The Problem of Pain

- Scope
- Assessment
- Treatment
- Fear
- Keeping current

...we do not “manage pain”.

To be in charge of; to regulate; to control

Who’s in Pain? Institute of Medicine

- Estimates that over 116 million Americans experiences chronic pain syndromes
- A cost of 600 billion dollars annually
- Far exceeds the cost to healthcare economy of that than of diabetes, CV disease
- So how to create a culture for quality improvement at the point of care?

Three Issues

- Matching the patient in pain to the correct treatment
- Assessment, treatment
- Keeping abreast of issues in pain management
- Medications for pain, adjunctive treatments, new strategies
- Recognizing the issues with these medications and learning best practices to deal with them
- Dealing with tolerance, abuse, diversion

What Defines the Patient in Pain?

- Chronicity
- Disease process
- Gender
- Age
- Genetics
- Tolerance
- Drug seeker/abuse issues
- Intractability
- Strategies
Types of Pain
- **Acute Pain**: Recent onset, transient, from an identifiable cause
- **Chronic Pain**: Persistent or recurrent; lasting beyond the usual course of illness or injury or more than 3-6 months, and which adversely affects the individual's well-being
- **Breakthrough or Flare-up Pain**: Transient pain which is severe or excruciating; unpredictable. May indicate changes in underlying disease.

Classification of Pain
Pathophysiology
- Nociceptive pain is due to tissue injury.
- Eudynia describes nociceptive pain
  - Somatic and visceral subtypes
  - Responds well to opiates and NSAIDs
- Neuropathic pain results from damage to brain, spinal cord, or peripheral nerves.
- Maldynia describes neuropathic pain
  - Responds well to adjuvant analgesics

Assessment of Pain
- Assess pain location, type of pain (dull, sharp, stabbing, throbbing, etc.), what makes pain better, worse, how pain changes with time
- Some patients over-report
  - Drug seekers
  - Low pain tolerance
  - Some patient under-report
  - Fear of addiction
  - Fear of treatment
  - Feel a need to be stoic
  - Male patients under-report to female nursing staff

“I Feel Like A Number…”
- The Oath of Maimonides says “may I never see in the patient anything but a fellow creature in pain”
- Although the Numerical Rating Scale is a useful first step, it may not connect on a human level

“Rate Your Pain”
- Question….In the patient who cannot self-report pain….
  - How should the NP assess pain in a patient?
    - Rate the patient's pain intensity using the 0-10 numerical or faces pain rating scale
    - Ask a family member to rate the patient's pain intensity using the 0-10 numerical or faces pain scale
    - Assume that pain is present on the basis of underlying known painful pathology and care activities
    - Use a behavioral assessment tool, such as the Critical Care Pain Observation Tool
Hierarchy of Pain Measures

- Attempt to obtain self-report
  - Single most reliable indicator of pain
  - Many cognitively impaired patients are able to use a self-report tool, such as the Wong-Baker FACES Scale, Faces Pain Scale-Revised, or Verbal Descriptor Scale.
  - Consider the patient’s condition or exposure to a procedure that is assumed to be painful. If appropriate, assume pain is present (APP) and document APP when approved by institution policy and procedure.

- Consider underlying pathology or conditions and procedures that might be painful

- Observe behaviors

- Evaluate physiologic indicators

- Conduct an analgesic trial

Hierarchy of Pain Measures

- Observe behavioral signs (e.g., facial expressions, crying, restlessness, and changes in activity).
  - Behavioral score is not the same as a pain intensity score. Pain intensity is unknown if the patient is unable to provide it.
  - A surrogate who knows the patient well (e.g., parent, spouse, or caregiver) may be able to provide information about underlying painful pathology or behaviors that may indicate pain.

Hierarchy of Pain Measures

- Evaluate physiologic indicators
  - The least sensitive indicators of pain
  - May signal the existence of conditions other than pain or a lack of it (e.g., hypovolemia, blood loss).
  - Patients may have normal or abnormal vital signs in the presence of severe pain.
  - The absence of elevated blood pressure or heart rate does not mean the absence of pain.

