Managing Common Pain Co-morbidities: Current Practice and Future Directions

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MDC has no conflict of interest related to the topic of this presentation
Chronic Pain Comorbidities

- Mood Disorders
- Anxiety Disorders
- PTSD
- Sleep Disorders
- Personality Disorders
- Secondary Medical Conditions
Pain, Mood and Anxiety Disorders
Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample

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\begin{itemize}
  \item National Comorbidity Survey to evaluate the association between chronic pain and common mood and anxiety disorders
  \item Participants (n= 5877) completed the Composite International Diagnostic Interview based on the DSM
\end{itemize}
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of participants meeting diagnostic criteria (% in parentheses)</th>
<th>Inferential statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chronic pain (n = 382)</td>
<td>General population (n = 5495)</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>83(21.7)</td>
<td>551(10.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>77(20.2)</td>
<td>510(9.3)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>20(5.2)</td>
<td>128(2.3)</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>134(35.1)</td>
<td>992(18.1)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>28(7.3)</td>
<td>144(2.6)</td>
</tr>
<tr>
<td>Panic disorder with or without agoraphobia</td>
<td>25(6.5)</td>
<td>103(1.9)</td>
</tr>
<tr>
<td>Simple phobia</td>
<td>60(15.7)</td>
<td>456(8.3)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>45(11.8)</td>
<td>428(7.8)</td>
</tr>
<tr>
<td>Agoraphobia with or without panic</td>
<td>32(8.4)</td>
<td>182(3.3)</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>41(10.7)</td>
<td>182(3.3)</td>
</tr>
</tbody>
</table>

Diagnoses were made using the Composite International Diagnostic Interview. Psychiatric diagnostic categories were not mutually exclusive.
Pain, SUD and Suicidal Ideation
There is robust literature that there is a high prevalence of SI in patients with pain ranging from 18% to > 50%


A systematic review by Tang and Crane revealed that the risk of successful suicide was doubled in patients with CP as compared to non-pain controls

Approximately 40% of patients seeking treatment for substance use disorders report a history of suicide attempts. Compared to the general population, those with alcohol use disorders are almost 10 times more likely to die by suicide and those who inject drugs are about 14 times more likely to commit suicide.

% of Population

Cheatle et al Clinical and genetic characteristics of opioid addiction in patients with chronic pain 1R01DA032776-01 NIH/NIDA
Pain and Sleep Disorders
Chronic pain is associated with multiple symptoms that may impair a patient's quality of life, including emotional distress, fatigue and sleep disturbance.

Studies have demonstrated that 50% of patients with a number of different chronic pain conditions complain of sleep disturbance, with estimates as high as 70%-88%.

% Population Sleep Disturbance (n= 1038)

Cheatle M et al “Clinical and Genetic Characteristics of Opioid Addiction in Chronic Pain” 1RO1DA032776-01 NIH/NIDA unpublished data
Untreated or Undertreated Insomnia

Patients with chronic pain and sleep disturbance report:

- Increased pain
- Excessive fatigue
- Poorer mood
- Higher rates of disability

Experimental Studies

Short term:
- Sleep deprivation or disruption increases pain & inflammation; dampen mood and pain inhibitory response

Long term:
- Development of depression, anxiety, widespread pain, diabetes, hypertension, CHD

Pain and sleep are bidirectional
**Pain and sleep are bidirectional**

Pain and Sleep: Mechanisms of Action

- Reduced pain tolerance
- Pro inflammatory process
- Increased anxiety/lower mood

Treatment Approaches

- Pharmacologic
- Psychosocial and CAM
Antidepressant medication

- The role of antidepressant medication may relate, in part, to the high prevalence of co-occurring depression in chronic pain
- There is evidence of the analgesic properties of tricyclics and certain SNRIs
- TCAs, SNRIs like opioids are used to modulate descending inhibitory pain pathways
Patients with fibromyalgia display less functional connectivity in the brain’s pain inhibitory network

Karin B Jensen¹², Rita Loitoile¹², Eva Kosek³⁴, Frank Petzke⁵, Serena Carville⁵, Peter Fransson³, Hanke Marcus⁷, Steven CR Williams⁸, Ernest Choy⁹, Yves Mainguy¹⁰, Olivier Vitton¹⁰, Richard H Gracely¹¹, Randy Gollub¹², Martin Ingvar³⁴ and Jian Kong¹²

