Pharmacology, Pain and the Brain

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Island Health
Pharmacology, Pain & the Brain

Addiction
Tolerance
Cognitive Impairment
Hyperalgesia
Pseudo-addiction
Aberrant drug behaviors
Physical dependence
Conflicts of Interest

• Clinical Coordinator VGH
• I work in the Island Health Pain Program
• I have been paid honorariums for educational presentations by Pfizer, Merck, MSD
• Thanks to Pain BC for asking me to participate in this program today
COGNITIVE IMPAIRMENT
Prevalence of Cognitive Impairment (CI) in Chronic Pain

- Cognitive complaints 85-90% chronic pain patients
- Affects multiple cognitive domains

<table>
<thead>
<tr>
<th>Performance domain</th>
<th>% positive studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>88.2</td>
<td>Most delayed memory, verbal tasks, new learning</td>
</tr>
<tr>
<td>Verbal</td>
<td>88.9</td>
<td>Word/category fluency</td>
</tr>
<tr>
<td>Speed</td>
<td>82.3</td>
<td>Verbal processing, psychomotor speed</td>
</tr>
</tbody>
</table>

Pain = psychological stress = cognitive impairment

- Independent of pain intensity & sensory experience
- Associated with emotional suffering & illness behavior
  - Depression, anxiety, worries about relevance of pain can cause deficits in attention and processing
  - Maladaptive pain behaviors contribute further to pain and cognitive impairment

Is it really the drug?

• Step 1 – Is it a listed adverse effect or mechanistically plausible?
• Step 2- Is there a temporal relationship to the effect and the start of the drug?
• Step 3- If I stop the drug (or decrease the dose)(de-challenge) does the effect go away?
• Step 4- If I re-start the drug (re-challenge) does the effect come back?

Adopted WHO
# Incidence of Cognitive Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drowsiness/Somnolence</th>
<th>Cognitive impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>9-48%*</td>
<td>Amnesia 1-10%*</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>????</td>
<td>??</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Somnolence 7-25%*</td>
<td></td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Somnolence 15%*</td>
<td>Confusion 1%*</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>???</td>
<td>??</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Somnolence 19-21%*</td>
<td>Amnesia/abnormal thinking 1-2%*</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Somnolence 4-36%*</td>
<td>Memory impairment 1-4%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Attention disturbances 4-6%*</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Drowsiness 52-66%*</td>
<td>Decreased concentration 12%*</td>
</tr>
</tbody>
</table>

*Lexicomp on-line; accessed October 12, 2013*
## Cannabinoids & Cognitive Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis “medical marijuana”</td>
<td>• Unknown constituents $\rightarrow$ variable effects?</td>
</tr>
<tr>
<td></td>
<td>• Rapid onset, high peaks with smoking $\rightarrow$ acute cognitive changes/euphoria</td>
</tr>
<tr>
<td></td>
<td>• Oral – slow, erratic absorption; long terminal half life due to storage in fat prolongs effects</td>
</tr>
<tr>
<td></td>
<td>• Amotivational syndrome seen with chronic use</td>
</tr>
<tr>
<td>Nabilone</td>
<td>• Sedation; dysphoria prominent $\rightarrow$ contributes to CI</td>
</tr>
<tr>
<td>Oral cannabis spray (Sativex®)</td>
<td>• 1:1 THC: cannabidiol (less psychoactive potential)</td>
</tr>
<tr>
<td></td>
<td>• Reduced peak (1/70$^{th}$ of cannabis) $\rightarrow$ less potential for acute intoxication</td>
</tr>
<tr>
<td></td>
<td>• Studies show minimal cognitive impairment apart from dose titration</td>
</tr>
</tbody>
</table>

Drugs causing CI
Systematic Review-Tannenbaum

- Review of anticholinergics, antihistamines, benzodiazepines, Z-drugs (zopiclone), opioids
- Evaluated amnestic & non-amnestic domains
- Quality assessed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach
- Opioids studies were of low quality, single-use and inconsistent

