Evolving Insights into Acute Pain:
Diagnosis and Treatment

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Introduction

Historically, acute pain was primarily viewed as a symptom of an underlying condition, with the focus on treating the cause rather than the pain itself.

Early medical practices often involved rudimentary methods of pain relief. In the late 19th and early 20th centuries, the development of anesthesia and analgesic medications marked a significant advancement in the management of acute pain. The discovery of opiates like morphine revolutionized pain treatment, providing effective relief for severe pain. However, the potential for addiction and other side effects posed significant challenges.

The latter half of the 20th century saw further advancements in the understanding of pain mechanisms. Research into the neurobiology of pain revealed the complex interplay between the peripheral and central nervous systems, leading to the development of more targeted therapies. The recognition of the biopsychosocial model of pain emphasized the importance of psychological and social factors in pain perception and management.

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Key Characteristics and an Evolving Understanding

Key Characteristics

Acute pain is characterized by its sudden onset and relatively short duration. It can manifest in various forms, such as sharp, stabbing, throbbing, or burning sensations. The intensity of acute pain can vary significantly, from mild discomfort to excruciating pain that interferes with daily activities. It is often localized to the area of injury or pathology, but it can also radiate to surrounding tissues.

The response to acute pain involves multiple physiological processes, including the activation of nociceptors (pain receptors), transmission of pain signals through the nervous system, and the release of inflammatory mediators. These processes lead to the perception of pain and the initiation of protective behaviors to prevent further injury.

Onset: Sudden

Duration: Short-term, usually less than three months

Intensity: Can vary from mild to severe

Causes: Surgery, injury, infection, inflammation, and other medical conditions

Contributing Factors

Biological Factors:

- Biological factors play a central role in the initiation and modulation of acute pain. The activation of nociceptors in response to tissue damage triggers the release of inflammatory mediators such as prostaglandins, bradykinin, and cytokines. These mediators sensitize the nociceptors, enhancing pain perception.

Psychological Factors:

- Emotions such as anxiety, fear, and stress can amplify pain perception. Past experiences with pain, individual pain tolerance, and coping mechanisms also play a role. Cognitive-behavioral strategies, including relaxation techniques, cognitive restructuring, and mindfulness, have been shown to effectively manage acute pain by addressing these psychological aspects.

Environmental Factors:

- Environmental factors, including the context of the injury or medical condition, social support, and access to healthcare, can impact the experience and management of acute pain.

Diagnostic Evolution and Criteria

Classification and Diagnosis

The classification and diagnosis of acute pain have evolved over the years, leading to the establishment of standardized codes and criteria that aid in the accurate identification and treatment of this condition. The International Classification of Diseases (ICD-11) provide distinct frameworks for categorizing acute pain, with its own set of diagnostic criteria and subgroups.

ICD-11 Codes

Acute pain is classified under the code **MG31**. This category encompasses a wide range of acute pain conditions, recognizing the diverse etiologies and clinical presentations associated with acute pain.

The ICD-11 defines acute pain as pain that typically lasts for less than three months and is usually associated with tissue damage or the potential for such damage. This definition underscores the transient nature of acute pain and its role as a warning signal for the body. The ICD-11 also acknowledges the importance of differentiating between acute and chronic pain.

Evolution Over Time

The classification systems for acute pain have evolved to reflect advancements in understanding pain mechanisms and recognizing pain as a significant medical issue. Earlier versions of the ICD and DSM focused mainly on the physical aspects of pain, often ignoring psychological and social dimensions. Over time, these systems have adopted a more holistic view, acknowledging the interplay between physical, psychological, and environmental factors.

The transition from ICD-10 to ICD-11 marked a significant advancement, introducing specific codes for different types of pain, including acute, chronic, and cancer-related pain, facilitating more accurate diagnosis and treatment planning.

Impact on Clinical & Research Perspectives

Clinically, the refined diagnostic criteria and codes enable more accurate diagnosis and categorization of acute pain, leading to more targeted and effective treatment plans. These changes support evidence-based practices and multimodal pain management strategies.

From a research perspective, the standardized classifications enhance the quality and comparability of studies, allowing researchers to stratify patients based on specific pain categories, leading to more nuanced insights into pain mechanisms and treatment outcomes.

