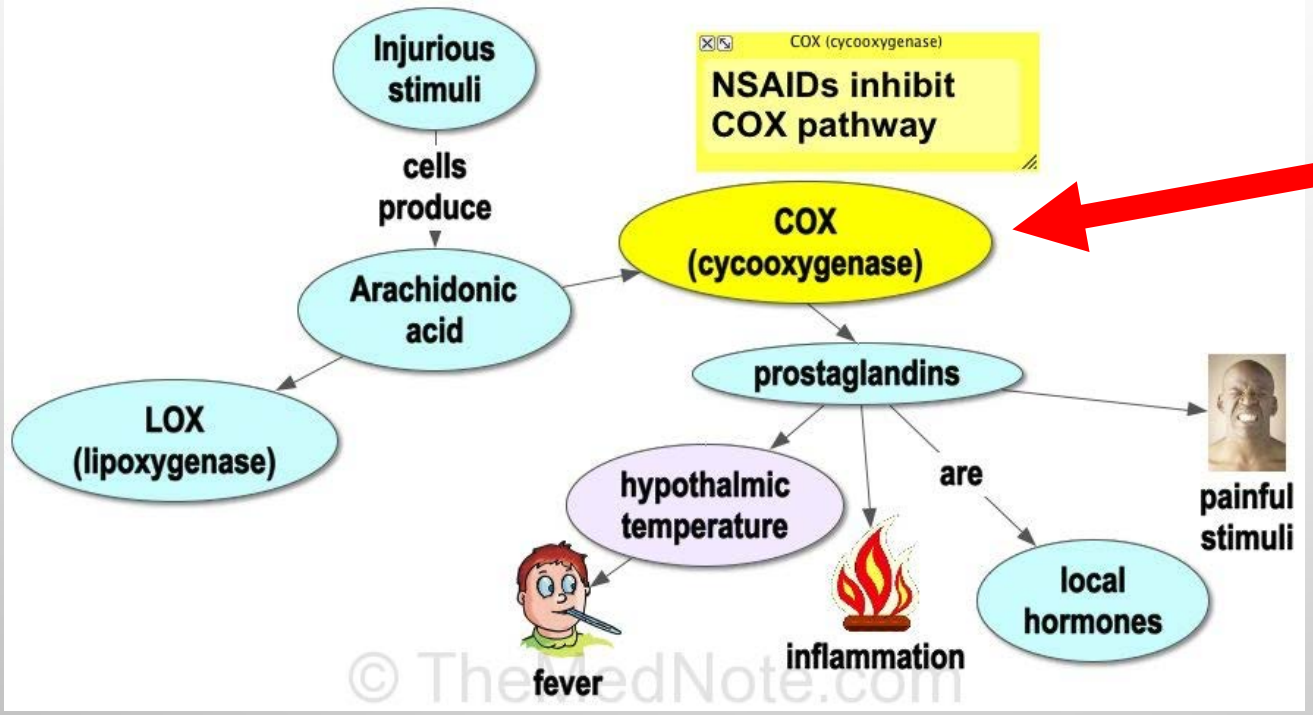
- BE AWARE OF OTHER ACETAMINOPHEN-CONTAINING PRODUCTS
- 2000MG/DAY WITH HEPATIC DISEASE

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

- WORLD'S MOST WIDELY PRESCRIBED CLASS OF MEDICATION
  - $6-8 BILLION WORLDWIDE, $2 BILLION IN US
- 5TH CENTURY: HIPPOCRATES
  - WILLOW BARK
- EARLY 20TH CENTURY
  - BAYER REDISCOVERED ACETYLSALICYLIC ACID - FEVER, PAIN, INFLAMMATION
- MID/LATE 20TH CENTURY
  - ASA BECOMES GENERIC NAME
  - 1960S: INDOMETHACIN, IBUPROFEN
  - 1971: DISCOVERED THAT ASA INHIBITS COX ENZYME
  - 1998: COX-2 SELECTIVE INHIBITORS AVAILABLE