Hierarchy of Pain Measures

- Conduct an analgesic trial to confirm the presence of pain and to establish a basis for developing a treatment plan.
  - Administer a low dose of nonopioid or opioid and observe patient response.
  - May increase if the previous dose was tolerated, or another analgesic may be added. If behaviors continue despite optimal analgesic doses, other possible causes should be investigated. In patients who are completely unresponsive, no change in behavior will be evident and the optimized analgesic dose should be continued.
Areas of Research in Pain That Are Influencing How Pain Meds are Used

- Age and pain
- Genetics
- Pharmacogenomics
- Race/ethnicity
- Monitoring
- Looking past the opiates as drugs for pain

Age as a Determinant of Pain

- Is pain ‘different’ across the lifespan?
- New studies indicate pediatric pain is equal to that of adults
- Analysis and use of pain medications by teens
- Pain in the elderly is likely undertreated

Neonatal Pain Management

- Morphine is the opioid analgesic most commonly used to control moderate-to-severe postoperative pain in neonates.
- Surgical procedures after which morphine is given may include craniotomy, thoracotomy, sternotomy, and laparotomy.
- Dosing: Incremental IV boluses of 20 mcg/kg, not to exceed 100 mcg/kg, for acute pain management in the postanesthesia recovery unit. If continuous IV infusion is used for postoperative pain management in neonates, the initial rate varies depending on the patient’s age.
- Neonatal Infant Pain Scale is useful for assessment.

Pediatric Pain Management

- For children as young as 3 years, the revised FACES scale, Wong-Baker Faces scale and the 10-cm Visual Analog Scale are useful for assessment.
- For infants and those with cognitive impairment, use face, legs, activity, crying and consolability (FLACC) scale.

Pediatric Pain Management—ER

- Local anesthetics alone or with vasoconstrictors are often appropriate for children, infants, and even neonates for painful procedures.
- In neonates administration of a 12-25% sucrose solution (pacifier) has been very helpful in reducing response to noxious stimuli.
- Sedative hypnotics that are short-acting offer ‘escape’ from pain and procedural sedation in children.
- Propofol, ketamine
In One ‘Snapshot’ Study of Teens...

- Over half reported back pain!
- Girls reported higher pain levels than boys
- 52% used drugs including:
  - Prescription-strength ibuprofen: 36%
  - Acetaminophen with codeine: 30%
  - Acetaminophen and hydrocodone: 12%
  - Long-acting opioids (such as controlled-release morphine): 4%.

Pain Medication Use In Teens

- Likelihood of use of pain meds increased 140-200% with each grade of high school
- Girls were more likely than boys to ask a parent (mother) about using a pain med
- But only 47% do
- Pain scales/intensity were not predictors of use of drugs; having an additional site of pain (headache, backache, sore knees) was a better predictor
- Each additional site increased odds of use by 120-150%

Opiates in Pregnancy

- Linked to:
  - Conoventricular, atrioventricular, and atrial septal defects
  - Hypoplastic left heart syndrome
  - Tetralogy of Fallot
  - Pulmonary valve stenosis
  - Spina bifida
  - Gastroschisis

Role of Sex in Pain and Analgesia

- Females experience more painful situations, have a lower threshold for pain
- This changes over the lifespan, so hormones may play a role in the pain response
- With mu-opioid agonists, women experience more nausea, vomiting, and respiratory depression than men
- Morphine seems to have greater potency but slower onset and offset in women
- With kappa-opioid agonists, women experience longer and more intense analgesia
- Buprenorphine, butorphanol

Prevalence of Pain in the Elderly

- The Centers for Disease Control and Prevention (CDC, 2006), the American Geriatrics Society (2002), and the American Pain Foundation (2008) estimate that 21%-70% of community-dwelling older adults (i.e., >60 years of age) experience persistent pain, with a significant tendency toward underreporting.
  - In community-dwelling adults, predominant pain is musculoskeletal