## Summary Results - Tannebaum

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>oxazepam, lorazepam, alprazolam, clonazepam, diazepam</td>
</tr>
<tr>
<td></td>
<td>• Impairment across a range of cognitive functions; reduced in younger</td>
</tr>
<tr>
<td></td>
<td>adults</td>
</tr>
<tr>
<td></td>
<td>• Dose-response gradient present</td>
</tr>
<tr>
<td></td>
<td>• Only partial tolerance to effects with chronic use</td>
</tr>
<tr>
<td><strong>Zopiclone</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low quality evidence</td>
</tr>
<tr>
<td></td>
<td>• Some impairment in attention and memory recall</td>
</tr>
<tr>
<td><strong>TCA – amitriptyline</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Significant effects on vigilance &amp; attention</td>
</tr>
<tr>
<td></td>
<td>• Inconsistent effects on memory</td>
</tr>
<tr>
<td></td>
<td>• Dose-response effect</td>
</tr>
<tr>
<td></td>
<td>• Some tolerance to effects in younger patients</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td>hydroxyzine, diphenhydramine, triproloidine</td>
</tr>
<tr>
<td></td>
<td>• Decreased alertness, vigilance, attention</td>
</tr>
<tr>
<td></td>
<td>• Partial tolerance develops</td>
</tr>
<tr>
<td></td>
<td>• Unclear dose-response relationship</td>
</tr>
<tr>
<td></td>
<td>• 2\textsuperscript{nd} generation (cetirizine, desloratadine, fexofenadine) showed no/minimal impact on cognition</td>
</tr>
</tbody>
</table>

- 20/38 studies pain-related
- 16/20 (80%) reported adverse cognitive effects
Gabapentin

- Somnolence/drowsiness 16% at doses of 1200mg/day or more
- Risk Ratio = 3.2 (95% CI, 2.5-4.2)
- NNH=9.2 (7.7-12)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>% patients with SE</th>
<th>Mild (No.)</th>
<th>Moderate (No.)</th>
<th>Severe (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>15% (11)</td>
<td>8</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11% (8)</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>8% (6)</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Opioid therapy included: hydrocodone, methadone, propoxyphene, oxycodone, morphine at doses not to exceed morphine daily equivalent of 90mg per day.

Opioid-cognition literature

• Studies showing impairment, no changes & actually **improvement** in cognitive function

• Deficits in memory, attention/concentration associated with:
  - First several days of therapy initiation
  - Following dose escalation
  - Dose related
  - Use of mixed-activity (mu/kappa) opioids
  - High sedation scores
  - Receiving supplemental doses $\rightarrow$ poor attention


Improved Cognitive Function with Opioids

• Correlated with pain relief & improved function

• Dose-related
  – `Watchful dose’ less than 200mg MEDD

• Stable regimen

• Minimal use of supplemental IR doses
Driving Ability

• **No evidence** of impairment for patients on stable opioid regimens (Fishbain et al, 2006)

• **Pain itself** significantly affects reaction time and driving ability (Nilsen et al, 2011)


## Approach to Cognitive Impairment

### Complaints - Patient

<table>
<thead>
<tr>
<th>Factor</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled pain</td>
<td>- Utilize drugs that have minimal impact on cognition</td>
</tr>
<tr>
<td></td>
<td>- Engage in pain education and optimize self-management strategies/non-drug ways of dealing with pain</td>
</tr>
<tr>
<td>Depression</td>
<td>- Treat depression</td>
</tr>
<tr>
<td>Emotional distress</td>
<td>- Engage psychology and/or social worker if available</td>
</tr>
<tr>
<td></td>
<td>- Council non-drug measures to deal with stress &amp; anxiety</td>
</tr>
</tbody>
</table>
# Approach to Cognitive Impairment

## Complaints-Medications

<table>
<thead>
<tr>
<th>Factor</th>
<th>Approach</th>
</tr>
</thead>
</table>
| Evaluate meds that could be contributing to CI-temporal relationship -Prescriptions- TCAs; Gabapentanoids; 1<sup>st</sup> generation antihistamines | - Evaluate alcohol, cannabis or use of other illicit medications  
- Consider de-challenge – tapering or stopping  
- Optimize non-drug approach/self-management strategies |
| Unstable opioid regimen Initiating/titrating dose | -Council patient that sedation/CI can occur initially but will go away  
-Take precautions when initiating/titrating opioids  
-Remember watchful dose of 200mg/day of MEDD  
-Utilize adjunctive meds as “opioid sparing”? Many have CI themselves |
| Frequent use of IR opioids for BT | -Titrate long acting to dose that covers pain  
-Utilize adjunctives & non-drug measures |
TOLERANCE
Opioid Tolerance