NSAIDs

COX Inhibitors: Prevent inflammatory cascade



NSAIDs

NSAIDs

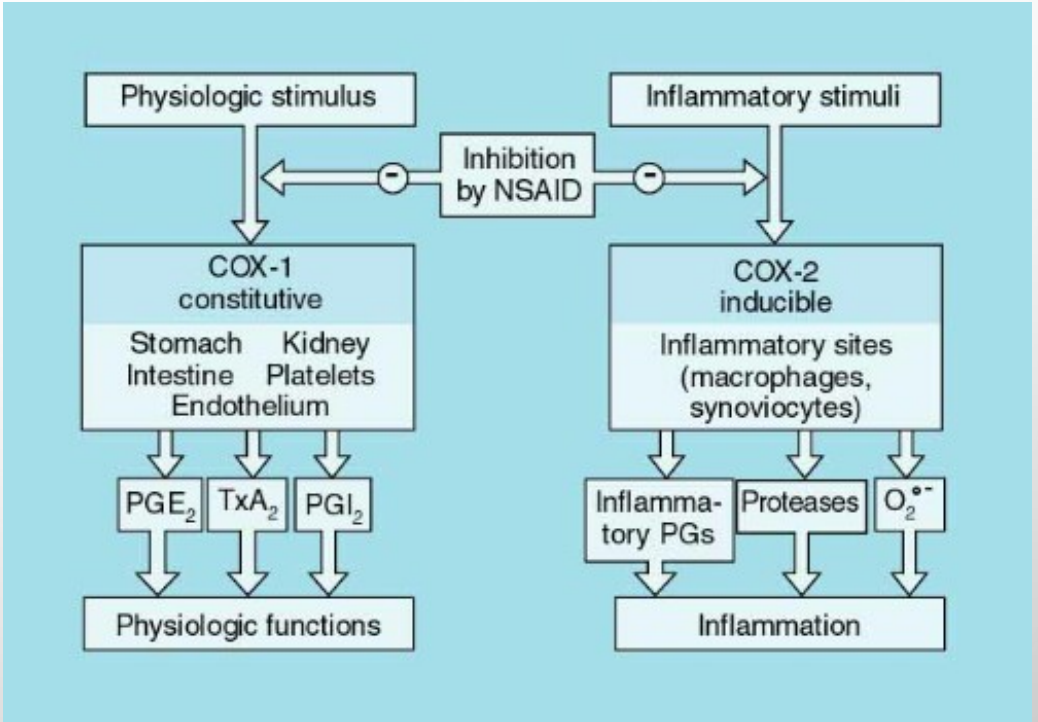
Two isoforms of COX enzyme

COX-1

- Constitutive
- "Housekeeping enzyme"
  - GI tract
  - Kidneys
  - Platelets

COX-2

- Inducible with inflammatory stimulus



NSAIDS

- ASPIRIN
- IBUPROFEN
- KETOROLAC
- NAPROXEN
- INDOMETHACIN
- DICLOFENAC
- MELOXICAM
- ETODOLAC
- CELECOXIB

Non-Selective, Permanent COX-Inhibitor

Non-Selective, Temporary COX-Inhibitors

Selective, Temporary COX-2 Inhibitors

ASA VERSUS OTHER NSAIDS

- ASA CAUSES IRREVERSIBLE COX-1 AND COX-2 INHIBITION
  - IMPORTANT IN PLATELETS WHICH CAN'T REGENERATE THEIR OWN COX ENZYMES
  - THUS THE EFFECTS LAST FOR THE LIFESPAN OF THE PLATELET (10-14 DAYS)
- OTHER NSAIDS CAUSE TEMPORARY INHIBITION OF COX ENZYME
  - LASTS FOR A FEW HOURS AFTER DOSE

NSAIDS ADVERSE EFFECTS

GI - Gastritis, gastric/peptic ulcers

Hematologic – Increased risk of bleeding

Orthopedic – Impaired bone healing?

Decreased incidence with COX-2 Inhibitor

Renal - Acute kidney insufficency (AKI)

Cardiovascular - Increased risk of MI - all NSAIDs

Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data

Cite this as: *BMJ* 2017;357:j1909
http://dx.doi.org/10.1136/bmj.j1909

Accepted: 10 April 2017

- "TAKING ANY DOSE OF NSAIDS FOR ONE WEEK, ONE MONTH, OR MORE THAN A MONTH WAS ASSOCIATED WITH AN INCREASED RISK OF MYOCARDIAL INFARCTION."

