Challenges in the Development of Pain Therapies – A Patient’s Perspective

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Many Treatments

But ... what works for whom? At what risk? At what cost?

"Unfortunately, the field of chronic pain treatment is strikingly deficient in high-quality scientific evidence."

Former FDA Commissioner Dr. Robert Califf
NEJM 2016;374:1480-5
Susan: A “Success” Story

History:

- Some Gene x Environment Risk
- Trigger – accident, surgeries
- 1 year later - neck/back pain started, but manageable with self-care, PT & chiropractic care
- 2 years later, cascade of chronic pain conditions began
... 4 years ....

hydrocodone

gabapentin
nortriptyline
cyclobenzaprine
duloxetine
milnacipran
propranolol
pregabalin
tizanidine

self-care
ice/heat
injections
physical therapy
chiropractor
TENS
yoga
massage
Susan Today – 20 years later

- Occipital Neuralgia
- Chronic Migraine
- Temporomandibular Disorder
- Myofascial pain syndrome
- Chronic pelvic pain
- Chronic back pain
- Endometriosis
- Pelvic Congestion Syndrome
- Inflammatory Bowel Disease
- Painful Bladder Syndrome
- Premenstrual Disorder
- Depression
- Chronic Fatigue

still has moderate, sometimes severe, daily pain
↓ works part-time, stopped volunteer activities
cannot exercise w/o flare, but can tolerate “activity in moderation”

significant impact on mood, sleep, cognition, energy & social function

Success?
Biomarker Types & Potential Uses in Chronic Pain

**FDA “BEST”: Biomarkers, Endpoints and other Tools**

- **Susceptibility Risk**: Potential for developing condition
- **Diagnostic**: Disease detection & subtype identification
- **Monitoring**: Disease status over time or exposure to environ agent
- **Prognostic**: Identify disease recurrence or progression
- **Predictive**: Identify treatment responders-nonresponders
- **Pharmacodynamic Response**: Shows a biological response to treatment
- **Safety**: Identifies toxicity after treatment
An Example ... Pharmacogenetic Testing
**Pharmacogenetic Testing**

### ANTIDEPRESSANTS

<table>
<thead>
<tr>
<th>USE AS DIRECTED</th>
<th>MODERATE GENE-DRUG INTERACTION</th>
<th>SIGNIFICANT GENE-DRUG INTERACTION</th>
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<tbody>
<tr>
<td>desvenlafaxine (Pristiq®)</td>
<td>sertraline (Zoloft®)</td>
<td>citalopram (Celexa®)</td>
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<tr>
<td>levomilnacipran (Fetzima®)</td>
<td>vilazodone (Viibryd®)</td>
<td>escitalopram (Lexapro®)</td>
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<td>selegiline (Emsam®)</td>
<td>bupropion (Wellbutrin®)</td>
<td>fluoxetine (Prozac®)</td>
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<td></td>
<td>mirtazapine (Remeron®)</td>
<td>venlafaxine (Effexor®)</td>
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<td></td>
<td>trazodone (Desyrel®)</td>
<td>amitriptyline (Elavil®)</td>
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<td></td>
<td>duloxetine (Cymbalta®)</td>
<td>clomipramine (Anafranil®)</td>
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<tr>
<td></td>
<td>fluvoxamine (Luvox®)</td>
<td>desipramine (Norpramin®)</td>
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### CLINICAL CONSIDERATIONS

1. Serum level may be too high, lower doses may be required.
2. Difficult to predict dose adjustments due to conflicting variations in metabolism.
3. Use of this drug may increase risk of side effects.
4. Serum level may be too low in smokers.
5. FDA label identifies a potential gene-drug interaction for this medication.
When science advances and produces clinically useful tools, why aren’t they being used?

