



Challenge of Developing New Pain Medicines - Developing Novel Analgesics and Abuse-Deterrent Opioid Formulations

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The Problems

- Few existing classes of analgesics, lots of adverse effects
- Many failed development programs
 - Nonclinical models poorly predictive of clinical success
 - Clinical trials unpredictable
 - “A number of pharmacologic treatments examined in recent randomized clinical trials (RCTs) have failed to show statistically significant superiority to placebo in conditions in which their efficacy had previously been demonstrated.”*

The Possible Fixes

- Better study designs
- Abuse-deterrent opioids
 - Guidance for Industry
 - Approved products
 - Future products
- New drug classes

Existing Analgesics

- Opioids
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
- Anticonvulsants
- Antidepressants
- Local Anesthetics
- Other
 - Capsaicin, Ziconotide

Opioids

- 16 drug substances
- Indications
 - Acute pain, pain
 - Mild to moderate pain
 - Moderate to severe pain
 - Pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Opioids – Boxed Warning

- Addiction, abuse and misuse
- Life-threatening respiratory depression
- Accidental ingestion
- Neonatal opioid withdrawal syndrome
- Drug interactions
- Dosing errors (oral solutions)

Opioids –Warnings

- Interactions with Central Nervous System Depressants
- Use in Elderly, Cachectic, and Debilitated Patients
- Use in Patients with Chronic Pulmonary Disease
- Hypotensive Effects
- Use in Patients with Head Injury or Increased Intracranial Pressure
- Use in Patients with Gastrointestinal Conditions
- Use in Patients with Convulsive or Seizure Disorders
- Avoidance of Withdrawal
- Driving and Operating Machinery

NSAIDs

- 18 drug substances
- Indications
 - Rheumatoid arthritis and osteoarthritis: 14, +/- ankylosing spondylitis, gout, tendinitis, bursitis
 - Pain: naproxen, ketoprofen
 - Acute pain: celecoxib
 - Mild to moderate pain: ibuprofen, diclofenac, diflunisal, fenoprofen, mefanamic acid
 - Moderate to severe pain: ketorolac, diclofenac

NSAIDs - Boxed Warning

- **Cardiovascular risk**
 - serious cardiovascular thrombotic events, myocardial infarction and stroke
 - may increase with duration of use
- **Gastrointestinal (GI) risk**
 - serious GI adverse events - bleeding, ulceration, perforation which can be fatal
 - occur at any time, without warning symptoms
 - elderly patients are at greater risk

NSAIDs- Warnings

- Hepatic Effects
- Hypertension
- Congestive Heart Failure and Edema
- Renal Effects
- Anaphylactoid Reactions
- Anemia, platelet inhibition
- Adverse Skin Reactions: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis
- Premature Closure of Ductus Arteriosus
- Bronchospasm in aspirin-sensitive asthma

Anticonvulsants- Indications

- Pregabalin
 - Neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia (PHN), fibromyalgia, neuropathic pain associated with spinal cord injury
- Gabapentin
 - PHN
- Carbamazepine
 - Trigeminal Neuralgia

Anticonvulsants - Warnings

- Pregabalin
 - Angioedema, Hypersensitivity, Suicidal Behavior and Ideation, Dizziness and Somnolence, Weight Gain, Tumorigenic Potential, Ophthalmological Effects, Decreased Platelet Count, PR Interval Prolongation
- Gabapentin
 - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity, Anaphylaxis and Angioedema, Effects on Driving and Operating Heavy Machinery, Somnolence/Dizziness
- Carbamazepine
 - Serious Skin Reactions, Hypersensitivity, Aplastic Anemia, DRESS, Suicidal Behavior and Ideation

Antidepressants - Indications

- Duloxetine
 - Diabetic Peripheral Neuropathic Pain
 - Fibromyalgia
 - Chronic Musculoskeletal Pain
- Milnacipran*
 - Fibromyalgia

*Not approved as an antidepressant in the US

Antidepressants - Warnings

- **Duloxetine**
 - Suicidal Thoughts and Behaviors, Hepatotoxicity - hepatic failure, Orthostatic Hypotension, Falls and Syncope, Serotonin Syndrome, Abnormal Bleeding, Severe Skin Reactions, Angle-Closure Glaucoma, Seizures, Hypertension, Hyponatremia, Glucose Control in Diabetes, Urinary Hesitation and Retention
- **Milnacipran**
 - Suicidality, Serotonin Syndrome, Elevated blood pressure and heart rate, Seizures, Hepatotoxicity, Abnormal Bleeding, Worsened Dysuria, Angle Closure Glaucoma

Others - Indications

- Lidocaine topical patch
 - PHN
- Capsaicin
 - PHN
- Ziconotide
 - severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or intrathecal morphine

Others

- Lidocaine topical patch
 - Accidental pediatric exposure, allergy/anaphylaxis, lidocaine toxicity
- Capsaicin
 - Eye and mucous membrane irritation, pulmonary irritation, application site pain and increased blood pressure
- Ziconotide
 - Cognitive and neuropsychiatric adverse reactions (confusion, memory impairment, hallucinations), meningitis, CNS depression, elevated creatinine kinase

Failed Programs –Nonclinical

- Limitations with nonclinical models
 - Nonclinical models result in false positives
 - Most measures are reflexive, not measures of spontaneous pain
 - Models are pharmacodynamic models not disease models
 - Mechanisms and metabolism may be different in animals vs. man