Trends Seen in Pain Treatment

- Patients older than 75 are 20% LESS likely to receive pain meds than adult counterparts.
- Worry about side effects?
- Concern about drug interactions?
- Concern that drug regimens will become too complicated?
- This compounds the problem of underreporting!
- Interference with QOL activities such as walking, mood, sleep
Risks of Opiates in the Elderly
- Chronic opiate use in the elderly is associated with immunosuppression. Pneumonia risk has been known to increase as a result.
- Elevated risk of compound fracture of the wrist, hips
- Increased need for laxative use...and an increased risk for falls
- Five percent of all adults over 65 using opiates in chronic regimens have been hospitalized

The Elderly Patient and Pain Meds
- Women are more likely to take meds than men
- Report “poor” or “fair” health
- Have osteoarthritis
- Have mobility or ADL difficulty
- Report that pain definitely affects QOL
- Use nonpharmacologic strategies—maybe to their detriment

What About the Nonverbal Patient with Dementia?
- Ask the patient about pain—considering dx and hx
- Search for causes of pain—dx, but also position, constipation, falls, too hot/cold
- Seek surrogate reports—not always reliable! Consider diversion!
- Empiric analgesic trial
- Observe behaviors—BODIES

BODIES
Mnemonic for Assessment of Pain in Demented and Nonverbal Elders
B What behaviors did you see?
O How often did the behaviors occur?
D What was the duration of behaviors?
I How intense were the behaviors?
E How effective was the treatment, if given?
S What made the behaviors start or stop?

Ethnicity and Race
- In a large meta-analysis of post-op patients, pain levels were significantly higher among African American children than among Caucasian children, and African American children (especially those with a history of obstructive sleep apnea) required more analgesic interventions and more postoperative morphine than did Caucasian children.
- Overall opioid-related adverse effects were 2.8 times more common in Caucasian patients than in African American patients.
- Race may determine morphine’s clearance

Genetic Trends in Opiate Response
- Based on a 121 twin-pair double blind placebo controlled study...
  - Nausea, slowed breathing and potential for addiction may be heritable traits
  - Itchiness and sedation are also likely heritable
  - Heritability was found to account for 30 percent of the variability for respiratory depression, 59 percent of the variability for nausea and 36 percent for drug disliking. Additionally, up to 38 percent for itchiness, 32 percent for dizziness and 26 percent for drug-taking could be due to heritable factors.
Genetic Trends in Opiate Response

- Genetics may account for 60% of the variability in the effectiveness of opiates in relieving pain.
- “That doesn’t work for me.....”
- Pharmacogenomics
- Linked to several genes/alleles/enzymes
  - OPRM1—gene that encodes the opiate receptor
  - CYP2D6—hepatic enzyme that metabolizes opiates
  - UGT2B7—hepatic enzyme that metabolizes opiates
- Recent deaths in children given codeine highlight the importance of understanding pharmacogenetic-opiate link
- Likely to blame: Overdose and CYP2D6 ultra rapid metabolism status
- Other opiates using this enzyme include tramadol, hydrocodone, oxycodone: They are converted to more potent mu agonists by this enzyme and may require greater rescue analgesia in rapid metabolizers

The Nurse Practitioner and Pain Management

Keeping Current With Drugs to Manage Pain

- Opiates are and will be mainstays of chronic pain management
- Problems associated with use fall into 2 categories
  - Prescriber education, liability, prescriptive authority
  - User abuse, diversion

Prescription Opiate Facts

- US consumes 80% of the world’s opioids and 99% of the world’s hydrocodone
- Accidental overdoses of Rx opiates kill more people in 17 states than do car accidents
- Males are 1.5 times more likely to become addicted
- Hydrocodone/APAP is the #1 prescribed drug in the US!!!!
- 1 in 20 people in US take opiates for nonmedical use
- Enough Rx painkillers were prescribed in 2010 to medicate EVERY adult in the US around-the-clock for one month
### Opioid Sources in the Last 6 Months