- 28 matched FM pts compared to 14 healthy volunteers
- FM patients required significantly less pressure stimulus to reach a 50/100mm on a VAS
- Hypo-connectivity between the rostral anterior cingulate cortex and the amygdyla, hippocampus, and brainstem in healthy volunteers compared to FM patients
- Evidence that there is a dysfunction of the descending pain modulatory network
Fibromyalgia patients endogenous opioid activity may be elevated at baseline (i.e. already working at full levels and thus can’t increase with new pain stimuli)

- CSF of FM patients show higher enkephalins compared to controls
- High Baseline occupancy of opioid receptors in FM patients who have never received exogenous opioids
- Opioids usually ineffective in most patients with FM
- Naltrexone-blocking endogenous release of opioids

Unlike the opioid system the serotenergic/noradrenegric system is hypofunctional

- Decreased norepinephrine and serotonin metabolites in CSF
- Efficacy of compounds that raise serotonin and norepinephrine may be effective
  - Duloxetine, Venlafaxine, TCA, ?tramadol
  - Exercise and TENS units help potentiate this descending inhibition
## Antidepressant Selection and Dosing

<table>
<thead>
<tr>
<th>Priority</th>
<th>Drug</th>
<th>Class</th>
<th>Indications and Precautions</th>
<th>Initial Dose</th>
<th>Possible Increases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Venlafaxine (Effexor)</td>
<td>SNRI</td>
<td>Avoid if CV disease, ABN ECG, poorly-controlled HTN</td>
<td>75</td>
<td>150, 225</td>
</tr>
<tr>
<td>2</td>
<td>Fluoxetine (Prozac)</td>
<td>SSRI</td>
<td>SSRI of choice</td>
<td>20</td>
<td>30, 40</td>
</tr>
<tr>
<td>2</td>
<td>Sertraline (Zoloft)</td>
<td>SSRI</td>
<td>SSRI of choice in patients with CV disease</td>
<td>50</td>
<td>100, 150</td>
</tr>
<tr>
<td>3</td>
<td>Citalopram (Celexa)</td>
<td>SSRI</td>
<td>Use if failed with first SSRI</td>
<td>20</td>
<td>30, 40</td>
</tr>
<tr>
<td>4</td>
<td>Bupropion (Wellbutrin)</td>
<td>Other</td>
<td>Use if obese, have unacceptable weight gain with other agent, or if sexual AEs reported</td>
<td>200</td>
<td>300, 400</td>
</tr>
<tr>
<td>4</td>
<td>Mirtazapine (Remeron)</td>
<td>Other</td>
<td>Use if insomnia a problem; avoid if obese</td>
<td>15</td>
<td>30, 45</td>
</tr>
<tr>
<td>5</td>
<td>Desipramine</td>
<td>TCA</td>
<td>Avoid with CV disease, advanced age, ABN ECG, poorly-controlled HTN</td>
<td>25</td>
<td>50, 100</td>
</tr>
</tbody>
</table>

Kroenke K et al JAMA 2009; 301 (20): 2099-110
## How modest is the effect?

<table>
<thead>
<tr>
<th>Drug</th>
<th>RCT / participants</th>
<th>30% pain reduction (drug vs placebo, %)</th>
<th>Drop out rate due to adverse events, (drug vs placebo, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>duloxetine</td>
<td>5 / 1,884</td>
<td>46.8 vs 34.0</td>
<td>18.7 vs 10.4</td>
</tr>
<tr>
<td>milnacipran</td>
<td>5 / 4,110</td>
<td>36.4 vs 28.1</td>
<td>21.5 vs 11.0</td>
</tr>
<tr>
<td>SSRIs</td>
<td>7 / 414</td>
<td>36.4 vs 20.6</td>
<td>9.5 vs 7.0</td>
</tr>
<tr>
<td>TCAs</td>
<td>9 / 542</td>
<td>48.3 vs 27.8</td>
<td>5.2 vs 6.5</td>
</tr>
<tr>
<td>pregabalin</td>
<td>5 / 3,259</td>
<td>40.0 vs 29.1</td>
<td>19.4 vs 11.0</td>
</tr>
</tbody>
</table>
Pharmacogenetics of antidepressant response: A polygenic approach