Epidemiological Landscape of Acute Pain

Age

- **Children and Adolescents:** In younger populations, acute pain often results from injuries, surgeries, or acute illnesses such as infections. Children's pain management requires careful consideration of developmental and psychological factors.
- **Adults:** In adults, acute pain is commonly associated with musculoskeletal injuries, surgical procedures, and acute medical conditions like kidney stones or myocardial infarctions.
- **Older Adults:** Older adults are more prone to acute pain due to a higher incidence of falls, fractures, and surgeries. Additionally, age-related changes in pain perception and medication metabolism can complicate pain management in this population.

Racial and Ethnic Groups

- **Biological Differences:** Genetic variations can affect pain sensitivity and the effectiveness of certain pain medications.
- **Socioeconomic Factors:** Socioeconomic status can impact access to healthcare and pain management resources, with lower-income individuals often experiencing higher barriers to effective treatment.
- **Cultural Attitudes:** Cultural beliefs and practices can influence how individuals perceive and report pain, as well as their willingness to seek treatment.

Location

- **Urban Areas:** Higher rates of injuries, accidents, and surgical procedures in urban areas contribute to the prevalence of acute pain. Urban residents may have better access to healthcare facilities and pain management services.
- **Rural Areas:** Individuals in rural areas may face unique challenges, including limited access to healthcare providers, longer travel times to medical facilities, and fewer resources for pain management.

Genetic Predisposition

- **Pain Sensitivity:** Genetic variations can affect nociceptor function and pain threshold, leading to differences in pain perception among individuals.
- **Medication Metabolism:** Polymorphisms in genes encoding drug-metabolizing enzymes can impact the efficacy and safety of pain medications. For example, variations in the CYP2D6 enzyme affect the metabolism of opioids like codeine and tramadol.
- **Inflammatory Response:** Genetic differences in the inflammatory response can influence the intensity and duration of acute pain. Certain genetic markers are associated with increased production of pro-inflammatory cytokines, contributing to heightened pain sensitivity.

Pivotal Endpoints for Acute Pain Clinical Trials

Endpoints in clinical trials for acute pain are critical measurements used to determine the effectiveness and safety of a treatment. Selecting appropriate endpoints is essential to ensure that the clinical trial results are relevant and can lead to meaningful improvements in patient care. These endpoints serve as benchmarks that guide researchers in assessing whether the treatment under investigation provides significant clinical benefits compared to standard care or placebo.

1. Pain Intensity Reduction:

This endpoint measures the decrease in pain intensity experienced by patients, typically assessed using self-report scales like the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS).

2. Functionality Improvement:

Functionality improvement evaluates a patient's ability to perform daily activities and return to normal life roles.

3. Side Effect Profile:

This endpoint assesses the adverse effects associated with pain treatments, balancing effective pain relief with minimizing negative side effects.

4. Time to Onset of Pain Relief:

Measuring how quickly a treatment provides pain relief is crucial for acute pain management.

5. Duration of Pain Relief:

This endpoint evaluates the length of time a treatment maintains pain relief, which is important for managing chronic pain conditions.

6. Patient Satisfaction:

Patient satisfaction encompasses the overall experience with the pain treatment, including effectiveness, side effect management, and ease of use.

Challenges in Determining Endpoints in Acute Pain Clinical Trials

1. Pain Intensity Reduction:

Measuring pain intensity is inherently subjective, as it relies on patient self-reporting, which can vary based on individual pain tolerance, emotional state, and external influences. Variability in pain scales can also affect consistency in reporting.

2. Functionality Improvement:

Assessing improvements in functionality, such as the ability to perform daily activities or return to work, is another crucial endpoint. However, measuring functionality can be challenging due to the wide variability in baseline functional levels among patients and the influence of comorbid conditions.

3. Side Effect Profile:

Balancing the efficacy of pain relief with the side effect profile of treatments is a critical endpoint. Many effective pain medications, such as opioids, have significant side effects that can limit their use. Assessing and managing these side effects while ensuring adequate pain control presents a substantial challenge.

4. Time to Onset of Pain Relief:

Measuring how quickly a treatment begins to provide pain relief can be difficult, especially with varying patient pain thresholds and subjective reporting. Additionally, rapid-onset pain relief must be balanced against the risk of adverse effects that might occur with fast-acting medications.