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<th>Source</th>
<th>Patients, %</th>
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<tr>
<td>Bought from a dealer</td>
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<tr>
<td>Someone gave them</td>
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<tr>
<td>Bought from a patient who sells their medication</td>
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<tr>
<td>Legitimate prescription for pain</td>
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<tr>
<td>Stolen</td>
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<tr>
<td>Prescription from physician but no legitimate reason</td>
<td>30.6</td>
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<tr>
<td>Prescription from multiple physicians</td>
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<tr>
<td>Internet</td>
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<tr>
<td>Prescription from physician who prescribes illegally</td>
<td>3.4</td>
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<tr>
<td>Forged prescription</td>
<td>2.8</td>
</tr>
<tr>
<td>Other source</td>
<td>3.8</td>
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</tbody>
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### NP Prescriptive Authority
- Any prescription for a CS will have the NP’s DEA#, denoting the NP’s independent or plenary authority to prescribe within the state’s scope of practice.
- Standard Rx information
  - Name, title, license, specialty, ID/Rx #, address, phone #, all patient information, refill info, generic substitution info
  - Cosignature of a collaborating physician is NOT required in any state where an NP is authorized to write.

### NPs and Pain Management
- The Nurse Practitioner Healthcare Foundation recently noted goals for NPs:
  - To keep current with multimodal approaches to chronic pain control
  - To follow evidence-based guidelines to treat chronic pain in their current practice, particularly with respect to prescribing opioids

### To Ensure Safe Practice and Prescribing for NPs
- American Pain Society and American Academy of Pain Medicine have put together strategies for safer prescribing
- For the patient on Chronic Opiate Therapy (COT)—14 recommendations
  - A thorough history including that of prior substance abuse
  - Risk/benefit ratio should be explained
  - COT management plan with endpoints

### COT Plan, Continued
- A plan for continuance of COT
  - Patient monitoring, including urine drug screens
  - Discuss referral to a specialist if addiction issues arise
  - Discontinue patients suspected of diverting
  - Treat opioid ADRs including constipation, sedation, itching, respiratory depression

### COT Plan, Con’t
- Use of psychotherapeutic cointerventions
- Educate patients about cognitive changes caused by COT
- Patient must have continuous access to a primary HCP
- Educate patient about breakthrough pain
- Educate patient regarding the use of COT (or NOT) in pregnancy
- Keep abreast of current treatments and guidelines and laws
The Pendulum Swings
- Issues with pain meds
  - Overuse
  - Abuse
  - Overprescribing
  - Diversion
  - Across the lifespan
  - Across the medication span

And Swings Again....
- Due to fear of addiction, about 25% of patients receive opioids in doses sufficient to relieve suffering.
  - Physical dependence: Abstinence syndrome will occur if drug is abruptly withdrawn
  - Abuse: Drug use inconsistent with medical or social norms
  - Addiction: Continued use of a drug despite physical, psychologic, or social harm

A Quick Review of Opiates
- Activate mu and kappa receptors
- Activation of the mu receptor produces analgesia, sedation, euphoria...but also respiratory depression
- Activation of the kappa receptor produces analgesia and sedation
- Both receptors are responsible for causing constipation
- Drugs are pure agonists, agonist-antagonists (sometimes called partial agonists), or pure antagonists on these receptors

Examples of Opiates
- Pure Agonists
  - Morphine, codeine, meperidine, fentanyl, hydromorphone, methadone, levorphanol, oxymorphone, oxycodone, tapentadol, hydrocodone
- Agonist-Antagonists
  - Buprenorphine, butorphanol, nalbuphine, pentazocine

Adverse Effects of Opiates
- Respiratory depression
  - Most common cause of death due to overdose
  - Varies with route: Seven min. after IV, 30 min. after IM, 90 min. after subQ, hours after spinal
  - Reverse with Naloxone
- Constipation
  - Prophylaxis with stimulant laxatives may help
  - Methylnaltrexone will reverse GI effects
- Hypotension, urinary retention, cough suppression, biliary colic, emesis, elevation of ICP, euphoria/dysphoria, birth defects, sedation, miosis

