Chronic Pain Patients Who Fail Standard Treatment: Identification and Strategies

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Disclosures

- Editor: Practical Pain Management
- Speaker: Regenesis Biomedical
Learning Objectives

- Define standard chronic pain treatment
- Identify which patients may have metabolic and genetic defects that require high dose opioids
- Explain how to implement treatment strategies for patients who fail standard treatment


Failure or minimal results from standard treatment is now the major unmet need in pain management
What Is Standard Pain Treatment?

- A regimen of nonpharmacologic measures (physical therapy, electromagnetic, psychotherapy) and pharmacologic therapies to include anti-inflammatories, antidepressants, neuropathic (“antiseizure”), topical analgesics, corticosteroid injections, and a daily opioid dosage below 80 to 100 mg of morphine equivalence.

World Health Organization

3 Step Analgesic Ladder

1982-1986

Figure 1: World Health Organization Analgesic Step Ladder—Derived from a consensus guideline published in 1982, the three-step approach to analgesic therapy for cancer pain was published in its final form in 1986.
Definition of Pain Treatment Failure

- A regimen of nonopioid measures and a daily oral opioid dosage of 80 to 100 mg of morphine equivalence that doesn’t keep the patient mentally and physically functional enough to carry on activities of daily living

Approximately 90 mg of Morphine Equivalence a Day: CDC Guidelines

<table>
<thead>
<tr>
<th>No.</th>
<th>Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-9</td>
<td>Morphine 10 mg</td>
</tr>
<tr>
<td>8-9</td>
<td>Hydrocodone/APAP 10/325 mg</td>
</tr>
<tr>
<td>8-9</td>
<td>Methadone 10 mg</td>
</tr>
<tr>
<td>3-4</td>
<td>Hydromorphone 4 mg</td>
</tr>
<tr>
<td>5-6</td>
<td>Oxycodone/APAP 10/325 mg</td>
</tr>
</tbody>
</table>
Approximate Fentanyl Patch Morphine Equivalence

<table>
<thead>
<tr>
<th>Morphine (PO)</th>
<th>Transdermal Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-134 mg/d</td>
<td>25 mcg/h</td>
</tr>
<tr>
<td>135-224 mg/d</td>
<td>50 mcg/h</td>
</tr>
<tr>
<td>225-314 mg/d</td>
<td>75 mcg/h</td>
</tr>
<tr>
<td>315-404 mg/d</td>
<td>100 mcg/h</td>
</tr>
</tbody>
</table>

Recognition of the Failing Patient

- Constant complaints of poor pain relief
- Runs out of medication
- Emergency room visits
- Doctor shopping
- Bed- or housebound
- Angry/hostile
- Uncontrolled drug use
- Seen multiple physicians
- Tried multiple therapies
Pejorative Labels for Treatment-Failure Patients

- Drug seeker
- Addict
- Noncompliant
- Unmotivated
- Difficult
- Uncooperative
- Catastrophizer
- Opioid use disorder

Profile of the Most Common Drug Seeking Addict

- Male
- Single
- Under age 30
- No family; unaccompanied
- Cigarette smoker
- Marijuana user
- Unemployed
- Complaints of spine, hip, or neck pain
- Mobile—travels a great distance for drugs
### Consecutive Treatment Failures N=101
#### Los Angeles: 2012-2015

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>62 (61.4%)</td>
</tr>
<tr>
<td>Males</td>
<td>39 (38.6%)</td>
</tr>
<tr>
<td>Centralized constant pain</td>
<td>100 (100%)</td>
</tr>
<tr>
<td> With insomnia, fatigue, and excess sympathetic discharge</td>
<td></td>
</tr>
<tr>
<td>No. with cyp450 defects</td>
<td>91 (90.1%)</td>
</tr>
<tr>
<td>No. with ineffective response to oral opioids—malabsorption</td>
<td>20 (19.8%)</td>
</tr>
</tbody>
</table>

### Los Angeles
#### 40 Consecutive Treatment Failures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total physicians consulted</td>
<td>461</td>
</tr>
<tr>
<td>Total pain specialists consulted</td>
<td>172</td>
</tr>
<tr>
<td>Total psychologists/psychiatrists consulted</td>
<td>104</td>
</tr>
<tr>
<td>Total universities consulted</td>
<td>23</td>
</tr>
</tbody>
</table>
Etiologies of Patients Who Require Over 100 Mg Morphine

N=154

- Arachnoiditis
- RSD/CRPS/neuropathies
- Genetic connective tissue disease
- Peritoneal adhesions with neuropathies
- Postviral syndromes
- Lyme neuropathies/arthropathies
- Autoimmune disorder
- Traumatic brain injury

46 Y/O Male Postlumbar Fusion With Constant Disabling Pain and Partially Paralyzed Left Leg Nerve Roots Displaced and Clumped
Ehlers-Danlos Chiari Malformation Arachnoiditis

Marfan’s and autoimmune characteristics
Major Causes of Treatment Failure

- Inability to use oral opioids/gastrointestinal malabsorption
- Multiple genetic defects
  - CYP 450 enzymes
  - Receptor binding
- Severe, centralized pain
  - Neuroinflammation
  - Hormone deficiencies