5. Duration of Pain Relief:

Determining the duration of pain relief provided by a treatment involves consistent and accurate patient reporting over extended periods, which can be influenced by the patient's adherence to the treatment regimen and other external factors.

6. Patient Satisfaction:

Patient satisfaction is a multifaceted endpoint influenced by the effectiveness of pain relief, side effect management, ease of use, and overall experience with the treatment. Capturing this data accurately requires comprehensive and holistic assessment tools.

Five FDA-Approved Treatments for Acute Pain

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
OxyContin	1995	Purdue Pharma	• Binds to opioid receptors in the brain and spinal cord. • Mimics the effects of endogenous opioids (endorphins)	• Relief of moderate to severe acute and chronic pain. • Used in pain management where continuous, around-the-clock analgesia is needed.
Acetaminophen	1955	McNeil Consumer	• Inhibits prostaglandin synthesis in the central nervous system • Cyclooxygenase inhibitor	• Pain relief • Fever reduction
Celebrex	1998	Pfizer	• Selective inhibition of cyclooxygenase-2 (COX-2) enzyme. • Reduces production of prostaglandins, which are involved in inflammation and pain.	• Relief of pain and inflammation associated with osteoarthritis and rheumatoid arthritis. • Management of acute pain. • Treatment of primary dysmenorrhea.
Ibuprofen	1974	Pfizer	• Non-selective inhibitor of cyclooxygenase (COX) • Reduces the production of prostaglandins • Nonsteroidal anti-inflammatory drug (NSAID)	• Anti-inflammatory • Particularly effective for musculoskeletal pain
Nucynta	2008	Janssen	• Binds to opioid receptors in the CNS. • Inhibits norepinephrine reuptake. • Provides a dual mechanism for analgesia, combining opioid effects with noradrenergic modulation.	• Management of moderate to severe acute pain. • Treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Approved Product Analysis: OxyContin

Adult and Pediatric Clinical Study

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with persistent moderate to severe pain	Pain Reduction	Pain assessment scale	2 weeks	N=133 (20 mg, 10 mg, and placebo)	• Significant improvement with 20 mg vs. placebo • OXYCONTIN 10 mg was not significant
Opioid-tolerant pediatric patients with moderate to severe pain	Chronic Pain Control	Clinical assessment of pain	Mean duration: 20.7 days (range 1 to 43 days)	N=155 (open-label, opioid-tolerant pediatric patients)	• Starting total daily doses: 20 mg to 100 mg based on prior opioid dose. • Mean daily dose: 33.30 mg (range 20 to 140 mg/day) • Safety Data were not specified(Too few patients less than 11 years were enrolled in the clinical trial to provide meaningful safety data in this age group)
Opioid-tolerant pediatric patients with moderate to severe pain	Chronic Pain Control	Clinical assessment of pain	Beyond 4 weeks (extension study)	N=23 (subset of 155 patients) *(13 for 28 weeks)*	Safety Data were not specified(Too few patients less than 11 years were enrolled in the clinical trial to provide meaningful safety data in this age group)

Approved Product Analysis: Acetaminophen

Adult Acute Pain

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with moderate to severe pain following total hip or knee replacement	Pain reduction and opioid consumption	Not specified	24 hours	N=101 (acetaminophen 1,000 mg vs. placebo every 6 hours)	Statistically superior reduction in pain intensity over 24 hours; decreased opioid consumption (clinical benefit not demonstrated)
Patients with moderate to severe postoperative pain after abdominal laparoscopic surgery	Pain reduction	Not specified	24 hours	N=244 (acetaminophen 1,000 mg every 6 hours or 650 mg every 4 hours vs. placebo)	Statistically significant greater reduction in pain intensity over 24 hours compared to placebo

Adult Fever

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Healthy adult males with endotoxin-induced fever	Fever reduction	Not specified	6 hours	N=60 (acetaminophen 1,000 mg vs. placebo, single dose)	Statistically significant antipyretic effect through 6 hours compared to placebo