“\textit{It takes 17 years to turn 14 per cent of original research to the benefit of patient care}” *

Plans for Implementation Need to Start Now & Include All Necessary Stakeholders

Policy Makers
Government Agencies
Patients
Scientists
Payers
Health Systems
Clinicians
Funders
Industry
“The most common chronic condition experienced by adults is multimorbidity, the coexistence of multiple chronic diseases or conditions.”

Tinetti et al. JAMA, 2012
HHS Multiple Chronic Conditions Initiative
Multimorbidity

- Approximately 1 in 4 Americans has MCC, including 1 in 15 children
- In those >65 years, 3 in 4 have MCC
- Increased risk for mortality and poorer functioning
- 66% of the total health care spending associated with MCC
Pain Comorbidity
Notable Findings Related to Comorbidity

As # of pain diagnoses (or body sites of pain) increase:

- Worsening of localized and systemic symptoms
- Decreased treatment efficacy
- Reduced health & psychosocial outcomes
- Increased disability
- Markedly diminished QOL
- Increased costs (personal, societal)

- But, most RCTs enroll patients with more than 1 pain condition, but only track the index condition
- Existence of multiple disorders ↓ likelihood of effect?
- Could “flares” in non-index pain condition(s) create a “false negative” outcomes?
- Sleep, mood & other factors have known deleterious effect on pain severity. These are often not tracked – or tracked but not analyzed
- Do other comorbid chronic diseases impact outcomes?

Comorbidity | Clinical Trials

EFFECTS OF POLYPHARMACY?

EFFECTS OF COMBINATION DRUG & NON-DRUG TREATMENTS?
The classification of most chronic pain disorders gives emphasis to anatomical location of the pain to distinguish the disorder from another, or to define subtypes. However, anatomical criteria overlook etiology, potentially hampering treatment decisions.


EPPIC-Net will incorporate innovative designs to accelerate therapy development in well-phenotyped subpopulations of patients with well-characterized pain conditions.
COPCs Cluster Analysis

Orofacial Pain Prospective Evaluation & Risk Assessment (OPPERA) Study

- Prominent NIH-funded longitudinal TMD study. Comorbidity assessed as important disease modifier.
- Cluster analysis of 1031 chronic TMD cases & 3,247 TMD-free controls

Cluster 1
Adaptive

- “Normal” psychosocial & autonomic profiles
- Greater muscle pain sensitivity
- Male ≠ Female
- Chronic TMD cases ≠ non-cases
- Chronic TMD cases moderately symptomatic
- Few COPCs

Cluster 2
Pain Sensitive

Cluster 3
Global Symptoms

- “Normal” psychosocial & autonomic profiles
- Normal muscle sensitivity
- Males > Females
- Few chronic TMD cases
- Chronic TMD cases moderately symptomatic
- Few COPCs
- Few negative life events

- “Abnormal” psychosocial, sensory function and autonomic profiles
- Male < Female
- Older
- Many chronic TMD cases
- Chronic TMD cases very symptomatic
- Many COPCs
- Many negative life events

COPCs Co-Prevalence Rates & Major Findings

Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP)

- Prominent longitudinal NIH-led, IC/PBS study. Comorbidity assessed as important disease modifier.
- Of 424 participants, 38% reported at least 1 comorbid pain syndrome (44% female vs. 31% male)
- Co-prevalence rates:

  - ME/CFS (8%)
  - FM (9%)
  - IBS (57%)
  - >1 Diagnosis 25%

- Two constructs associated with comorbidity:

  **Generalized Sensory Sensitivity (GSS)**
  - Increased sensitivity to *external* stimuli across multiple sensory modalities
  - Increased sensitivity to *internal* symptoms/sensations (somatic awareness)
  - Hyperalgesia/allodynia in multiple body regions

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<tr>
<th>S.P.A.C.E.</th>
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<tbody>
<tr>
<td>S Sleep disturbance</td>
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<tr>
<td>P Pain (widespread)</td>
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<td>A Affect (negative)</td>
</tr>
<tr>
<td>C Cognitive dysfunction</td>
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<td>E Energy depletion/fatigue</td>
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