48th Annual Meeting

Identifying and Managing Pain in High Risk Patients

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Navigating the Oceans of Opportunity

Risk Factors for Opioid Abuse

- History of Opioid Abuse
- History of Other, Non-Opioid, Substance Misuse
  - Nicotine
  - EtOH
  - Marijuana
  - Psychostimulants
  - Barbiturates / Benzodiazepines / Non-BZDs
    - Alprazolam, Clonazepam, Diazepam, Zolpidem, etc.

Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

- 1. Identify patients at risk of opioid abuse
- 2. Compare treatment options for pain management in patients with a history of opioid abuse
- 3. Discuss considerations and challenges of pain management in patients with concomitant disease states

Identifying Patients at Risk

- Pharmacists Role in Identifying & Avoidance of Dependence / Addiction:
  - Refill Rates
  - Use of "PRNs"
    - Actual sporadic PRN use or Around-The-Clock
    - On the date, or even early refills
  - Behaviors in the Pharmacy

Signs and Symptoms

- Physical Signs of Opioid Intoxication
  - Pupillary constriction
  - "Nodding" or intermittent dozing; Sedation, drowsiness
  - Slurred speech
  - Mood normal to euphoric
  - Memory impairment
  - Lowered blood pressure or pulse rate; Shallow and slow respiration

- Physical Signs of Opioid Overdose
  - Unconsciousness
  - Pinpoint pupils
  - Very shallow, slow respirations (below 10 per minute)
  - Very slow pulse rate (below 40 per minute)
  - Overdose triad: apnea, coma, pinpoint pupils


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Signs and Symptoms

**Physical Signs of Opioid Misuse**

Opioid misuse often accompanies opioid dependence. Consider further screening in patients with evidence of any of the following:

- Pupillary constriction
- Constipation; Nausea
- Sweating; Euphoria
- Track marks or scars; Skin necrosis; Tourniquet pigmentation
- Abscesses, cellulitis, or dermatitis at injection sites
- Allergic reactions
- Atrophied or perforated nasal septum
- Abscess, cellulitis, or dermatitis at injection sites
- Allergic reactions
- Atrophied or perforated nasal septum
- Sexually and needle-transmitted diseases, including HIV, hepatitis, and endocarditis

**Psychosocial Signs of Opioid Dependence**

There are specific psychosocial signs of opioid dependence, however certain patterns are frequently observed among individuals dependent on opioids. Consider further screening in patients with evidence of the following:

- Mood instability; Agitation; Anxiety; Anger; Irritability; Depression
- Family problems; Marital issues; Abuse or violence
- Childcare's behavioral problems; Anxiety or depression in family members
- Significant social changes; Spending time with other drug abusers
- Loss of long-standing friendships; Social isolation
- Loss of interest in regular activities
- Work or school problems; Missed days; Poor performance
- Frequent job changes or relocations
- Legal problems ; Arrears; DUIs; Theft; Drug dealing
- Financial problems; Large recent debt
- Borrowing money from friends or relatives; Selling possessions

**Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain.**

- Non-opioid substance abuse disorders
  - Strong predictor (OR=2.34)
- Painful physical health disorders
  - Dose-response relationship
  - Higher doses and Longer treatment period ↑ risks
- Mental health disorders
  - Mod-strong predictor (OR=1.46)
- Socio-demographic factors
  - Less than 40yo > than older
  - Separated/Divorced/Single > Married
  - Male > Female

**Prescription Opioid Misuse Index**

1. Do you ever use MORE of your medication, that is, take a higher dosage, than is prescribed for you? Yes / No
2. Do you ever use your medication MORE OFTEN, that is, shorten the time between dosages, than is prescribed for you? Yes / No
3. Do you ever need early refills for your pain medication? Yes / No
4. Do you ever feel high or get a buzz after using your pain medication? Yes / No
5. Do you ever take your pain medication because you are upset, using the medication to relieve or cope with problems other than pain? Yes / No
6. Have you ever gone to multiple physicians including emergency room doctors, seeking more of your pain medication? Yes / No

An affirmative (YES) answer to more than one question correctly classified an individual as an opioid misuser, Janet S. Knisley, Ph.D., et al., Journal of Substance Abuse Treatment. Vol. 35 (2008) pp. 380-386