Pediatric Acute Pain and Fever

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Pediatric patients (2-12 years) with acute pain	Pain reduction	Not specified	Not specified	N=483 (safety and pharmacokinetic data)	1. Supported by evidence from adult studies 2. For pediatric patients younger than 2 years, efficacy was not demonstrated in a double-blind, placebo-controlled study.
Pediatric patients (≥2 years)	Fever reduction	Not specified	Not specified	N=244 (supported by adult studies)	Supported by adequate and well-controlled studies in adults
Pediatric patients (<2 years, including neonates ≥32 weeks gestational age)	Fever reduction	Not specified	Not specified	N=239 (safety and pharmacokinetic data)	Supported by safety and pharmacokinetic data

Approved Product Analysis: Celebrex

Osteoarthritis

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with osteoarthritis (OA) of the knee and hip	Reduction in joint pain, stiffness, and functional improvement	WOMAC Index	12 weeks	N= not specified (Three 12-week studies)	• Significant reduction in pain within 24-48 hours of dosing. • Comparable effectiveness to naproxen 500 mg twice daily. • No additional benefit with 200 mg twice daily vs. 100 mg twice daily.

Rheumatoid Arthritis

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with rheumatoid arthritis (RA)	Reduction in joint tenderness/pain and joint swelling	ACR20 Responder Index	24 weeks	N= not specified (100 mg twice daily, 200 mg twice daily, placebo, naproxen 500 mg twice daily)	• Significant reduction in joint tenderness/pain and swelling. • Comparable effectiveness to naproxen 500 mg twice daily. • No additional benefit with 400 mg twice daily vs. 100-200 mg twice daily.

Juvenile Rheumatoid Arthritis

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Pediatric patients (2 to 17 years) with JRA	Reduction in joint pain, tenderness, and swelling	JRA DOI 30 (≥30% improvement)	12 weeks	N= 225 (celecoxib 3 mg/kg twice daily, celecoxib 6 mg/kg twice daily, naproxen 7.5 mg/kg twice daily)	• Significant improvement in JRA DOI 30 response rates • 69% (celecoxib 3 mg/kg BID) • 80% (celecoxib 6 mg/kg BID) • 67% (naproxen 7.5 mg/kg BID)

Approved Product Analysis: Celebrex (cont.)

Ankylosing Spondylitis

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with ankylosing spondylitis (AS)	Reduction in pain intensity, global disease activity, and functional impairment	Visual Analogue Scale (VAS), Bath Ankylosing Spondylitis Functional Index (BASFI)	6 weeks	N= not specified Placebo, CELEBREX 100 mg BID, CELEBREX 200 mg QD, CELEBREX 400 mg QD	• Significant improvement in global pain intensity, global disease activity, and functional impairment.
Adults with ankylosing spondylitis (AS)	Reduction in pain intensity, global disease activity, and functional impairment	Visual Analogue Scale (VAS), Bath Ankylosing Spondylitis Functional Index (BASFI), ASAS 20	12 weeks	N= not specified Placebo, CELEBREX 100 mg BID, CELEBREX 200 mg QD, CELEBREX 400 mg QD	• Significant improvement in global pain intensity, global disease activity, and functional impairment. • No difference in mean change between 200 mg and 400 mg doses, but higher responder rate with 400 mg (53%) vs. 200 mg (44%) using ASAS 20.

Analgesia, including Primary Dysmenorrhea

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea	Pain relief in moderate to severe pain	Patient-rated pain intensity	Single dose	N= not specified (acute analgesic models: post-oral surgery pain, post-orthopedic surgical pain, primary dysmenorrhea)	Significant pain relief within 60 minutes with single doses of CELEBREX

Approved Product Analysis: Celebrex – Special Studies

Adenomatous Polyp Prevention Studies

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with Sporadic Adenomatous Polyps	Composite endpoint of cardiovascular death, myocardial infarction, or stroke	Adjudicated endpoints	3 years	APC trial: N=671 (400 mg BID), N=685 (200 mg BID), N=679 (placebo)	Hazard Ratios: 3.4 (400 mg BID), 2.8 (200 mg BID), cumulative rates: 3.0% (400 mg BID), 2.5% (200 mg BID), 0.9% (placebo)
Patients with Sporadic Adenomatous Polyps	Composite endpoint of cardiovascular death, myocardial infarction, or stroke	Adjudicated endpoints	3 years	PreSAP trial: N=933 (400 mg QD), N=628 (placebo)	• Hazard Ratio: 1.2 (400 mg QD), cumulative rates: 2.3% (400 mg QD), 1.9% (placebo) • Did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated)