Judit García-González a, Katherine E. Tansey b, Joanna Hauser c, Neven Henigsberg d, Wolfgang Maier e, Ole Mors f,g, Anna Placentino h, Marcella Retschel i, Daniel Souery j, Tina Zagar k, Piotr M. Czerski l, Borut Jerman k,m, Henriette N. Buttenschøn n, Thomas G. Schulze o, Astrid Zobel e, Anne Farmer a, Katherine J. Aitchison p, Ian Craig a, Peter McGuffin a, Michel Giupponi q, Nader Perroud r, Guido Bondolfi s, David Evans t, Michael O’Donovan u, Tim J. Peters v, Jens R. Wendland w, Glyn Lewis x, Shitij Kapur a, Roy Perlis y, Volker Arolt z, Katharina Domschke aa, Major Depressive Disorder Working Group of the Psychiatric Genomic Consortium b, Gerome Breen a, Charles Curtis a, Lee Sang-Hyuk a, Carol Kan a, Stephen Newhouse a, Hamel Patel a, Bernhard T. Baune ab, Rudolf Uher ac, Cathryn M. Lewis a,k,2, Chiara Fabbri a,ad,2

Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants

JK Hicks1, JJ Swen2, CF Thorn3, K Sangkuhl3, ED Kharasch4, VL Ellingrod5,6, TC Skaar7, DJ Müller8, A Gaedigk9 and JC Stingl10

The right drug for you

Personalized prescribing is gaining momentum, but is there enough evidence for it to become standard clinical practice?

Pharmacologic Approaches to Sleep Disorders

- Benzodiazepine and Receptor Agonists (BzRAS)
- Non-benzodiazepine receptor agonists
- Melatonin receptor agonists
- Sedative antidepressants
- Atypical antipsychotic medications,
- Antiepileptic Drugs
Benzodiazepine and Receptor Agonists (BzRAS)

- BzRAS include benzodiazepines (example Temazepam, Triazolam) and a newer class of non-benzodiazepine drugs (for example, Zolpidem).

- This class of drugs binds to GABA-A receptors and induces sedative/hypnotic, amnestic, anxiolytic and anticonvulsant effects.

- Many short term clinical trials show that BzRAS improve sleep quality, sleep latency, wakefulness after sleep onset and total sleep time.

- Most benzodiazepines (excluding Triazolam) have intermediate to long half-life, helping patients fall asleep and stay asleep longer.
Benzodiazepines may work well in short-term efficacy trials, but there is a paucity of data on long-term use and there are many documented adverse effects:

- Cognitive impairment
- Decreased attention
- Anterograde amnesia
- Depressive symptomatology with cognitive and psychomotor slowing
- Abruptly discontinuing benzodiazepines may lead to rebound insomnia, seizure activity

Given these multiple safety concerns, benzodiazepines have fallen out of favor as a class of drugs for use in sleep disorders.
Non-Benzodiazepine Receptor Agonists (NBzRAS)

- Non-benzodiazepine receptor agonists include Ambien (Zolpidem), Sonata (Zalepon), and Lunesta (eszopiclone) are the newest class of FDA approved hypnotics used for insomnia.

- These class of drugs improve sleep latency and have potential for fewer daytime side effects, given their short half-life and receptor binding profile.
Antidepressants
Antidepressants

- Sedative antidepressants, such as tricyclic antidepressants mirtazapine and Trazodone, are useful in treating chronic pain patients with insomnia.

- These classes of drugs help to relieve:
  1. Insomnia
  2. Any associated depression that negatively influences pain perception
  3. The pain condition itself

- Tricyclic antidepressants have pro-serotonergic, noradrenergic, dopaminergic and sodium channel blocking effects that may account for their efficacy in pain and depression, along with anticholinergic and antihistaminic effects that lead to sedation.
Gabapentin and pregabalin often used to treat chronic pain conditions with comorbid insomnia.

In multiple studies of patients with neuropathic pain and fibromyalgia, self-reported sleep outcomes suggest positive effects on sleep latency and wakefulness after sleep onset, as well as increased deep sleep.

Both have adjunctive effects on depression and anxiety.

Pregabalin showed increased efficacy in promoting sleep in patients with diabetic neuropathy, compared to amitriptyline in a recent study.