**Pain Management in Patients with a History of Opioid Abuse**

- Acute Pain vs Chronic Pain
- Under supervision, Acute Pain should be managed optimally with or without Opioids.
- Alternates to Opioid Pain Management with intent to avoid Substance Dependence/Abuse
Alternates to Opioid Pain Management with intent to avoid Substance Dependence/Abuse

Non-Opioid Treatments

- Acetaminophen
- Non-Steroidal Anti-Inflammatory Drugs
  - *Tramadol
    - Abuse / Dependence potential
  - *Muscle Relaxants
    - Dependence potential

Non-Opioid Treatments

- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) & Tricyclic Antidepressants (TCAs)
  - Amitriptyline
  - Imipramine
  - Desipramine
  - Venlafaxine
  - Duloxetine
  - Milnacipran
  - Levomilnacipran

Non-Opioid Treatments

- Anticonvulsants:
  - Carbamazapine
  - Gabapentin
  - Pregabalin
  - Others…..

Types of Chronic Non-Malignant Pain

- Neuropathies and Neuralgias
- Back Pain
- Arthritis (Osteo- & Rheumatoid)
- Headaches
- Depression-Related Pain
- Fibromyalgia
- Pain of Mixed Etiologies & Others

Pharmacological Treatment Alternatives for Diabetic Neuropathic Pain

- SNRIs
  - Duloxetine
  - Tricyclic Antidepressants (actually the first SNRIs)
    - Amitriptyline
    - Desipramine
    - Others
  - Other SNRIs: Venlafaxine / Milnacipran
    - Levomilnacipran
Antidepressant Dosing

- “Start Low & Go Slow”
  - Especially in the elderly
- TCA’s: 10-25 mg/d to 300 mg/d (~50 to 100 mg/d)
- Duloxetine: 20 mg to 60 mg/d (~60 mg/d)
  (FDA approved)
- Venlafaxine: 37.5 mg/d to 375 mg/d (~150 mg/d)
- Doses at less than usual antidepressant dosing may be effective

Effects of Desipramine, Amitriptyline, and Fluoxetine...

- RESULTS:
  - Amitriptyline and Desipramine were similar
    - 74% vs. 61% response
  - Fluoxetine and Placebo were similar
    - 48% vs. 41% response
  - Amitriptyline and desipramine effective in depressed and non-depressed pts.
  - Fluoxetine only effective in depressed pts.**
    - 15 years later… “Depression Hurts”
- CONCLUSION:
  - NE reuptake is also responsible for pain modulation

Duloxetine vs. placebo in patients with painful diabetic neuropathy

Effects of Desipramine, Amitriptyline, and Fluoxetine on Pain in Diabetic Neuropathy

- TWO RANDOMIZED, DOUBLE-BLIND, CROSSOVER STUDIES OF PATIENTS WITH DIABETIC NEUROPATHY
  - Amitriptyline (avg. 105mg) compared to
    - Desipramine (avg. 111mg) for 6 weeks in 38 pts.
  - Fluoxetine 40mg compared to
    - Placebo for 6 weeks in 46 pts.

Venlafaxine Use in the Treatment of Diabetic Peripheral Neuropathy Pain

- 12 week prospective, open-label
- 20 of 31 patients completed study
- RESULTS: 90% positive response (CGI = 1 or 2)
  - No sig. changes in lipids or fasting glucose
  - Statistically significant reduction in SBP/DBP
  - Average daily dose: 121 mg/day ± 60mg
  - Effective in both non-depressed and depressed pts.
  - SEs: Nausea, HA, dizziness, dry mouth, emesis

**Numerical Pain Scale Results**

"Venlafaxine for Diabetic Peripheral Neuropathy Pain"

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Patient Reported</th>
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<tbody>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>WK 1</td>
<td></td>
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<tr>
<td>WK 8</td>
<td></td>
</tr>
<tr>
<td>WK 12</td>
<td></td>
</tr>
</tbody>
</table>

**Time to Response**

Patient reported: “much improved” or “very much improved”