Endoscopic Studies

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
RA Patients	Incidence of endoscopic ulcers	Endoscopic examination	6 months	N=430	• CELEBREX 200 mg BID: 4% incidence of endoscopic ulcers, Diclofenac SR 75 mg BID: 15% incidence of endoscopic ulcers. • CELEBREX was not statistically different from diclofenac for clinically relevant GI outcomes in the CLASS trial.
OA and RA Patients	Incidence of endoscopic ulcers	Endoscopic examination	12 weeks	N=2157	2.7%-5.9% (CELEBREX 50-400 mg BID), 16.2%-17.6% (Naproxen 500 mg BID), 2.0%-2.3% (Placebo)

Approved Product Analysis: Celebrex – Special Studies (cont.)

Celecoxib Long-Term Arthritis Safety Study (CLASS)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
All Patients (OA and RA)	Complicated ulcer rates	Kaplan-Meier rates	9 months	CELEBREX alone: N=3105, CELEBREX with ASA: N=882	0.78% (CELEBREX alone), 2.19% (CELEBREX with ASA)
Patients < 65 Years	Complicated ulcer rates	Kaplan-Meier rates	9 months	CELEBREX alone: N=2025, CELEBREX with ASA: N=403	0.47% (CELEBREX alone), 1.26% (CELEBREX with ASA)
Patients ≥ 65 Years	Complicated ulcer rates	Kaplan-Meier rates	9 months	CELEBREX alone: N=1080, CELEBREX with ASA: N=479	1.40% (CELEBREX alone), 3.06% (CELEBREX with ASA)
Patients with history of ulcer disease	Complicated and symptomatic ulcer rates	Kaplan-Meier rates	48 weeks	CELEBREX alone: N=243, CELEBREX with ASA: N=91	2.56% (CELEBREX alone), 6.85% (CELEBREX with ASA)
All Patients (OA and RA)	Serious cardiovascular thromboembolic events	Kaplan-Meier rates	9 months	CELEBREX: N=3987, Diclofenac: N=1996, Ibuprofen: N=1985	1.2% (CELEBREX), 1.4% (Diclofenac), 1.1% (Ibuprofen)
Non-ASA Users	Serious cardiovascular thromboembolic events	Kaplan-Meier rates	9 months	CELEBREX, Diclofenac, Ibuprofen	< 1% (all groups)
Non-ASA Users	Myocardial infarction rates	Kaplan-Meier rates	9 months	CELEBREX, Diclofenac, Ibuprofen	< 0.2% (all groups)
All Patients (OA and RA)	Peripheral edema rates	Kaplan-Meier rates	9 months	CELEBREX: N=3987, Diclofenac: N=1996, Ibuprofen: N=1985	4.5% (CELEBREX), 4.7% (Diclofenac), 6.9% (Ibuprofen)
All Patients (OA and RA)	Hypertension rates	Kaplan-Meier rates	9 months	CELEBREX: N=3987, Diclofenac: N=1996, Ibuprofen: N=1985	2.4% (CELEBREX), 2.5% (Diclofenac), 4.2% (Ibuprofen)

Approved Product Analysis: Ibuprofen

Analgesia (Pain)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Women who had undergone an elective abdominal hysterectomy	Reduction in morphine consumption and pain intensity	Not specified	24 hours	N=319 (CALDOLOR 800 mg or placebo every 6 hours)	• Statistically significant reduction in mean morphine consumption (47 mg vs. 56 mg) • Greater reduction in pain intensity with CALDOLOR
Patients who had undergone an elective abdominal or orthopedic surgery	Pain management and morphine consumption	Not specified	Not specified	N=406 (CALDOLOR 400 mg, 800 mg, or placebo every 6 hours)	No statistically significant difference; trends favoring CALDOLOR

