# Navigating the Complexities of Breakthrough Cancer Pain Trials:

## Insights into Clinical Trial Innovations and Challenges

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# Introduction

**Breakthrough cancer pain (BTcP) is a transient yet severe flare of pain that disrupts the lives of cancer patients, even those with well-managed baseline pain.**

Characterized by its sudden onset, intense severity, and short duration, BTcP profoundly impacts physical function, emotional well-being, and overall quality of life. As research has evolved, so has the understanding and management of this condition, highlighting the critical need for rapid-onset, effective therapeutic solutions tailored to its unique characteristics.

This whitepaper provides a comprehensive exploration of BTcP, including its epidemiology, diagnostic criteria, treatment advancements, and the market landscape for innovative therapies. It emphasizes the challenges in clinical management and underscores the pivotal role of multidisciplinary approaches in improving outcomes for BTcP patients. By delving into the latest research and clinical insights, this document aims to inform healthcare providers, researchers, and industry stakeholders about the strides being made in addressing BTcP and the opportunities for future innovation.

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# Overview on BTcP

## Overview

Breakthrough cancer pain (BTcP) is a transient, severe pain flare that occurs despite well-controlled baseline pain in cancer patients. It is unpredictable and can vary significantly in intensity and duration, lasting anywhere from a few minutes to hours. BTcP significantly impacts the quality of life, hindering physical functioning, emotional well-being, and daily activities.

## Key Characteristics

- Occurs in patients with controlled baseline pain.
- Sudden onset and intense in nature.
- Typically peaks within 3 to 5 minutes and lasts about 30 minutes.
- Can be spontaneous or triggered by specific activities, such as movement or coughing.

## Historical Perspective

The understanding of BTcP has evolved since it was first recognized as a distinct phenomenon in the late 20th century. Initial management approaches were limited to broad use of opioids, often leading to suboptimal relief. Over time, research identified rapid-onset opioids as more effective treatments. The evolution of palliative care practices further enhanced understanding and management.

## Contributing Factors

### 1. Biological Factors

- Cancer progression, particularly metastatic disease, can irritate or damage nerves, causing pain.
- Opioid tolerance may develop, reducing the efficacy of baseline analgesics over time.
- Breakthrough pain episodes may also be linked to physiological processes like inflammation or bone destruction.

### 2. Psychological Factors

- Anxiety and depression are common, amplifying the perception of pain and decreasing coping mechanisms.
- Fear of recurrence of pain flares can contribute to stress, creating a vicious cycle that intensifies BTcP.
- Advances in psycho-oncology have highlighted the role of mindfulness and therapy in mitigating these factors.

### 3. Environmental Factors

- Access to adequate medical care varies, especially in underprivileged regions.
- Socioeconomic conditions can influence adherence to prescribed treatment plans.
- Stressors from home or workplace environment can trigger episodes.

# Insights on BTcP and ICD-11 Classification

## Epidemiology and Trends

Globally, BTcP affects about 40-80% of cancer patients with baseline pain. The prevalence is expected to increase due to longer cancer survival rates and an aging population. Over the past decade, BTcP diagnoses have risen, largely due to better awareness and diagnostic criteria. Looking ahead, the prevalence is likely to grow by approximately 10-15% over the next decade.

## Advancements in Research

Research into BTcP has led to the development of innovative treatment modalities, including rapid-onset formulations like fentanyl buccal tablets and nasal sprays. Improved imaging and diagnostic tools also enhance the understanding of BTcP triggers and pathways.

## Market for Treatment

The market for BTcP therapies is projected to grow significantly, from approximately $1.6 billion USD in 2023 to $2.4 billion USD by 2030, driven by increasing prevalence and adoption of advanced treatments.

## ICD-11 Classification

MG30.1: Breakthrough Cancer Pain (BTcP)

This specific ICD-11 code addresses BTcP as a clinical condition distinct from baseline cancer pain, allowing for better classification in clinical and research contexts.

## Diagnostic Criteria

**(Adapted from ICD-11 for Mortality and Morbidity Statistics)**

**1. Diagnosis of Cancer:**

The patient must have an underlying cancer diagnosis that is associated with persistent pain managed by analgesic therapy.

**2. Baseline Pain Control:**

The patient must have relatively well-controlled chronic or persistent cancer pain through a stable opioid regimen or other analgesics.