- Physiologic state resulting from regular use of a drug
- Repeated exposure to a drug (opioid) results in:
  - Decreased therapeutic effect
  - Need for a higher dose to maintain the same effect

Tolerance can be:

• Innate-pharmacogenetic make-up
  – Is usually acute (on initial dosing) or sub-acute

• Acquired:
  – Pharmacodynamic;
    • Desensitization of opioid receptors
    • Increased receptor density
  – Pharmacokinetic;
    • Altered drug disposition, usually metabolism
    • Reduction of drug in blood/site of action
  – Learned – conditioned/behavioral
Clinically, an increase in pain/requirement for more drug

• Could be:
  – Opioid tolerance
  – Psychological/psychiatric processes
  – Disease progression – usually in malignant pain
  – Opioid-induced hyperalgesia
Opioid-induced hyperalgesia (OIH)

- A (paradoxical) increase in pain sensitivity caused by opioid drugs
- More likely with high doses/sustained treatment course but not always
- Differential diagnosis for OIH:
  - More diffuse and less defined in quality as compared to the pre-existing state
  - Extends beyond areas of pre-existing pain
  - A DECREASE in dose with result in an DECREASE in pain
Approach to Increased pain/dose

Increased dose requirement previously stable regimen

Rule out disease progression & Psychological factors

Trial dose escalation

**Improvement**
- Likely tolerance – P/K or PD
- Consider opioid rotation-lower equianalgesic dose
- Engage adjunctive/non-drug interventions

**No improvement**
- Assess for OIH-features of diffuse nature; less defined quality; beyond existing area
- Decrease dose or wean off
- Consider opioid rotation
- Consider adjunctive therapies.

P/K= pharmacokinetic
P/D= pharmacodynamic
OIH = Opioid-induced hyperalgesia
Addiction

• Source of much concern for patients & prescribers
What is Addiction?

- Primary, chronic, neurobiologic disease
- Influenced by genetic, psychosocial and environment factors
- Characterized by the certain behaviours- aka-the 4 C’s:
  - Control –loss of control over drug use
  - Craving-physical drive/urge to use drugs
  - Compulsive use- “Can’t get drugs out of my mind”
  - Consequences- Continued use despite harm
Pseudo-addiction

- Result of under-treatment or inadequate treatment of pain
- Relief-seeking behaviors are mis-interpreted to be drug-seeking behaviors associated with addiction.
- Common in chronic pain patients
Under-treatment of chronic pain enhances risk of addiction

• Stress of pain augments:
  – Dopamine flow in the reward axis
  – Reinforces the rewarding effects of addictive drugs
  – Promotes drug-seeking & drug taking behaviors
Prevalence of Addiction in Chronic Pain Patient on Opioids

Review Article

What Percentage of Chronic Nonmalignant Pain Patients Exposed to Chronic Opioid Analgesic Therapy Develop Abuse/Addiction and/or Aberrant Drug-Related Behaviors? A Structured Evidence-Based Review

David A. Fishbain, MD, FAPA,*†‡§¶** Brandly Cole, PsyD,†† John Lewis, PhD,** Hubert L. Rosomoff, MD, DMedSc, FAAPM,†§¶†† and R. Steele Rosomoff, BSN, MBA†§¶††

*Miller School of Medicine at the University of Miami. Departments of †Neurological Surgery, ‡Psychiatry and §Anesthesiology, **Department of Psychiatry, Miami VA Medical Center, Miami, Florida; †The Rosomoff Comprehensive Pain Center, ††at Douglas Gardens, Miami, Florida, USA

ABSTRACT

Design. This is a structured evidence-based review of all available studies on the development of abuse/addiction and aberrant drug-related behaviors (ADRBs) in chronic pain patients (CPPs) with nonmalignant pain on exposure to chronic opioid analgesic therapy (COAT).