Opioid Related Deaths
- Graph showing number of deaths from opioid-related causes over time
**Morphine Preps**
- IR tablets—15, 30 mg
- CR tablets (MS Contin, Oramorph SR)—15-200 mg
- ER tablets—15-200 mg
- SR tablets (Kadian)—10-200 mg
- ER capsules (Avinza)—30-120 mg
- Standard oral solution (MSIR)—10 and 20 mg/5mL
- Concentrated oral solution (MSIR, Roxanol)—100mg/5mL
- Rectal suppositories (RMS)—5-30 mg
- Soluble tablets for injection—10-30 mg
- Standard solution for injection (Astramorph PF, Duramorph, Infumorph)—0.5-50 mg/mL
- Extended release liposomal solution for injection (DepoDur)—10 mg/mL
- Morphine/Naltrexone (Embeda)

**Fentanyl**
- Sublimaze, Duragesic, Abstral, Actiq, Fentora, Onsolis, Lazanda
- 100 times more potent than Morphine
- Watch with coadministration of other CYP3A4 inhibitors (ritonavir, ketoconazole) as adverse effects will increase
- Parenteral use for maintenance of anesthesia
- Patch wearers need to be opiate tolerant; no heat on the patch
- Transmucosal, nasal preps approved for breakthrough cancer pain only in opiate tolerant patients

**Other Strong Opioids**
- Meperidine
  - May accumulate as a toxic metabolite, so dosing should not exceed 600mg/24h. Some utility for patients with post-anesthesia shivering.
- Methadone
  - Long duration of action, but prolongs the QT interval. Avoid use in patients taking amiodarone, TCAs, erythromycin, quinidine. Patients need ECG prior to and 30 days after treatment. Stop treatment if QT interval exceeds 500 msec.
  - Avoid concomitant use of CNS depressants

**Other Opiate Agonists**
- Codeine
  - About 10% gets metabolized to morphine in the body by CYP2D6. Individuals who are ultrarapid metabolizers may have an increase in analgesia or adverse effects.
  - Dosing is PO, IV, IM, SubQ. Usual adult dose is 15-60 mg/3-6 h (max 120mg/24h). Pediatric dose is 0.5 mg/kg PO, IM or SubQ every 4-6 h (max 60 mg/24h)

**Other Opiate Agonists**
- Hydrocodone
  - Vicodin, Vicoprofen, Lortab
  - Analgesia equivalent to codeine
  - Most widely prescribed drug in the US
  - Usual dose is 5 mg; acetaminophen dose should be less than 4 g/day (less in liver disease).
  - Ibuprofen preps should be limited to 5 tablets a day and no more than 10 days.

**Other Opiate Agonists**
- Oxycodone
  - OxyContin, Roxicodone, Combunox, Oxecta, Percocet, Percodon
  - Analgesia equivalent to codeine. Patients must be opiate-tolerant to get 80 mg strength.
  - Metabolized by CYP3A4 so watch concomitant use of inhibitors/inducers of this enzyme
  - Oxycodone has been reformulated to be impossible to inject.
  - Oxecta will burn nose if snorted, and forms a gel if put in solution
  - FDA labeling changed to note this; no generics
Agonist-Antagonist Opiates
- Pentazocine (Talwin)
  - Agonist at kappa, antagonist at mu
  - Little euphoria, limited respiratory depression, but increases cardiac work
- Nalbuphine (Nubain)
  - Agonist at kappa, antagonist at mu
  - Not a CS; injectable only
  - Has a ceiling for pain relief

Butorphanol (Stadol)
- Agonist at kappa, antagonist at mu
- Analgesia less than morphine, low abuse potential, CS-IV
- Increases cardiac work
- Parenteral (IM, IV) and nasal spray
- Buprenorphine (Buprenex, Butrans, Subutex, Suboxone)
  - Partial agonist at mu, antagonist at kappa
  - Analgesia like morphine, less tolerance, some respiratory depression, hard to reverse toxicity with naloxone, prolongs QT, cause biliary colic.
  - Butrans is patch formulation with strict guidelines for patch site rotation; lowest dose may be used in opioid naive patients. Initial 5 mcg/h patch every 7 days