Failed Programs - Clinical

- Failure to demonstrate efficacy in early clinical development phases
- For every 100 candidate small molecules identified, 50 make it to phase 1 studies, 30 to phase 2, just 2 get past phase 2*
 - Limited by off-target effects
 - Inadequate bioavailability
 - Inappropriate patient population for mechanism

Failed Programs – Clinical, 2

- Clinical trial design challenges
 - Pain is subjective, patient reported
 - No objective endpoint
- Limits on how long patients can remain in pain, need for rescue medication
 - May lessen effect size, confound adverse events
- Need to choose a pain population able to respond (target)

Failed Programs – Clinical, 3

- Many sources of variability, can make treatment effect difficult to measure
- Can be difficult to blind the studies when study drug has particular adverse events

Possible Fixes

- Improved clinical and nonclinical study design
 - Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)
 - Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTION) Initiative

IMPACT

- Mission: develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain
- 18 consensus meetings on clinical trials of treatments for acute and chronic pain in adults and children
- Participants from academia, regulatory agencies (FDA, European Medicines Agency), NIH, VA, consumer support and advocacy groups, and industry
- Publications – 15 consensus recommendations, 2 systematic reviews, 4 research articles

ACTTION

- Public-private partnership (academia, industry, government)
- Goal: address major gaps in scientific information which can slow down analgesic clinical trials and analgesic drug development, streamline the discovery and development process for new analgesic drug products for the benefit of the public health. Optimizing clinical trial methods to increase assay sensitivity and study efficiency
- 45 publications
- June 23 and 24, 2014 Third ACTTION Scientific Workshop: Transformative Strategies-Development of Pain Therapies

Possible Fixes

- Abuse-Deterrent Opioids Analgesics
 - Guidance for Industry, Abuse-Deterrent Opioids —Evaluation and Labeling, Promised as part of ONDCP Rx Drug Abuse Plan (2011)
 - Mandated under FDASIA
 - Draft 2013, final 2015

Abuse-Deterrent Opioid Analgesics

- Potentially abuse-deterrent properties can be expected to result in a significant reduction in that product's abuse potential
 - Labeling must be based on scientific data
 - Labeling based on pre-market studies must be evaluated using post-market data
- The product must deliver the opioid analgesic for pain patients
 - Potential for addiction
 - Abuse deterrent, NOT abuse proof

Guidance on Development of Abuse-Deterrent Formulations

- Types of Abuse-Deterrent Formulations
- Pre-Market Assessment of Abuse-Deterrent Features
 - Manufacturing: e.g., crushing, extraction
 - Pharmacokinetics (PK)
 - Clinical Abuse Potential Studies
 - Statistical analysis
- Post-Market Assessment of Impact on Abuse
- Labeling for Abuse-Deterrent Formulations
 - Physical/chemical Barriers to Abuse
 - PK Data
 - Demonstration of Reduced Abuse Potential
 - Demonstration of Reduced Abuse (Postmarket)
- Areas of Additional Research Needs

Types of AD Technologies

- Physical/Chemical
 - limit drug release following mechanical manipulation (crush, grind) into small particles or limit preparation of a small volume solution
- Agonist/antagonist combinations
 - reduce or defeat the euphoria associated with abuse
- Aversion
 - Chemicals produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed.

Types of AD Technologies, cont'd

- Delivery System
 - include depot injectable formulations and implants
- New molecular entities and prodrugs
 - enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid.
- Combination - two or more of the above methods could be combined to deter abuse
- Novel approaches

Approved AD Opioid Analgesics

- Five products with abuse-deterrent labeling
 - OxyContin (oxycodone, crush/extraction resistant)
 - Embeda (morphine/naltrexone, naltrexone is an antagonist, blocks euphoria)
 - Targiniq (oxycodone hydrochloride and naloxone, naloxone antagonist)
 - Hysingla (hydrocodone, crush/extraction resistant)
 - Morphabond (morphine, crush/extraction resistant)
- >30 active INDs being discussed with CDER
 - New technologies being explored

Novel AD Opioid Analgesics Approaches

- pH dependent – requires acidic environment of stomach to release opioid, inactivates at higher pH
- Enzyme dependent- requires enzymatic cleavage to release opioid
- Pegylated prodrugs

Areas of Additional Research Needs

- Characterization of the quantitative link between:
 - Changes in the pharmacokinetics of opioids in different formulations,
 - Results of clinical studies using those same formulations, and
 - Differences in abuse in the community
- Characterization of the best methods to analyze clinical data on abuse
- Characterization of the best methods to analyze the impact of formulations on rates of abuse in the community

Novel Analgesic Compounds

- Anti-nerve growth factor antibodies
- Sodium channel blockers
 - Nav1.7, Nav1.8, Nav1.5
- Voltage-dependent calcium channel blockers
- Transient receptor potential vanilloid 1 (TRPV1) receptor antagonists, TRPV3
- N-methyl-D-aspartate (NMDA) antagonists, partial agonists

Novel Analgesic Compounds, 2

- Fatty acid amide hydrolase (FAAH) inhibitors
- Nitric oxide synthase (NOS) inhibitors
- Cannabinoids
- Kappa opioid agonists, central and peripheral
- Delta opioid agonists

Novel Analgesic Compounds, 3

- New targets along the inflammatory cascade
 - selective reversible inhibitor of microsomal prostaglandin synthase 1 (mPGES-1) enzyme and PGE2 production
 - interleukin-6 (IL-6) antagonist

Moving Forward

- Await newer and better abuse-deterrent opioids over time
- Try to facilitate novel analgesics
 - Better nonclinical models
 - More reliable clinical trial designs