Adverse effects include dizziness, next day sedation, GI symptoms and peripheral edema.
Psychosocial and CAM Interventions

- Acupuncture
- Neurofeedback & Biofeedback
- CBT
- Physical Therapy
- Massage
- 12-step programs
- Herbs
- Manipulation
- Mindfulness
- Yoga
CBT
Cognitive Behavioral Therapy

- CBT focuses on maladaptive thought patterns (catastrophizing) and behaviors (kinesiophobia) that occur frequently in patients with CNCP.

- The objective of CBT is to guide the patient in recognizing and reconceptualizing his/her personal view of pain, identifying their role in the process of healing and promoting the patient being proactive rather than passive, and competent rather than incompetent.

- CBT include specific skill acquisition (relaxation therapy, stress management, cognitive restructuring) followed by skill consolidation and rehearsal, and relapse training (Turk, Flor, 2006).
CBT cont’d

◆ CBT has been found to be efficacious for a number of chronic pain disorders including:

  ▪ Arthritis (Keefe & Caldwell, 1997)
  ▪ Sickle Cell disease (Chen et al, 2004)
  ▪ Chronic low back pain (Lamb et al, 2010; Glombiewski et al, 2010)
  ▪ TMJ (Turner et al, 2006)
  ▪ Lupus (Greco et al, 2004)
  ▪ Pain in breast cancer patients (Tatrow et al, 2006)
Cheatle et al Clinical and genetic characteristics of opioid addiction in patients with chronic pain
1R01DA032776-01 NIH/NIDA
16 high catastrophizing patients with fibromyalgia were randomized into a group that received a 4 week course of CBT or a control group that received only fibromyalgia education material.

Resting state fMRI evaluated functional connectivity between key pain processing brain regions at baseline and post-treatment.

Results revealed that catastrophizing correlated with increased resting state functional connectivity between S1 and anterior insula.

The CBT group demonstrated a larger reduction in both pain and catastrophizing as compared to the control group at the 6-month follow-up and reduced resting state connectivity between S1 and anterior/medial insula at post-treatment and these changes were associated with concurrent treatment-related reduction in catastrophizing.

The authors concluded that CBT via reducing catastrophizing helps normalize pain-related brain responses.
CBT-I has been demonstrated to be equally effective or even superior to pharmacotherapy in patients with chronic primary insomnia.
CBT-I cont’d

♦ CBT-I consists of:
  • Psychoeducation about sleep and insomnia
  • Stimulus control
  • Sleep restriction
  • Sleep hygiene
  • Relaxation training
  • Cognitive restructuring
This was a parallel-group, randomized, single blind trial of CBT-I with a contact/measurement control condition.

Twenty-eight subjects with chronic neck and back pain were randomized into the 2 groups.

Results revealed that patients who received CBT-I had significantly improved sleep and these patients maintained a statistically and clinically improved total sleep time even 6 months after treatment ended, despite the persistence of moderate to severe pain.
An RCT design comparing a Hybrid CBT P-I to a monitoring control group

Compared to symptom monitoring, the hybrid intervention was associated with greater improvement in sleep at post-treatment. Although pain intensity did not change, the Hybrid group reported greater reductions in pain interference, fatigue and depression than the Monitoring Group. Changes associated with the hybrid intervention were clinically significant and durable at 1- and 6-month follow-ups.
Access Issues
Interventions

- **Office-based interventions**
  - Training non-BH staff on CBT etc
  - Antidepressant therapy/pain self-management program
    Kroenke et al 2009

- **E-health**
  - Computer-assisted CBT
  - Telemedicine
  - Smartphone Apps
Multimodal Approach

- CBT/ACT
- Functional Restoration
- Social Support
- Pharmacotherapy
- CAM

PAIN

Interventions
Future Directions

- Develop and test novel delivery systems for CBT/CAM and other non-pharmacologic interventions
- Healthcare economics research to support improved access to interdisciplinary pain care, behavioral health and SUD treatment
- Pharmacogenomics research supporting decision making for non-opioid pharmacotherapeutics (precision medicine)
- Research on biological substrates of non-pharmacologic interventions
- Investigate phenotypic and genotypic characteristics of suicidal ideation and behavior in patients with pain and SUD
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