Causes of Gastrointestinal Malabsorption

- Multiple abdominal-pelvic surgeries
- Multiple CYP450 defects
- Traumatic brain injury
- Cervical neck degeneration
- Autoimmune disorders
## Commercially Available Nonoral Opioids

<table>
<thead>
<tr>
<th>Transdermal patch</th>
<th>Transmucosal</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Fentanyl</td>
<td>▪ Fentanyl</td>
</tr>
<tr>
<td>▪ Buprenorphine</td>
<td>▪ Buprenorphine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injections</th>
<th>Suppository</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Hydromorphone</td>
<td>▪ Opium</td>
</tr>
<tr>
<td>▪ Meperidine</td>
<td>▪ Hydromorphone</td>
</tr>
<tr>
<td>▪ Morphine</td>
<td></td>
</tr>
</tbody>
</table>

## Pharmacogenetic Testing CYP450 Enzymatic Defects N=101

**2D6 – 2C9 – 2C19**

(Genelex®, Seattle)

Normal = extensive

Defective = rapid, poor, intermediate
### CYP450 Defects in 101 Severe Chronic Pain Patients

<table>
<thead>
<tr>
<th>Total number of defects</th>
<th>132</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with 1 or more defects</td>
<td>91 (90.1%)</td>
</tr>
<tr>
<td>No. with 2 defects</td>
<td>28 (27.7%)</td>
</tr>
<tr>
<td>No. with 3 defects</td>
<td>8 (7.9%)</td>
</tr>
<tr>
<td>No. of 2C19 defects</td>
<td>52 (51.5%)</td>
</tr>
<tr>
<td>No. of 2D6 defects</td>
<td>43 (42.6%)</td>
</tr>
<tr>
<td>No. of 2C9 defects</td>
<td>37 (36.6%)</td>
</tr>
</tbody>
</table>

### Opioid Mu Receptor 1 (OPRM 1)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Opioid Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Less opioid dosage</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal opioid dosage</td>
</tr>
<tr>
<td>Low</td>
<td>High opioid dosage</td>
</tr>
</tbody>
</table>
Strategy With CYP450 Defects Use Opioids That Bypass the CYP450 System

- Morphine
- Hydromorphone
- Tapentadol
- Levorphanol
Alternate Strategy

Use the One Opioid That Only Uses the CYP450 – 3A4 Enzyme

FENTANYL

- Available as transdermal and transmucosal formulations to avoid oral administration
- Genetic defects in 3A4 are rare

The 4 “Legs” Must be Simultaneously Administered to Be Optimally Effective
The Missing Link

Control and suppression of neuroinflammation

May not totally disappear

#1—Neuroinflammation Control

- Determine severity
  - Symptoms of ↑ temp
  - Serum inflammatory markers
    - CRP-HS
    - ESR
    - Interleukins
  - Challenge with ketorolac/corticoid
  - MRI—nerve root clumping/adhesions
Definitions

- CYTOKINE: Generic term for nonantibody proteins released by a cell on contact with a specific antigen
- CHEMOKINE: Family of low molecular weight cytokines that promote chemotaxis in leukocytes
- INTERLEUKIN: A generic term for a group of multifunctional cytokines involved in the early phase of the inflammatory process. At least 18 in number

#2—“The Missing Link” Neuroinflammation Control

- Ketorolac
- Corticoids: dexamethasone or methylprednisolone

NOTE: Peripheral acting anti-inflammatories have little benefit
#3—Option: Microglial Suppressors

1. Acetazolamide
2. Minocycline
3. Pentoxifylline
4. Metformin
5. Low Dose Naltrexone

OPTION: ADD 1 AT LOW STARTING DOSE

#4—Neuroinflammation Protocol

- Dietary supplements
  1. L-Carnitine, 1000-2000 mg/dl
  2. Omega fatty acids, 2000-4000 mg/dl
  3. Curcumin/turmeric
  4. Serrapeptase

ALSO: HIGH PROTEIN ANTI-INFLAMMATORY DIET
#5—Option: Replacement of Serum Deficient Hormones

1. DHEA
2. Estradiol
3. Pregnenolone
4. Progesterone
5. Testosterone

Neurogenesis

- B-12
- High protein diet
- Physical and breathing exercise (02)
- Hormone replacement
- Human chorionic gonadotropin
- Oxytocin
- Pentoxyfylline/vitamin E
Spinal Cord Exercises

- Increase spinal fluid flow
- Prevent adhesions and contractures

Symptomatic Pain Control Pharmacologic Categories

- Neuropathic agents
- Opioids
- Adrenergic (catecholaminergic) Agents
- NMDA antagonists (ketamine or other)
- GABA agents/precursors (gabapentin)
- Sleep aid
- Topical analgesics
Summary

- There is a subgroup of chronic pain patients who fail standard treatment
- Opioid daily dosages below 80-100 mg of morphine equivalence is the new “standard”
- Major causes for failure
  - Centralized, severe pain
  - Opioid malabsorption
  - Genetic defects
  - Failure to control neuroinflammation

References