Buprenorphine, Con’t.
- Buprenex is given by IM or IV injection (0.3 mg) every 6 hours as needed
- Subutex are PO tablets containing 2 or 8 mg buprenorphine
- Suboxone is tablets or films that contain the drug plus naloxone used for managing opioid addiction—or off-label for pain.
  - For addiction, dosing is once-a-day
  - For analgesia, dosing is 3-4 times/day

Oxycodone plus Naloxone
- Targinact For chronic pain
- Offsets opioid-induced constipation
- Targinact was designed to reduce the challenge of opioid-induced constipation in chronic pain management.
  - Naloxone PO is metabolized in the liver, so that peripheral antagonism of opioids exists in the gut, but after that, little naloxone passes into the central nervous system.

Opioid Antagonists as Adjuncts
- Methylnaltrexone (Relistor, s.c. dose: 150 mg kg⁻¹, given once a day).
  - For opioid-induced constipation in advanced wasting illness
- Alvimopan [Entereg, 12 mg] mu receptor antagonist given by mouth just before surgery and then another 12 mg dose given twice daily for up to 7 days, with a maximum dose of 15 capsules.
  - This preparation was designed to address the problem of opiate-induced constipation after intestinal surgery. Bowel recovery time ranged from 10 to 26 hours shorter for patients who were given alvimopan.

With Respect to Costs...
- Prescription drug abuse accounts for 1 million ED visits/year
  - Equal to the number due to illegal drugs
  - Sixty percent of hospital costs related to opioid overdoses are paid for with public funds
- What to do?
What To Do? Team-Based Approach to Prescribing
- Institute clear policies and stick to those policies.
- If patients report that their medications have been stolen, require that they report that to the police and bring a police report to visit for verification.
- Statewide databases that allow for tracking of patient prescriptions, including prescriptions for all schedule II drugs.
- REMS programs
- Fire the patient!

REMS—What is it?
- Risk Evaluation and Mitigation Strategies are a way to decrease adverse outcomes with these drugs. They include:
  - Medication guides with pertinent patient information
  - Black box warnings to alert the prescriber to potentially harmful side effects
  - Additional prescriber education, if needed
  - For instance, “Dear Prescriber” letters, drug-company-sponsored education, pharmacy registration

Risk Evaluation and Mitigation Strategies
- REMS is being proffered as a way to decrease the risks associated with long-term opiate use/abuse—long-acting drugs were included first
  - Morphone, morphine SR, hydrodromorphone ER, methadone, oxycodone CR, oxymorphone ER, transdermal fentanyl and transdermal buprenorphine, morphine/naltrexone ER
- Drug companies paid to educate prescribers

Will REMS Work?
- FDA is asking that the training be mandatory for anyone with a DEA#
- Advantages? OBVIOUS!
  - Helpful to the patient, prescriber
- Disadvantages? OBVIOUS!
  - Though most prescribers are on board with the idea... there is some hesitancy in investing time for training
  - The fear is that other drugs will be “switched to”

IR Products Recently Added to REMS
- Fentanyl Products
  - Approved products with the brand names Abstral, Actiq, Fentora, Lazanda, Onsolis
  - Indicated to treat cancer breakthrough pain in opioid-tolerant patients
  - Added to REMS because of high home use and high potential for abuse or accidental misuse

Other Trends in Opiates
- Tightened controls for hydrocodone?
  - Schedule III to Schedule II?
  - Still in the consideration stage....
- More preparations that are opiate-only, with no acetaminophen
  - Will help with liver issues, hurt with diversion/abuse issues
- Oxycodone plus niacin (Oxecta): Causes skin flushing and irritation if patient exceeds the prescribed amount
- Oxycodone (Remoxy): Oxycodone that forms a gelatinous paste if the user tries to dissolve and inject it
- No more generic oxycodone formulations
Making Opiates Safer--
Latest Legislation
- A bill introduced July 19, 2012 in the U.S. House would require most painkillers to have safeguards to prevent abuse
- If pain medications did not adopt the safety features outlined in the bill, they would be removed from the Food and Drug Administration’s (FDA) approved list of generic drugs

In the Meantime....
- What other drugs are useful in the chronic pain patient?
- Which drugs have proven track records?
- Which drugs may be prescribed by a broader base of NPs?
- Anything new? Safer? Better?