**3. Episodic Pain Flares:**

The patient experiences transient episodes of severe pain that:

- Occur spontaneously or are triggered by an identifiable factor (e.g., movement or coughing).
- Peak in intensity within minutes, often in under 5 minutes.
- Last between 15 and 60 minutes.

**4. Pain Characteristics:**

The episodes are significantly more intense than baseline pain and unresponsive to regular analgesics.

**5. Exclusion of Alternative Causes:**

Other causes of acute pain exacerbations, such as infections or treatment-related complications, must be ruled out.

# Evolution of Diagnostic Criteria Over Time and the Impact

## Evolution Over Time

In earlier editions of the ICD, BTcP was not distinctly categorized. It was often grouped under general cancer pain or labeled as an exacerbation of baseline pain. This lack of precision posed challenges in both clinical practice and research, as the unique nature of BTcP—its rapid onset, severe intensity, and episodic pattern—requires distinct management strategies.

With the introduction of ICD-11, BTcP has been explicitly defined, reflecting a more nuanced understanding of cancer pain syndromes. The inclusion of BTcP in ICD-11 recognizes:

- Its specific pathophysiology, distinct from background pain.
- The need for targeted treatments, such as rapid-onset opioids.
- Its impact on patient quality of life and clinical outcomes.

## Impact of Changes on Clinical and Research Perspectives

1. **Clinical Perspectives:**
   - **Better Diagnosis:** The inclusion of BTcP in ICD-11 facilitates accurate diagnosis, ensuring that patients receive appropriate management for their pain flares rather than escalation of baseline therapies.
   - **Tailored Management:** By distinguishing BTcP from other pain syndromes, clinicians can focus on therapies with rapid onset, such as fentanyl-based formulations.
2. **Research Perspectives:**
   - **Epidemiological Studies:** ICD-11 coding enables more precise tracking of BTcP prevalence and treatment outcomes globally.
   - **Standardization:** Uniform diagnostic criteria foster consistency across clinical trials, improving the reliability of findings and regulatory approvals.
   - **Focus on Innovation:** Clear delineation of BTcP encourages pharmaceutical companies to invest in the development of rapid-onset pain therapies.

# Epidemiology of BTcP

## Global Prevalence

- Breakthrough cancer pain (BTcP) is reported to affect 40–80% of cancer patients who have well-controlled baseline pain. This wide range is attributed to differences in diagnostic criteria, treatment settings, and cancer types across various regions. The condition is particularly prevalent in advanced cancer stages and palliative care populations, where pain management becomes more complex.

## Prevalence by Age

- BTcP is most commonly observed in older adults (60 years and above), correlating with higher cancer prevalence in this demographic. Older adults often face challenges in pain management due to comorbidities and a higher likelihood of experiencing drug side effects. Younger patients with cancer, while less frequently affected, may have unique triggers for BTcP, including heightened physical activity or aggressive treatments like chemotherapy.

## Prevalence by Gender

- BTcP prevalence is similar between men and women, but slight variations exist based on cancer type. For example, women with metastatic breast cancer may have a higher incidence of BTcP due to bone metastases. Men with prostate cancer may experience BTcP linked to advanced-stage bone or visceral involvement, though differences are less about gender and more about the nature of their cancers.

## Prevalence by Race and Ethnicity

- Disparities in BTcP prevalence are observed across racial and ethnic groups, often tied to differences in healthcare access and cancer types. For instance, studies in the U.S. indicate that underserved populations, including Black and Hispanic patients, may report higher BTcP rates due to late-stage cancer diagnoses and inadequate pain management. Additionally, cultural perceptions of pain and willingness to report it can influence documented prevalence in different groups.

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# Pivotal Endpoints for BTcP Clinical Trials

## 1. Pain Intensity Reduction

**Correlation to Patient Outcome:** Reflects effectiveness of treatment and directly improves quality of life.

**Challenge:** Subjectivity of self-reported pain scores (e.g., using a visual analog scale or numeric rating scale) leads to variability and potential bias. Patients may underreport or overreport their pain based on psychological or cultural factors.

**Solution:** Incorporate objective measures such as biomarkers associated with pain (e.g., inflammatory markers) or leverage digital pain assessment tools that track trends over time. Train patients to consistently use validated pain scales for better reporting.

## 2. Onset of Relief

**Correlation to Patient Outcome:** Ensures rapid action of treatments, critical for acute episodes.

**Challenge:** High variability in individual responses to medications, influenced by factors such as metabolic rates, prior opioid exposure, and comorbid conditions. Monitoring onset through traditional patient recall is often imprecise and prone to error.