Antipyretic (Fever)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Hospitalized febrile patients	Temperature reduction	Not specified	24 hours	N=120 (CALDOLOR 100 mg, 200 mg, 400 mg, or placebo every 4 hours)	Statistically greater percentage of patients with temperature <101°F after 4 hours (65%, 73%, 77% vs. 32%)
Hospitalized patients with uncomplicated P. falciparum malaria	Fever reduction	Area above temperature curve vs. time	72 hours (measured w/in first 24 hours)	N=60 (CALDOLOR 400 mg or placebo every 6 hours)	Significant reduction in fever within first 24 hours
Hospitalized pediatric patients (6 months and older)	Temperature reduction	Area under the curve analyses	First 2 hours and entire dosing interval	N=100 (CALDOLOR 10 mg/kg or low dose active comparator every 4 hours as needed)	• Statistically significant greater reduction in temperature for the primary endpoint • 74% became afebrile (temperature <99.5°F) by end of first dosing interval

Approved Product Analysis: NUCYNTA

Moderate to Severe Chronic Low Back Pain

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with chronic low back pain (LBP)	Pain relief as measured by 24-hour average pain severity	11-point Numerical Rating Scale (NRS)	15 weeks	NUCYNTA ER (N=327), Placebo (N=329), Active-Control (N=325)	• NUCYNTA ER showed significantly greater pain reduction compared to placebo. Completion rates: Placebo (51%), NUCYNTA ER (54%), Active-Control (43%) • The mean baseline pain intensity score was 8 (SD 1) • Lack of efficacy was the most common reason for discontinuation among placebo-treated patients (21%), whereas adverse events were the most common reason for discontinuation among the active treatment groups (17% for NUCYNTA ER and 32% for active-control)

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with pain due to diabetic peripheral neuropathy (DPN)	Pain relief as measured by 24-hour average pain severity	11-point Numerical Rating Scale (NRS)	12 weeks	Study DPN-1: Open-label: N=591, Randomized: NUCYNTA ER (N=194), Placebo (N=195)	• Significant pain reduction with NUCYNTA ER vs. placebo • 66% completed the study • Common discontinuation reasons: lack of efficacy (placebo: 14%), adverse events (NUCYNTA ER: 15%)
Adults with pain due to diabetic peripheral neuropathy (DPN)	Pain relief as measured by 24-hour average pain severity	11-point Numerical Rating Scale (NRS)	12 weeks	Study DPN-2: Open-label: N=459, Randomized: NUCYNTA ER (N=160), Placebo (N=160)	• Significant pain reduction with NUCYNTA ER vs. placebo • 74% completed the study • Common discontinuation reasons: adverse events (placebo: 9%, NUCYNTA ER: 14%)

Summary of Failed Drug Candidates for Pain

Name of Drug	Clinical Trial Identifier	Reason for Termination / Drug Failure
Tanezumab	NCT01089725	The trial was terminated due to US FDA clinical hold for tanezumab osteoarthritis clinical studies which halted dosing and enrollment of subjects on June 23, 2010 for potential safety issues.
Fulranumab	NCT00973024	The trial was terminated because of lack of efficacy in PAI2003.
Vixotrigine	GDCT0252702	Although the trial was completed, findings suggest that BIIB074 was safe but not effective in subjects with painful lumbosacral radiculopathy (PLSR).
Bicifadine	NCT00553592	The development of the drug was halted for treating diabetic neuropathic pain due to lack of efficacy.

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Unique Failure Points in Clinical Trials for Acute Pain

1. High Placebo Effect:

Acute pain trials often experience a significant placebo effect. This effect can dilute the apparent efficacy of the active treatment. The high placebo response can lead to difficulties in demonstrating a statistically significant difference between the treatment and placebo groups, potentially resulting in the failure of the trial to show efficacy.

2. Variability in Pain Perception:

Pain perception is highly subjective and influenced by numerous factors, including psychological state, previous pain experiences, and cultural background. This variability can result in inconsistent pain reporting among participants. This variability can obscure the true effect of the treatment, leading to inconclusive or misleading results.

3. Short-Term Nature of Acute Pain:

Acute pain is typically short-lived, making it challenging to capture and measure pain relief over a relevant time frame. Pain levels can fluctuate rapidly, and the window for effective measurement can be narrow. The transient nature of acute pain can lead to difficulties in timing assessments accurately, potentially resulting in underestimation of efficacy.

4. Ethical Concerns in Placebo Use:

In acute pain trials, the use of placebos can raise ethical concerns, particularly when effective pain relief is available. Withholding effective treatment from patients in severe pain for the sake of a placebo-controlled trial can be ethically problematic. Ethical constraints may limit the use of placebos, complicating trial design and interpretation of results.