Tramadol
- Tramadol (Ultram, Ryzolt, Rybix)
  - Weak agonist at mu receptors, also blocks NE and serotonin reuptake
  - Good PO for moderate to moderately severe ACUTE pain
  - 50 mg; 100, 200, 300 mg extended release
  - Not a CS, but... avoid prescribing to patients with a history of drug abuse—diversion a problem
  - Many drug interactions—watch for serotonin syndrome, seizures!!
  - Try limit use to about 5 days
  - Requires metabolism, and 5-15% of the population are slow metabolizers
  - Do NOT use ER tablets in patients with hepatic impairment!

Tapentadol (Nucynta)
- A moderate mu-opiate agonist and only effects the uptake of norepinephrine into nerve endings
- No metabolic activation is required for analgesia and there are no active metabolites
- This is an advantage over Tramadol
- It does not appear to cause the confusional states sometimes associated with tramadol
- May be able to reduce morphine dose
- 50, 75, 100 mg
- Useful for ACUTE pain

Nonopioid Pain Relievers—Centrally Acting
- Clonidine (Duraclon)
  - Uses are for hypertension and for severe pain
  - Binds to alpha-2 receptors in the SC and disrupts impulses of pain signals
  - For pain relief, given by an implanted epidural catheter, usually given in combination with an opioid
  - Causes profound hypotension and bradycardia
  - Dexmedetomidine (Precedex) for acute use

Nonopioid Pain Relievers—Centrally Acting
- Ziconotide (Prialt)
  - Administered intrathecally only in patients with severe, chronic pain not controlled by other drugs (including intrathecal morphine)
  - Causes cognitive impairment and psychiatric syndromes as SE
  - Hallucinations, mood changes, risk of suicide. May take up to two weeks after discontinuance to resolve.
NSAIDs for Pain
- Most widely used group of drugs for pain
- Side effects include GI bleeds/distress and renal and hepatotoxicity
- No reduction of inflammation with acetaminophen
- Watch use in children, in alcohol use, high BP, liver disease, renal disease

Newer Formulations of NSAIDs
- Ibuprofen
  - Sprix nasal spray; Caldolor IV
  - IV formulation (800 mg) reduces opiate need by about 25% post-op
  - No real worries about renal function since use is short-term
- Acetaminophen
  - IV for acute pain, or combined with an opiate
  - Ofirmev: fast, penetrates CNS, anti-pyretic
  - 1000 mg in those weighing >50 kg every 6 h

Droperidol
- Droperidol IV or IM has been somewhat successful in opiate tolerant patients
  - 0.625mg to 1.25 mg
- Pretreat with diphenhydramine to reduce akathisia related to droperidol treatment.
- May be added to opiates significantly reducing their effective dose.

Antidepressants for Pain
- Work best for neuritic or neuropathic pain, less helpful for musculoskeletal pain
- Agitated or anxious patients do best with antidepressants that are more sedating
- Most common SE are drowsiness, constipation, dry mouth, blurred vision. Watch for Serotonin Syndrome.

Antidepressants for Pain
- BENEFITS
  - Not as much GI upset as NSAIDs
  - May help with sleep
  - May reduce depression associated with chronic pain
  - May relieve anxiety associated with pain
  - May increase effects of other pain meds
  - Are non-addictive
  - Safety is documented

Antidepressants Commonly Prescribed for Pain
- TCAs: Amitriptyline (Elavil), Desipramine (Norpramin), Imipramine (Tofranil), and Nortriptyline (Aventyl, Pamelor)
- Desipramine has lowest SE profile
- SSRIs: Duloxetine (Cymbalta), Venlafaxine (Effexor), Mirtazapine (Remeron)
- Best profile for pain. Other SSRIs not as effective for chronic pain.
# Anticonvulsants Used for Pain
- Gabapentin (Neurontin), Pregabalin (Lyrica), Tiagabine (Gabatril), Topiramate (Topamax)
- Good for neuropathic pain, pain due to nerve injury, sensory neuropathy.
- May cause drowsiness, dizziness; report any vision changes!!