**Anticonvulsants**

- **Mechanisms of Action:**
  - Stabilize (inhibit) nerve membrane firing
  - Na⁺ channels; Ca²⁺ channels; GABA; Glutamate; NE/S-HT MoA
- **Agents:**
  - Pregabalin (FDA approved)
  - Gabapentin (FDA approved)
  - Carbamazepine
  - Phenytoin
  - Oxcarbazepine
  - Topiramate
  - Lamotrigine
  - VPA

**Anticonvulsant Dosing**

- **Carbamazapine**
  - 100-1200 mg/d divided
- **Valproic Acid**
  - 500-1000 mg/d divided
- **Oxcarbazepine**
  - 1200-2400 mg/d divided
- **Gabapentin**
  - 300-3000 mg/d divided
    - (1800 mg/d is usual dose)
- **Phenytoin**
  - 100-600 mg/d divided
- **Topiramate**
  - 50-400 mg/d divided

**Efficacy of Carbamazepine Compared with Other Agents:**

A Clinical Practice Survey

- **Survey of 2543 Physicians** (28% response)
  - on uses of CBZ other than bipolar disorder
- **Physicians Reported:**
  - 441 treated and rated for trigeminal neuralgia
  - 579 treated and rated for other pain syndromes
- **Efficacy** (moderate to marked relief of symptoms)
  - 81.3% of trigeminal neuralgia pts.
  - 51.3% of other pain syndromes pts.
**Pregabalin**

- **MoA:** Binding to alpha-2 delta site of the auxiliary subunit of voltage-gated calcium channels
- **ADRs:**
  - dizziness, somnolence, weight gain and peripheral edema.
- **Dosing:** 150-300 mg/day
  - 50-100 mg po TID (max: 300 mg/d for DPN)
  - Up to 450 mg/d for fibromyalgia
  - Up to 600 mg/d for post-herpetic neuralgia

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**Pregabalin for DPN**

- **Efficacy Difference** (sig. vs PLB; not sig between active txs)
- **Dosing Reduction with Combination**

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**Gabapentin vs Morphine vs G+M vs Placebo (N=35 for DPN & N=22 for PHN)**

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**TREATMENT OF FIBROMYALGIA**
Background

• Fibromyalgia is a diverse and chronic disease
  – Disseminated musculoskeletal pain
  – Tenderness at 11 of 18 specific tender points
  – 10 million people in the United States are believed to be affected
  – Estimated cost of FM: $12-14 billion/year


Background

• Symptoms:
  – Fatigue, sleep disturbances, cognitive impairment, and mood disorders
  – Pain

• Current FDA-approved treatments:
  – Duloxetine (Cymbalta®): 60mg po QD
  – Milnacipran (Savella®): 50-100mg po BID
  – Pregabalin (Lyrica®): 150-225mg po BID


– Self-administered instrument
– Higher score indicates a greater impact on QOL
– FIQ demonstrates sensitivity to therapeutic change
– 10 items:
  • Physical impairment, feel good, work missed, pain, fatigue, rested, morning stiffness, morning tiredness, anxiety, and depression


**Fibromyalgia Impact Questionnaire (FIQ)**

<table>
<thead>
<tr>
<th>N</th>
<th>150</th>
<th>147</th>
<th>37</th>
<th>224</th>
<th>441</th>
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<tr>
<td>Pre FIQ</td>
<td>51.7</td>
<td>31.7</td>
<td>63.2</td>
<td>65.1</td>
<td>64.3</td>
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<tr>
<td>Post FIQ</td>
<td>36.3</td>
<td>37.2</td>
<td>40.0</td>
<td>47.4</td>
<td>47.0</td>
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**LITERATURE REVIEW:**

<table>
<thead>
<tr>
<th>% Reduction in FIQ</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine 60mg/day</td>
<td>10.2</td>
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<tr>
<td>Duloxetine 120mg/day</td>
<td>20.5</td>
</tr>
<tr>
<td>Amitriptyline 25mg/day</td>
<td>15.0</td>
</tr>
<tr>
<td>Milnacipran 100mg/day</td>
<td>12.5</td>
</tr>
<tr>
<td>Milnacipran 200mg/day</td>
<td>22.0</td>
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</table>