5. Complex Comorbidities and Medication Interactions:

Patients with acute pain often have comorbid conditions or are taking multiple medications, which can interact with the study drug and influence pain perception or treatment efficacy. These interactions can confound trial results, making it difficult to attribute outcomes solely to the study treatment.

6. Patient Adherence and Retention:

As with many trials, ensuring patient adherence to treatment protocols and retaining participants throughout the study duration can be challenging, especially if side effects occur or if patients perceive inadequate pain relief. Poor adherence and high dropout rates can bias results and reduce the statistical power of the trial.

Safety Concerns

The primary safety concerns in the treatment of acute pain revolve around the use of medications, particularly opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. Each class of medication presents unique risks that must be carefully managed to prevent adverse effects and complications.

1. **Opioids**
    - **Dependency and Addiction:** Opioids, such as oxycodone and hydrocodone, are highly effective for severe acute pain but carry a significant risk of dependency and addiction. This risk is heightened with prolonged use or higher doses.
    - **Respiratory Depression:** High doses of opioids can lead to respiratory depression, a potentially life-threatening condition where breathing becomes dangerously slow and shallow.
    - **Side Effects:** Common side effects include nausea, vomiting, constipation, sedation, and dizziness, which can impact patient compliance and quality of life.
2. **NSAIDs**
    - **Gastrointestinal Issues:** NSAIDs like ibuprofen and ketorolac can cause gastrointestinal irritation, ulcers, and bleeding. Long-term use increases these risks significantly.
    - **Renal Impairment:** NSAIDs can impair kidney function, especially in patients with preexisting renal conditions or those who are dehydrated.
    - **Cardiovascular Risks:** Prolonged use of NSAIDs has been associated with an increased risk of cardiovascular events such as heart attacks and strokes.
3. **Acetaminophen**
    - **Liver Damage:** Acetaminophen is generally safe when used within recommended doses, but overdose can lead to severe liver damage or failure. This risk is particularly high in patients with existing liver disease or those who consume alcohol regularly.

Standard of Care Treatment Options

The standard of care for acute pain involves a multimodal approach that combines pharmacological and non-pharmacological treatments to achieve effective pain relief while minimizing adverse effects. The choice of treatment is tailored to the individual patient's pain severity, underlying conditions, and risk factors.

1. **Pharmacological Treatments**
   - **Opioids:** Used for moderate to severe acute pain, particularly post-surgical pain or pain from significant injuries. These are prescribed at the lowest effective dose for the shortest possible duration.
   - **NSAIDs:** Commonly used for mild to moderate pain and inflammation. They are often the first-line treatment for musculoskeletal injuries, dental pain, and post-surgical pain.
   - **Acetaminophen:** Often used for mild to moderate pain and fever. It is a preferred option for patients who cannot tolerate NSAIDs due to gastrointestinal or renal issues.

2. **Non-Pharmacological Treatments**
   - **Physical Therapy:** Helps in managing pain through exercises that improve strength, flexibility, and mobility. Physical therapy is particularly effective in post-operative care and musculoskeletal pain.
   - **Ice and Heat Therapy:** Applying ice can reduce inflammation and numb the pain, while heat therapy can relax muscles and improve blood flow to the area.
   - **Transcutaneous Electrical Nerve Stimulation (TENS):** Uses low-voltage electrical currents to relieve pain. TENS units are commonly used for various types of acute pain, including post-operative and injury-related pain.
   - **Cognitive Behavioral Therapy (CBT):** Addresses the psychological components of pain, helping patients develop coping strategies to manage their pain better.

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Enhancing Clinical Trial Protocols for Acute Pain

Improving clinical trial protocols is pivotal to advancing our understanding and treatment of the disease. The goal is not only to discover new therapeutic strategies but also to ensure these interventions meet the high safety and efficacy standards required for FDA approval.

1. Enhancing Patient Selection:

Acute pain can vary greatly in terms of intensity, duration, and underlying cause. Stratifying patients allows for more precise analysis of treatment effects and helps in identifying which subgroups benefit the most from the intervention.