NSAIDS

- ALWAYS TAKE WITH FOOD
- CONSIDER CONCURRENT PROTON PUMP INHIBITOR USE
- NAPROXEN 375 - 550MG BID
- MELOXICAM 7.5-15MG DAILY
  - 7.5MG DOSE IS COX-2 SELECTIVE
- CELEBREX 100-200MG BID – EASIEST ON GI SYSTEM, SAFER WITH ANTICOAGULANTS, EXPENSIVE
- IBUPROFEN 600-800MG TID
  - INCREASED RISK OF AKI

NEUROPATHIC MEDICATIONS

- GABAPENTINOIDS
  - GABAPENTIN
    - CALCIUM CHANNEL BLOCKER
    - 300MG QHS WITH TITRATION TO TOTAL DAILY DOSE 1800-3600MG (START WITH 100MG QHS WITH TITRATION TO 300MG TID IN ELDERLY)
    - NEUROPATHIC PAIN, GENERALIZED PAIN, OPIOID-SPARING
  - PREGABALIN
    - CALCIUM CHANNEL BLOCKER
    - 50MG QHS WITH TITRATION TO TOTAL DAILY DOSE 300-600MG
    - NEUROPATHIC PAIN, GENERALIZED PAIN, OPIOID-SPARING
    - COMING OFF PATENT DECEMBER 2018

NEUROPATHIC MEDICATIONS

- ANTIDEPRESSANTS
  - TRICYCLIC ANTIDEPRESSANTS (TCAS)
    - AMITRIPTYLINE AND IMIPRAMINE – TERTIARY AMINES, MORE SIDE EFFECTS
    - NORTRIPTYLINE AND DESIPRAMINE – SECONDARY AMINES, LESS SIDE EFFECTS
      - DESIPRAMINE CAUSES LEAST AMOUNT OF SLEEPINESS
    - START AT 25MG QHS, TITRATE TO 100MG QHS AS TOLERATED (LESS IN ELDERLY)
    - CAUTION WITH OTHER SERATONERGIC MEDICATIONS, ELDERLY PATIENTS, CARDIAC DISEASE
  - SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)
    - DULOXETINE (60-120MG/DAY)
    - VENLAFAXINE?
    - EVIDENCE IS UNDERWHELMING

NEUROPATHIC MEDICATIONS

- ANTICONVULSANTS
  - TOPIRAMATE
    - SODIUM CHANNEL BLOCKER
    - POOR EVIDENCE IN PAIN OTHER THAN MIGRAINE PROPHYLAXIS
  - CARBAMAZEPINE/OXCARBAZEPINE
    - SODIUM CHANNEL BLOCKERS
    - TRIGEMINAL NEURALGIA

MUSCLE RELAXANTS

- WORK BEST WITH SHORT-TERM USE (10 DAYS), TOLERANCE DEVELOPS QUICKLY
- CYCLOBENZAPRINE 5-10MG TID
  - TCA-LIKE, CAUTION WITH OTHER SERATONERGIC MEDS AND IN THE ELDERLY
- TIZANIDINE 2-8MG TID
- VALIUM, CARISOPRODOL, METHOCARBAMOL, METAXAOLONE ARE CNS SEDATIVES – NOT MUSCLE RELAXANTS. DON'T USE THEM.
  - CARISOPRODOL IS A DANGEROUS CNS-DEPRESSANT AND IMPLICATED IN MANY MULTIDRUG UNINTENTIONAL OVERDOSE DEATHS

TOPICAL MEDICATIONS

- DICLOFENAC GEL OR PATCH
  - GEL NOW GENERIC
  - APPLY TO AFFECTED AREA
  - GREAT FOR PATIENTS ON ORAL ANTICOAGULATION
  - WORKS BEST WHEN PAINFUL AREA IS CLOSE TO THE SKIN
- LIDOCAINE PATCHES
  - RX (5%, EXPENSIVE)
  - OTC (4%, CHEAP – SALON-PAS, ICY HOT, ETC)
- COMPOUNDED CREAMS
  - EXPENSIVE AND LARGELY INEFFECTIVE
  - EXCEPTION MAY BE KETAMINE CREAM FOR ALLODYNIA, LIDOCAINE CREAM FOR NEUROPATHY

OPIOIDS?