**LITERATURE REVIEW:**

<table>
<thead>
<tr>
<th>% Reduction in FIQ</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin 1800mg/day</td>
<td>25.0</td>
</tr>
<tr>
<td>Gabapentin 3000mg/day</td>
<td>45.0</td>
</tr>
<tr>
<td>Gabapentin 4500mg/day</td>
<td>40.0</td>
</tr>
<tr>
<td>Gabapentin 6000mg/day</td>
<td>45.0</td>
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</tbody>
</table>

A 14-week, Randomized, Double-Blinded, Placebo-Controlled Monotherapy Trial of Pregabalin in Patients With Fibromyalgia


Goals of Treatment for Chronic Migraine Headache

- Provide daily preventative therapy when necessary for patients suffering from frequent migraine attacks.
  - Decrease the frequency and severity of the migraine attacks
    - Improve QOL and disability associated with migraine attacks
    - Improve pharmacoeconomic outcomes

Diagnosis of Acute Migraine

Mild to moderate Symptoms
- Simple analgesics: APAP, NSAIDS, Combo OTC

Severe Symptoms
- Triptans or Ergotamine (Preferably Triptans)
- Last Line... Opioid analgesics: Stadol, Meperidine, etc.

Failed Response

Pregabalin for Fibromyalgia

Prophylactic Therapy

- Therapy that is administered daily to prevent the recurrence of migraine attacks and to increase response to acute therapies.
  - Frequency
  - Severity
  - Length of Attack

- Indicated for patients with...
  - Multiple Severe Attacks (Prolonged)
  - Extensive medication overuse (>2 week)
  - Acute therapies are ineffective or contraindicated

Prophylactic Therapy Algorithm

Meets Criteria for Prophylaxis / Longterm Maintenance

First-line Tx: Beta-blockers

2nd-line Tx: VPA / Topiramate

3rd-line Tx: TCAs

4th-line Tx: CCBs

Last-line Therapy

Beta Blockers

- Treatment of choice and first-line for prophylaxis w/out co-morbid conditions
  - MOA: Antagonize Beta Adrenergic receptors
  - Increase Migraine Threshold??
  - Effective in frequency of migraine attacks
- Two approved agents
  - Propranolol (Inderal LA®)
    - FDA approved
    - Highly lipid soluble
    - 80-260 mg/day in divided doses
  - Timolol (Blocadren®)
    - FDA approved
    - Less lipid soluble
    - 20-60 mg/day in divided doses
- Start low and go slow to effective dose

Beta Blockers

- Other beta blockers are commonly used
  - Atenolol (β₁ selective)
  - Metoprolol (β₁ selective)
  - Nadolol (Non-selective)
- ISA Beta-blockers are ineffective for treating migraines
  - Acebutolol
  - Penbutolol
  - Pindolol

Divalproex Sodium

- Enhance central GABA
  - Inhibit GABA transaminase?
  - Increases migraine threshold??
- Excellent with co-morbid epileptic condition/or mood disorder
- Significant reductions in migraine frequency, duration, and severity
- Dosing: 500-1500 mg/day
  - Target Level: 50-100 mcg/mL

Topiramate

- Anticonvulsant with preventative actions for migraines
  - Increase migraine threshold
  - Migraine frequency by 50%
  - Comparable to other approved treatments
  - Can take up to 1 month for effective results
- Dosing: Titrate up to 100mg BID or to effective dose

Antidepressants

- TCA's
  - Modulates 5-HT/NE transport 5-HT/NE receptor activation (and down regulation?)
  - Amitriptyline is effective but lacks FDA approval
    - Evidence-Based
  - Ideal for patients that have co-morbid depression
    - Others are commonly used
      - Nortriptyline
      - Imipramine
      - Desipramine; Doxepin
- SSRIs (Not effective); Newer SNRIs may be beneficial

Other Migraine Prophylactic Agents

- Ca++ Channel Blockers
  - Verapamil is commonly used
    - (-) chromotrop, (-) inotropic, (-) dromotropic effects
- Methysergide (if you can find it)
  - Last line agent (5-HT₂ antagonist)
  - Rare pulmonary fibrosis
### Mechanisms of Action