2. Rigorous Endpoint Selection:

Selecting appropriate primary and secondary endpoints that are clinically meaningful and statistically robust is crucial. Utilizing composite endpoints that combine multiple measures of efficacy and safety can provide a more comprehensive assessment of the treatment's impact.

3. Comprehensive Safety Monitoring:

Implementing real-time safety monitoring systems can detect adverse events promptly, allowing for immediate action to mitigate risks. This includes electronic health records (EHR) integration and patient-reported outcome measures (PROMs) that provide continuous feedback.

4. Adaptive Trial Designs:

Adaptive trial designs allow for modifications to the trial protocol based on interim results. This flexibility can improve efficiency, reduce costs, and enhance the likelihood of success. Examples include dose adjustments, sample size re-estimation, and changes in patient stratification.

5. Regulatory Insights & Compliance:

Engaging with the FDA early in the drug development process through pre-IND meetings can provide valuable feedback on trial design and regulatory expectations. This proactive approach helps in identifying potential issues and addressing them before formal submission.

6. Patient-Centric Approaches:

Involving patients in the design and implementation of clinical trials can enhance relevance and adherence.

Clear and frequent communication with trial participants about the purpose, procedures, and potential risks and benefits of the trial can improve engagement and retention.

Notable Key Opinion Leaders in Acute Pain Research

Name	Specialty	Designation	Location	Brief Bio
Paul E Rolan (MBBS, FRACP, FFPM, FFPMANZCA)	Clinical Pharmacology; Pain Medicine	Professor, The University of Adelaide	South Australia, Australia	Professor Paul E. Rolan is currently a Professor of Clinical Pharmacology at the University of Adelaide. He has also served as the Director of Innovation since October 2016. Dr. Rolan's academic and clinical work focuses on chronic pain and headache, exploring the development of biomarkers, novel therapies, and understanding disease mechanisms.
Kerry Mclaughlin (MBBS, FRACP, FFPMANZCA)	Anesthesiology; Pain Medicine	Consultant, Alfred Health Victoria	Victoria, Australia	Dr. Kerry McLaughlin currently serves as a Pain Specialist and Specialist Anesthetist at Alfred Health. She is also the Acting Head of Acute Pain Services at Alfred Health and works as a consultant at the Caulfield Chronic Pain Management Centre and Research Centre. She has a particular interest in interventions for pain management, focusing on complex cancer and non-cancer pain.
Keat Lee (MBBS, FANZA)	Anesthesiology; Pain Medicine	Head, The Royal Melbourne Hospital	Victoria, Australia	Dr. Keat Leong Lee is a Senior Staff Specialist in the Department of Anesthesia and Pain Management and serves as the Head of Clinical Operations at the Royal Melbourne Hospital (RMH). Dr. Lee's clinical and research interests include anesthesia for ENT (Ear, Nose, and Throat), vascular and trauma surgery, and the clinical care of perioperative patients. Dr. Lee's expertise extends to cardiothoracic anesthesia and patient safety, particularly in managing complex head and neck surgeries.
Alex H Konstantatos (MBBS, FANZA, MRCA)	Anesthesiology; Pain Medicine	Director, Alfred Health Victoria	Victoria, Australia	Dr. Alex H. Konstantatos is a Senior Staff Specialist Anesthetist and Pain Medicine Physician at Alfred Health in Melbourne. He is also an Adjunct Senior Lecturer at Monash University in the Department of Anesthesia and Perioperative Medicine. Dr. Alex provides anesthetic and perioperative services, with a focus on pain management. Dr. Alex is involved in the preoperative assessment and postoperative care of patients undergoing various surgical procedures.
Jeffrey Lipman (MBBCh, (DA, FFA), (FFA Crit Care, FCICM), AM	Anesthesiology; Critical/Intensive Care Medicine	Professor, University of Queensland	Queensland, Australia	Professor Jeffrey Lipman is an Emeritus Professor at the University of Queensland and a prominent figure in the field of Anesthesiology and Critical Care. He holds the title of Chair of Trauma-related Clinical Research at the Jamieson Trauma Institute, Royal Brisbane and Women's Hospital. Previously, he served as the Director of Intensive Care Services at the Royal Brisbane and Women's Hospital for over 20 years and was the Executive Director of the Burns, Trauma, and Critical Care Research Centre at the University of Queensland.

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

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