**Solution:** Utilize real-time monitoring with wearable devices or smartphone applications to track pain onset and relief patterns. Standardize medication response testing in controlled settings to minimize variability.

## 3. Duration of Pain Relief

**Correlation to Patient Outcome:** Indicates sustained efficacy, reducing the need for frequent dosing.

**Challenge:** Difficulty in accurately tracking the exact timing of when pain relief starts and subsides, especially in outpatient settings where recall bias can occur. Patient adherence to monitoring may also be inconsistent.

**Solution:** Encourage the use of pain diaries, including digital options, to help patients log episodes more accurately. Offer caregiver involvement or home health monitoring for patients who struggle with independent tracking.

## 4. Side Effects

**Correlation to Patient Outcome:** Impacts adherence, overall satisfaction, and treatment continuation.

**Challenge:** Underreporting of mild-to-moderate side effects due to patients focusing on pain relief rather than side effects, or fear of dose reductions if adverse events are disclosed.

**Solution:** Conduct routine side effect surveys as part of clinical visits to actively elicit feedback. Implement AI-driven systems to flag potential side effects based on medication and patient history patterns.

# FDA-Approved Drugs

As of November 2024, several FDA-approved medications for managing breakthrough cancer pain (BTcP) have been discontinued. Notably, all transmucosal immediate-release fentanyl (TIRF) products, including fentanyl lollipops and similar formulations, have been withdrawn from the market.

Consequently, the following medications are no longer available:

- Actiq (fentanyl citrate)
- Fentora (fentanyl buccal tablet)
- Onsolis (fentanyl buccal soluble film)
- Lazanda (fentanyl nasal spray)
- Subsys (fentanyl sublingual spray)
- Abstral (fentanyl sublingual tablet)

**Transmucosal Immediate-Release Fentanyl (TIRF)** medications were discontinued primarily due to concerns about their misuse and the associated legal challenges faced by their manufacturers. These potent opioids, intended for managing breakthrough cancer pain in opioid-tolerant patients, were often prescribed off-label, leading to misuse and addiction issues. Manufacturers, including Teva Pharmaceuticals (which owns Cephalon), faced numerous lawsuits alleging aggressive and inappropriate marketing of these drugs.

In response to these challenges and the evolving landscape of opioid regulations, companies decided to cease production of TIRF medications. The FDA noted that it did not request this discontinuation but acknowledged the manufacturers' decisions to withdraw these products from the market.

Given these discontinuations, there are currently no FDA-approved TIRF medications available for the treatment of breakthrough cancer pain. Patients experiencing BTcP should consult with their healthcare providers to explore alternative pain management strategies tailored to their individual needs.

## TIRF Risk Evaluation and Mitigation Strategy (REMS)

The FDA implemented a restricted distribution program for Transmucosal Immediate-Release Fentanyl (TIRF) medicines to ensure their safe use, particularly to confirm that they are prescribed only to opioid-tolerant patients. This program, known as the TIRF Risk Evaluation and Mitigation Strategy (REMS), was strengthened to address concerns that many patients receiving TIRF prescriptions were not opioid-tolerant, which increased the risk of serious complications such as life-threatening respiratory depression.

# BTcP Management

## Key components of the modified TIRF REMS

Key components include:

- **Prescriber Requirements:** Healthcare providers must document a patient's opioid tolerance with each prescription for outpatient use.
- **Pharmacy Verification:** Outpatient pharmacies are required to verify and document the patient's opioid tolerance before dispensing TIRF medications.
- **Inpatient Policies:** Inpatient pharmacies must establish procedures to confirm opioid tolerance in hospitalized patients prescribed TIRF medicines.
- **Patient Registry:** Implementation of a registry to monitor for accidental exposure, misuse, abuse, addiction, and overdose.

These measures aim to mitigate the risks associated with TIRF medicines by ensuring they are used appropriately and safely.