- SHOULD ONLY BE AN OPTION OF LAST RESORT IN CHRONIC PAIN
  - APPROPRIATE TYPE OF PAIN
  - FAILURE OF ALL OTHER AVAILABLE MEDICATIONS/THERAPIES
  - AFTER APPROPRIATE RISK ASSESSMENT
  - INFORMED CONSENT WITH PATIENT
- GUIDED BY THE CDC GUIDELINES FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN
  - HTTPS://WWW.CDC.GOV/DRUGOVERDOSE/PRESCRIBING/RESOURCES.HTML

INITIATION OF OPIOIDS

- TRIAL OF OPIOIDS
  - LOW DOSE (HYDROCODONE 5/325 BID-TID)
  - MILD ESCALATION REASONABLE (APPROACHING 30-50MG OME?)
- ASSESSMENT OF IMPROVEMENT
  - PAIN
  - FUNCTION!
- ROUTINELY ASSESS 4 A'S
  - ANALGESIA
  - ACTIVITY
  - ADVERSE EFFECTS
  - ABERRANT BEHAVIOR

CASUAL PRESCRIBING OF OPIOIDS

- IF YOU START OPIOIDS YOU HAVE BECOME THAT PATIENT'S OPIOID PRESCRIBER
  - MAY BE REASONABLE FOR ACUTE ISSUES
  - IMPORTANT FOR PATIENT TO HAVE APPROPRIATE EXPECTATIONS
  - DUE DILIGENCE
    - CONTROLLED SUBSTANCE DATABASE REPORT
    - KNOWLEDGE OF OTHER SEDATING MEDICATIONS
    - HEALTH HISTORY
  - DO NOT GIVE OPIOIDS AND TELL A PATIENT ANOTHER PROVIDER (PCP, PAIN SPECIALIST, SURGEON) WILL GIVE THEM MORE

SHORT-ACTING OPIOIDS

Medication	Equivalency	Starting Dose	Comments
Hydrocodone	15 mg	5mg bid-tid	Combined with tylenol 325mg
Oxycodone	10mg	5mg bid-tid	With or without tylenol 325mg
Hydromorphone	3mg	2mg bid-tid	Less nausea
Morphine IR	15mg	15mg bid-tid	Caution with renal failure
Nucynta	???	50mg bid-tid	Better for neuro-pathic pain?, more nausea
Oxymorphone	5mg	5mg bid-tid	Very potent
Tramadol	N/A	50mg tod	Seratonergic, lowers seizure threshold
Fentanyl	Varies widely 100-1600mcg	Varies – max qid Must be REMS certified	Nasal spray – Lazanda Transmucosal – Actiq Sublingual - Fentora Oral Spray - Subsus

LONG-ACTING OPIOIDS

Medication	Equivalence	Starting Dose	Comments
Morphine ER	60mg	15mg bid-tid (best dosed tid)	Caution in renal disease. Kadian is bid dosing, Avinza is daily dosing
Oxycodone ER	40mg	10mg bid	tid dosing in some patients
Fentanyl patch	25mcg/hr	12-25mcg/hr q72h TD	Good with renal disease, some patients need q48h
Methadone	??? 10-20mg?	5mg bid	Cheap, titrate only every 7-10 days, very long $T_{1/2}$, caution if QTC>450
Oxymorphone ER	20mg	10mg bid	High potency
Hydromorphone ER (Exalgo)	12mg	8mg bid	Less nausea?
Hydrocodone ER (Zohydro)	60mg	10mg bid	No abuse-deterrant form
Buprenorphine patch (Butrans)	20mcg/hr	5mcg/hr q7 days TD	Low potency, ok in renal failure and elderly, $$$
Nucynta ER	????	50mg bid	More nausea, Better for neuropathic pain?

OPIOID SIDE EFFECTS

- CONSTIPATION
  - SENOKOT (1-2 PILLS BID-TID), MIRALAX (DAILY-TID), ENEMAS, LACTULOSE (Q3-4H)
  - DO NOT USE METACLOPRAMIDE
  - TOLERANCE TO CONSTIPATION DOES NOT DEVELOP WITH INCREASING OPIOID DOSES
- NAUSEA
  - CHANGE TO ANOTHER AGENT, PREMEDICATE WITH ZOFRAN/PHENERGAN/COMPAZINE
- PRURITIS
  - CHANGE TO ANOTHER AGENT
- SEDATION
  - REDUCE DOSE/FREQUENCY
- DYSPHORIA, MOOD ACTIVATION, DRY MOUTH

THANK YOU!

- QUESTIONS OR COMMENTS?