Objectives. To determine what percentage of CPPs develop abuse/addiction and/or ADRBs on COAT exposure.
### Percent Signs of Abuse/Addiction in CPP on Chronic Opioid Therapy

<table>
<thead>
<tr>
<th>Studies on Addiction</th>
<th>% Total Population</th>
<th>% No hx abuse or addiction (de novo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Opinion</td>
<td>3.27</td>
<td>0.19</td>
</tr>
<tr>
<td>N=24 studies; 2507 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRB</td>
<td>11.5</td>
<td>0.59</td>
</tr>
<tr>
<td>n=17 studies; 2466 pts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CPP= chronic pain patients  
ADRB=Aberrant drug-related behaviors
Continuum of Pain & Addiction

“Not-addicted” Patient
- Looking for the “silver bullet”
- Run out of drug supply early
- Self-medicating for anxiety/stress
- Somatization
- ‘Treated’ psychiatric illness
- Past addiction but not active presently
- Not progressing towards goals
- Refusing to attend program/self mgt strategies

Vast Middle Ground
“Chemical Copers”
- Psychosocially unstable
- Overly ‘drug-focused’
- “Other addictions”-nicotine; cannabis
- Preference for IR formulations
- “I have a high tolerance”
- Refusal to consider non-opioid
- Reports “buzz” from meds
- Variable presentations

“Addicted” Patient
Screening for addiction/ ADB

• Predict/evaluate risk of opioid misuse
  ▪ Opioid Risk Tool (ORT)
  ▪ Screener & Opioid Assessment for Patients with Pain (SOAPP-R™)

• Aberrant drug behaviors (ADB) during treatment (Current Opioid Misuse Measure) -COMM™

• The four A’s on each visit:
  • Analgesia
  • Activities of Daily Living
  • Adverse effects of opioids e.g. sweating, constipation
  • Aberrant Drug Behaviours – 4 C’s – control, craving, compulsion and consequences.
## Opioid Risk Tool

<table>
<thead>
<tr>
<th>Factor</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Alcohol</td>
<td>3 points</td>
<td>1 point</td>
</tr>
<tr>
<td>• Illegal Drugs</td>
<td>3 points</td>
<td>2 points</td>
</tr>
<tr>
<td>• Prescription Drugs</td>
<td>4 points</td>
<td>4 points</td>
</tr>
<tr>
<td><strong>Personal history of substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Alcohol</td>
<td>3 points</td>
<td>3 points</td>
</tr>
<tr>
<td>• Illegal drugs</td>
<td>4 points</td>
<td>4 points</td>
</tr>
<tr>
<td>• Prescription drugs</td>
<td>5 points</td>
<td>5 points</td>
</tr>
<tr>
<td><strong>Age between 16 and 45</strong></td>
<td>1 point</td>
<td>1 point</td>
</tr>
<tr>
<td><strong>History of preadolescent sexual abuse</strong></td>
<td>0 points</td>
<td>3 points</td>
</tr>
<tr>
<td><strong>Psychiatric disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Attention deficit disorder, OCD, Bipolar disorder, schizophrenia</td>
<td>2 points</td>
<td>2 points</td>
</tr>
<tr>
<td>• Depression</td>
<td>1 point</td>
<td>1 point</td>
</tr>
</tbody>
</table>

Screener & Opioid Assessment for Patients with Pain - SOAPP-R™

• Simple 24 items, self-assessment tool that takes less than 10 mins
• Predict ADB- how much monitoring a patient might require on long term opioids
• Ideal to help decision making in regards to monitoring plan and/or referral

Current Opioid Misuse Measure-COMM™

• Patient already on opioids exhibiting ADB over course of treatment
• 17 items, 10 min, patient self assessment tool of:
  – Signs & symptoms of intoxication
  – Emotional volatility
  – Poor response to meds
  – Addiction
  – Healthcare use patterns
  – Problematic medication behaviors
• Better at ID those mis-using rather than those who are not -some false positives