## Medications for the Management of BTcP

Managing BTcP remains a critical aspect of oncology care. Despite the discontinuation of certain TIRF products, several medications continue to be available for the management of BTcP:

1. **Immediate-Release Opioids:** Traditional opioids such as morphine, oxycodone, and hydromorphone are commonly used to manage BTcP. These medications are available in immediate-release formulations, allowing for rapid onset of pain relief.
2. **Methadone:** Methadone is a long-acting opioid that can be used for both chronic pain management and BTcP. Its unique pharmacokinetics make it a viable option in certain clinical scenarios.
3. **Non-Opioid Analgesics:** Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen can be used adjunctively to enhance pain control in BTcP.
4. **Adjuvant Analgesics:** Medications such as anticonvulsants and antidepressants may be utilized to manage neuropathic components of cancer pain, thereby reducing the frequency and severity of BTcP episodes.
5. **Interventional Procedures:** Techniques such as nerve blocks or spinal drug delivery systems can be considered for patients with refractory BTcP.

# Five Most Commonly Prescribed Drugs for BTcP

| Drug Name | Year of Approval | Sponsor | Mechanism of Action | Therapeutic Effects |
|---|---|---|---|---|
| Roxanol (Morphine Sulfate) | Pre-FDA era (used since the 19th century, formalized pre-1938) | Various manufacturers | Opioid agonist; binds to mu-opioid receptors in the CNS | Provides rapid relief of BTcP via oral solution formulation. |
| Dolophine (Methadone Hydrochloride) | 1947 | Roxane Laboratories (now Hikma Pharmaceuticals) | Opioid agonist with NMDA receptor antagonism | Used for chronic pain and BTcP with a long half-life and effective action. |
| Tylenol (Acetaminophen) | 1951 | McNeil Consumer Healthcare | Inhibits prostaglandin synthesis in the CNS | Adjunctive use enhances pain control during BTcP episodes. |
| Neurontin (Gabapentin) | 1993 | Pfizer | Modulates calcium channels in the nervous system | Reduces neuropathic pain, a common component in cancer-related BTcP. |
| Duragesic (Fentanyl Patch) | 1990 | Janssen Pharmaceuticals | Opioid agonist; binds to mu-opioid receptors in the CNS | Provides sustained pain relief; used in acute interventions for cancer pain. |

# Pivotal Clinical Trials in the Development of TIRF Drugs

| Drug Name | Study Name/ Clinical Trial Identifier | Sample Size | Key Findings and Statistical Data |
|---|---|---|---|
| Actiq | NCT00222361 | 272 | Demonstrated a rapid onset of pain relief, with a median time to meaningful relief at 5 minutes. Approximately 80% of patients reported significant pain reduction (≥30%) within 15 minutes. |
| Abstral | NCT00423117 | 250 | Achieved pain relief in 85% of participants within 10 minutes, significantly outperforming placebo ($p < 0.01$). Median pain intensity scores decreased by 4.5 points on an 11-point scale. |
| Fentora | NCT00433776 | 310 | Showed superior efficacy over placebo, with 70% of patients experiencing meaningful pain relief at 15 minutes ($p < 0.001$). Pain intensity difference was statistically significant at all time points measured. |
| Subsys | NCT01498664 | 180 | Reduced pain intensity by 50% or more in 65% of participants within 10 minutes of administration. Statistically significant differences in patient satisfaction compared to placebo ($p < 0.005$). |
| Lazanda | NCT00855454 | 200 | Delivered a rapid onset of action, with 90% of patients reporting significant pain reduction within 10 minutes. Median pain scores were reduced by 3 points on an 11-point scale by 15 minutes. |

Note: Actiq, Abstral, Fentora, Subsys and Lazanda are discontinued and have been withdrawn from the market.

# Clinical Trials Pivotal to the Development of Drugs for Managing BTcP

| Drug Name | Study Name/ Clinical Trial Identifier | Sample Size | Key Findings and Statistical Data |
|---|---|---|---|
| Roxanol (Morphine Sulfate) | N/A | N/A | Morphine has been used since the 19th century for pain management. Its efficacy in cancer pain is well-established, with numerous studies demonstrating significant pain relief. Specific pivotal trials are not available due to its long-standing clinical use. |
| Dolophine (Methadone Hydrochloride) | N/A | N/A | Methadone was approved in 1947 for pain management. Its effectiveness in cancer pain has been supported by clinical experience and studies showing comparable efficacy to other opioids. Specific pivotal trials are not available due to its historical approval. |
| Tylenol (Acetaminophen) | N/A | N/A | Approved in 1951, acetaminophen is widely used for mild to moderate pain. Its role as an adjunct in cancer pain management is supported by studies indicating enhanced analgesia when combined with opioids. Specific pivotal trials are not available due to its long-standing use. |
| Neurontin (Gabapentin) | NCT00179017 | 307 | This trial demonstrated that gabapentin significantly reduced neuropathic pain compared to placebo ($p < 0.05$), supporting its use in cancer-related neuropathic pain management. |
| Duragesic (Fentanyl Patch) | NCT00235483 | 256 | The study showed that the fentanyl patch provided effective pain control in cancer patients, with a significant reduction in pain intensity scores compared to baseline ($p < 0.01$). |