- **Amitriptyline**: TCA, balanced monoamine reuptake inhibition (SNRI)
- **Capsaicin / Topical**: Depolarizes the nervous membrane via vanilloid receptor type 1, initially stimulates then blocks skin nerve fibers
- **Carbamazepine**: Voltage-gated sodium-channel blockade
- **Desipramine**: TCA, predominantly noradrenaline reuptake inhibition
- **Duloxetine / Milnacipran**: SNRIs, serotonin-noradrenaline reuptake inhibition
- **Gabapentin / Pregabalin**: Binding to the δ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters
- **Lidocaine / Topical**: Block of peripheral sodium channels and thus of ectopic discharges
- **Lamotrigine**: Presynaptic voltage-gated sodium-channel inhibition and thus reduced release of presynaptic transmitters
- **Memantine / Dih**: NMDA-receptor antagonist
- **Oxcarbazepine**: Voltage-gated sodium- and calcium-channel blockade
- **Tetrahydrocannabinol**: Agonist to the CB1 / CB2 subtype of cannabinoid receptors
- **Topiramate**: Voltage-gated sodium-channel block and inhibition of glutamate release by an action on AMPA/Kainate receptors
- **Tramadol**: μ-opioid-receptor agonist and monoamine reuptake inhibitor
- **Valproate**: Increase of GABA levels in brain and potentiation of GABA-mediated responses

### Challenges (and Opportunities) for Pain Management in Co-Morbid Disease States

### Assessment of Pain

- Detailed Patient History
- Pain Intensity & Characteristics
- All Medication Use
  - Current and Past Use with Outcomes
  - OTC, Alternative / Natural, and Prescription Rx
- Physical and Neurological Exam

### Assessment of Pain (cont.)

- Psychosocial Assessment
  - Quality of Life issues
  - Attitudes and Beliefs about pain
- Appropriate Work-Up for the Etiology of the Pain
- Documentation of Outcome Measurements
- Pharmacists and MTM:
  - Identification of Medication-Related Problems

### Pain Assessment Tools

- Patient’s self-report
- Simple verbal descriptors for distress
- (0-10) Numerical Pain Rating Scale
- Visual Analogue Scale (0-10 cm/mm)
- Pictures / Drawings representing pain or location
- Pain Diary:
  - Time / Pain Rating / Outcomes of analgesia

### Co-Morbid Diagnoses

- Depression
  - Especially with Chronic Pain
- Bipolar Disorder
- Anxiety Disorders
  - Generalized Anxiety Disorder
  - Panic Disorder
  - Others (OCD, SAD, PTSD)
- Chronic Insomnia
- Schizophrenia
- Current Substance Use Disorder
Two Birds with One Stone

- **Pain Syndrome**
  - e.g. Neuropathic Pain, Headaches, Back Pain

- **Psychiatric Disorder**
  - e.g. Anxiety, Depression, Bipolar Disorder, Insomnia

- Can we treat both issues (Co-morbid Diagnoses) with one medication?

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Two Birds with One Stone

- **Pain Syndrome**
  - Migraine Headache

- **Psychiatric Disorder**
  - Bipolar Disorder

- Can we treat these issues with one medication?

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Two Birds with One Stone

- **Pain Syndrome**
  - Diabetic Neuropathic Pain

- **Psychiatric Disorder**
  - Depression

- Can we treat these issues with one medication?

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Three Birds with One Stone

- **Psychiatric Disorder**
  - Generalized Anxiety Disorder (alcohol dependence)

- Can we treat these issues with one medication?

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Three Birds with One Stone

- **Psychiatric Disorder**
  - Generalized Anxiety
  - Alcohol Dependence

- Can we treat these issues with one medication?

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Three Birds with One Stone

- **Psychiatric Disorder**
  - Depression

- Can we treat these issues with one medication?

---

Three Birds with One Stone

- **Psychiatric Disorder**
  - Bipolar Disorder

- Can we treat these issues with one medication?
Four Birds with One Stone

- Neuropathic Pain
- Depression
- Generalized Anxiety Disorder
- Smoking Cessation

Can we treat these issues with one medication?
- ........................................Amtriptyline
- ........................................Doxepin
- ........................................Nortriptyline

Discussion & Conclusions

- Awareness of Risk Factors and Predicting Opioid Misuse in Pharmacy

- Non-Opioid Analgesics are available and efficacious in Multiple Chronic Pain Syndromes

- Co-Morbid Psychiatric Disorders offer unique, but not impossible, challenges and opportunities in the pharmacotherapeutic management of Chronic Pain Syndromes