Universal Precautions for Opioid Management

1. Diagnosis with appropriate differential
2. Psych assessment/risk of addiction
3. Informed consent
4. Treatment agreement
5. Pre/Post intervention assessment of pain/function
6. Trial of rationale pharmacotherapy
7. Reassessment – regularly
8. Assess four (five) A’s: analgesia; ADL/function; ADRs; aberrant behaviors; (affect)
9. Review pain diagnoses/comorbidities
10. Documentation

Group 1 Management-Primary Care

• Patient characteristics
  – Uncomplicated patients
  – Little or no past history of substance abuse
  – Treated or no co-morbid psychiatric issues
  – Psychosocially stable

• Management
  – Universal precautions?
  – 30 days supply of medications
  – Monthly follow-up for the 5 A’s (analgesia; ADLs; ADRs; Aberrant drug behaviors)
Group 2-Primary Care/Middle Ground

• Patient characteristics
  – History of substance abuse; use of nicotine/cannabis
  – Treated or stable psychosocial/psychiatric conditions
  – Aberrant drug behaviors/focused on getting drugs

• Management
  – Universal precautions
  – Access to specialty support as needed.
  – Focus on rehabilitation and pain education
  – Sliding scale time frame for office visits/supply of medications (daily to monthly)
  – 5 A’s for each visit
Group 3- Actively Addicted

• Patient characteristics
  – Active addition; aberrant drug behaviours
  – Signs of intoxication/withdrawal

• Management
  – Specialty management
  – Universal Precautions plus urine drug screening
  – Focus on rehabilitation and pain education
Case Studies

• Divide into 3 groups
• Try for an inter-disciplinary mix!
• 30 minutes to read the case, make an assessment and recommendation/plan
• Present to the group- 5 minutes each.
Case #1 - Is this patient addicted?

- 50 yr old man with back pain post-MVA – divorced; works part-time as a carpet layer
- Referred GP concerned about potential of addiction
- Pain `marginally controlled’ at present
- Meds for last year:
  - Morphine LA 60mg twice daily
  - Oxycodone 5mg x 2 IR mid-AM; mid-PM
  - Clonazepam 2mg at bedtime
  - Citalopram 20mg daily
- Smokes cannabis most nights for pain & sleep
Case #1-Is this patient addicted?

- ORT = 11-personal/family history abuse
- COMM= 8
- Weekend alcohol, smokes,
- PASS- 20- 5/5 for avoiding activity; taking meds when in pain; focus on pain.
- Roland Morris questionnaire – 22/25 positive responses
Case #2 - Are drugs causing cognitive impairment?

• 56 year old man lives with wife and runs a shoe store
• Referred to suggest meds that won’t impair his cognitive abilities
• Tends to `grin & bear’ all day- then take meds, smoke cannabis and drink wine at night
• Distressed about his pain and impact on life; ability to golf; role as husband and father
Case #2 - Are drugs causing cognitive impairment?

- MoCA= 23/30 – lost pts on attention; delayed recall; verbal fluency
- Medications
  - Hydromorphone 2mg -1-2 as required
  - Bupropion 300mg daily
  - Pregabalin 50mg – 1 AM; 2 @ bedtime
  - Pantoprazole 40mg daily
  - Oxazepam 15 or zopiclone 15mg at bedtime
  - Rosuvastatin 10mg daily
Case #3-My therapy doesn’t work anymore!

• 67 yr old retired woman living with her husband- chronic pain post-discsectomy
• Fentanyl patch worked for 4-5 years at incr doses – last 6 months decline pain control
• “Flares” of painful agitation of nerves – 2 ER visits for same in last few months
• ORT = 1 pt only for depression
Case #3-My therapy doesn’t work anymore!

- POQ- 10/10 – pain interfering with her ability to walk, do chores, climb stairs, affect self-esteem
- Roland Morris score-14/25
- Medications
  - Fentanyl 75 mcg/hr every 48hrs
  - Pregabalin 150mg three times a day
  - Esomeprazole 40mg at bedtime
  - Citalopram 20mg daily
  - Estrogen conjugated 0.3mg daily
  - Clonazepam 0.5mg daily as needed
  - Levo-thyroxine 100mcg daily
  - Hydrochlorothiazide 12.5mg daily
  - Trazodone 50mg at bedtime