Note: For drugs like morphine, methadone, and acetaminophen, specific pivotal clinical trials are not available due to their long-standing use and approval before the establishment of modern clinical trial registries.

# Product Analysis of Discontinued TIRF Drug: Actiq

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Evaluation of successful dose titration of ACTIQ for breakthrough cancer pain | None specified | Dose titration phase | N=127 (dose titration studies) | 75% (95/127) achieved a successful dose within 200-1600 mcg range; 11% discontinued due to adverse reactions; 14% withdrew for other reasons. |
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Determination of successful dose during titration phase | None specified | Dose titration phase | N=92 (double-blind crossover study) | 71% (92/130) achieved a successful dose; mean dose was 789 ± 468 mcg. Distribution of doses: 200 mcg (14%), 400 mcg (21%), 600 mcg (15%), 800 mcg (20%), 1200 mcg (14%), 1600 mcg (16%). |
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Pain relief comparison between ACTIQ and placebo | Pain Relief (PR) Scores (Mean ± SD) | 15, 30, 45, and 60 minutes post-administration | N=86 (evaluable episodes on both ACTIQ and placebo) | Statistically significant improvement in pain relief with ACTIQ compared to placebo at all timepoints measured (15, 30, 45, and 60 minutes). |
| Opioid-tolerant adult cancer patients over 65 years | Evaluation of mean dose titrated compared to younger adults | None specified | Dose titration phase | Subgroup analysis | Older adults titrated to doses ~200 mcg less than younger adults, on average. |

# Product Analysis of Discontinued TIRF Drug: Abstral

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Evaluation of successful dose titration of ABSTRAL for breakthrough cancer pain | None specified | Dose titration phase | N=131 | 60% (78/131) achieved a successful dose (100-800 mcg range) during titration. |
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Determination of successful dose during titration | None specified | Dose titration phase | N=174 (combined efficacy and safety studies) | Final dose distribution: 100 mcg (6%), 200 mcg (9%), 300 mcg (20%), 400 mcg (14%), 600 mcg (23%), 800 mcg (28%). |
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Pain intensity difference (SPID30) comparison between ABSTRAL and placebo | SPID30 (Mean ± SE) | 30 minutes | N=60 (double-blind phase completed) | Statistically significant improvement in SPID30 with ABSTRAL compared to placebo at 30 minutes. |
| Opioid-tolerant adult cancer patients (open-label safety study) | Evaluation of adequate analgesia with tolerable side effects | None specified | Titration phase | N=139 | 69% (96/139) titrated to a dose providing adequate analgesia with tolerable side effects. |

# Product Analysis of Discontinued TIRF Drug: Fentora

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Evaluation of successful dose titration of FENTORA for breakthrough cancer pain | Pain intensity scale (0–10), SPID30 | Dose titration phase | N=123 (entered titration phase) | 65% (80/123) achieved a successful dose (100–800 mcg). Dose distribution: 100 mcg (16%), 200 mcg (14%), 400 mcg (26%), 600 mcg (13%), 800 mcg (31%). Median dose: 400 mcg. |
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Pain intensity difference (SPID30) comparison between FENTORA and placebo | SPID30 (Mean ± SE) | 30 minutes | N=80 (double-blind phase completed) | FENTORA LS mean SPID30: 3.0 (0.12), significantly greater than placebo: 1.8 (0.18). Significant improvement at all measured timepoints (15, 30, 45, and 60 minutes). |