# Anticonvulsants Used for Pain
- Carbamazepine (Tegretol)
- Valproic acid (Depakote)
- Phenytoin (Dilantin)
- Clonazepam (Klonopin)
- Lamotrigine (Lamictal)
- Levetiracetam (Keppra)
- Oxcarbazepine (Trileptal)
- Zonisamide (Zonegran)

# New Updates on Seizure Drugs
- **Gabapentin Enacarbil (Horizant)** just approved for postherpetic neuralgia—10% incidence
  - Doses 600 mg bid
  - Prodrug of Gabapentin; not interchangeable
  - Somnolence, dizziness, suicidal ideation
- **Pregabalin (Lyrica)** approved for neuropathic pain in spinal injury—the first drug for this condition!
  - 40% of patients with SCI develop neuropathic pain
  - Somnolence, dizziness, sedation, angioedema have been reported
  - Doses 150-600 mg daily

# New Uses of Old Drugs for Pain
- **Cyclobenzaprine (Flexeril)**—this is really a TCA, so it has all the TCA side effects.
- **Carisoprodol (Soma)**—now banned by European Medicines Agency (our equivalent of the DEA) due to abuse issues—watch for abuse potential!
- **Methocarbamol (Robaxin) and Metaxolone (Skelaxin)**—older; sedation is main effect/SE
- **Orphenadrine (Norflex)**—this is actually Benedryl, so sedation and inhibition of motor function will be seen.

# New Uses of Old Drugs for Pain
- **Tizanidine (Zanaflex)**—an agent for spasticity that shows some evidence for the treatment of chronic pain, musculoskeletal pain, and neuropathic pain.
- Alpha-agonist similar to clonidine; since it causes significant sedation, should be reserved for night time use
- **Lioresal (Baclofen)**—antispasmodic that is being used (off-label) for musculoskeletal pain. Sedation is side effect of note.

# New Strategies for Pain Management
- **Opiorphin**: Blocks the endopeptidases that normally degrade opiates—this would prolong their duration of action. These agents as stand alone drugs would have little abuse potential but….
- **Ibudilast**: Inhibitor of glial activation, has some potential for neuropathic pain. May restore morphine tolerance.
- Also being tested for methamphetamine addiction.
New Drugs for Neuropathic Pain
- TRPV1 channel agonists
  - This is where capsaicin works (transdermal, 8%)
  - 8% patch is indicated for herpetic neuralgia
  - Possible for migraine, pruritus, musculoskeletal pain, osteoarthritis
- Endocannabinoid receptor agonists
  - These interact with the TRP channels and endorphin pathways; are neuromodulators on CB1 and CB2 receptors
  - Controlled studies are lacking

Treatment of Pain—Multimodal Therapies
- Opioids can help with ascending pain pathways in chronic pain management.
  - Plus an antagonist to deal with opioid ADRs
- NSAIDs can be used to decrease prostaglandin formation centrally, and also to affect substance P and serotonin pathways.
- Membrane stabilizing drugs such as seizure meds alter ion flux in nerve membranes, blunting depolarization, affecting both pain transmission and perception.

The Problem of Pain...Approached
- Clinicians are treating pain more aggressively as a result of the Joint Commission standards, and this may lead to more adverse events.
  - BUT...using multi-modal analgesia ("balanced analgesia")...
  - Benefit the patient in that it can bring sedation, pain relief, and reduce tissue destruction
  - Benefit the prescriber in that it may mitigate some of the adverse effects of opioids

Keep Approaching the Problem of Pain!
- Keep up with drugs and safety issues
  - Including REMS
  - Plan for prescribers to mitigate abuse/diversion
- Recognize that pain relief is multi-modal
  - This is good news for your patient
  - This requires more knowledge, skill, monitoring
- Other than new formulations, the drugs have not changed much, but regulations of these medications may be in flux.

The Big News in Pain Management
- Pharmacogenomics may allow for better prediction of response, of adverse effects—and may reveal the diverter!