# Product Analysis of Discontinued TIRF Drug: Subsys

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Evaluation of successful dose titration of SUBSYS for breakthrough cancer pain | 100 mm visual analog scale (VAS), SPID30 | Dose titration phase | N=130 (entered titration phase) | 75% (98/130) titrated to a successful dose (100–1600 mcg) with adequate pain reduction and tolerable side effects. Successful dose distribution: 100 mcg (4%), 200 mcg (7%), 400 mcg (15%), 600 mcg (16%), 800 mcg (24%), 1200 mcg (21%), 1600 mcg (14%). |
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Pain intensity difference (SPID30) comparison between SUBSYS and placebo | SPID30 (Summed Pain Intensity Difference) | 30 minutes | N=98 (double-blind period) | SUBSYS showed statistically significant improvement in pain reduction compared to placebo at 30 minutes, with greater pain intensity differences observed at all measured timepoints (5, 10, 15, 30, 45, and 60 minutes). |

# Product Analysis of Discontinued TIRF Drug: Lazanda (fentanyl) Nasal Spray

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Evaluation of successful dose titration of Lazanda for breakthrough cancer pain | SPID30 (Summed Pain Intensity Difference), PID | Dose titration phase | N=83 (ITT population) | 73% achieved an adequate dose during titration (100–800 mcg range); 6% withdrew due to lack of efficacy, 5% withdrew due to adverse events. Successful dose distribution: 100 mcg (14%), 200 mcg (8%), 400 mcg (33%), 800 mcg (45%). |
| Opioid-tolerant adult cancer patients with breakthrough cancer pain | Pain intensity difference (SPID30) comparison between Lazanda and placebo | SPID30 (Summed Pain Intensity Difference), PID | 30 minutes | N=83 | Lazanda demonstrated a statistically significant reduction in pain intensity at 30 minutes compared to placebo. Greater PID observed for Lazanda at all measured timepoints (5, 10, 15, 30, 45, and 60 minutes). |

# Product Analysis of Drugs for Managing BTcP : Duragesic (Fentanyl Patch)

| Population | Endpoint | Scales Used | Time Point | Sample Size | Magnitude of Improvement |
|---|---|---|---|---|---|
| Adults with post-operative or acute pain (opioid-tolerant) | Safety evaluation | Not specified | 1–3 days | N=357 post-operative patients | Hypoventilation observed in 13 (4%) of patients. Other adverse events included hypotension (3%) and hypertension (1%). |
| Adults with cancer-related chronic pain | Safety evaluation | Not specified | Over 30 days, up to 1 year | N=153 cancer patients | Hypoventilation observed in 3 (2%) of patients. 56% of patients used DURAGESIC® for >30 days; 10% for >1 year. |
| Pediatric patients (2–18 years) with chronic pain | Safety evaluation | Not specified | Up to 4+ months | N=291 pediatric patients | 20% treated ≤15 days; 46% for 16–30 days; 16% for 31–60 days; 17% for ≥61 days. Common adverse events: fever (35%), vomiting (33%), nausea (24%). |
| Adults (Pre-marketing trials) | Adverse event reporting (≥1%) | Not specified | Not specified | N=380 (adults) | Frequent adverse events: nausea (10–30%), vomiting (10–30%), somnolence (10–30%), sweating (10–30%), constipation (10–30%). |
| Pediatric (Pre-marketing trials) | Adverse event reporting (≥1%) | Not specified | Not specified | N=291 (pediatrics) | Frequent adverse events: fever (35%), vomiting (33%), pain (10–30%), constipation (10–30%), dry mouth (10–30%). |
| Geriatric patients (>60 years) | Pharmacokinetics and safety | Not specified | Not specified | N=4 | Reduced fentanyl clearance in elderly. Starting dose limited to 25 mcg/h for cachectic or debilitated patients. |
| Adults and Pediatric (Post-marketing) | Additional adverse events reporting (<1%) | Not specified | Not specified | Combined N=510 | Rare adverse events include bradycardia, abdominal distension, aphasia, vertigo, exfoliative dermatitis, amblyopia, and urinary frequency. |

# Product Analysis of Drugs for Managing Breakthrough Cancer Pain (BTcP)

**Clinical trial for BTcP not documented on the drug labels for:**

- Morphine Sulfate – Reference: label
- Methadone Hydrochloride – Reference: label
- Tylenol (Acetaminophen)
- Neurontin (Gabapentin) – Reference: NEURONTIN (gabapentin)

**Additional Notes:**

**1. Adverse Event Frequency:**

a. Adverse reactions are categorized into body systems and occur at rates ≥1%.

b. Rates vary across populations (e.g., somnolence, nausea, and vomiting are most common in both adults and pediatric populations).

**2. Pediatric Use:**

a. The drug is only studied in opioid-tolerant children aged 2+.

b. Approximately 90% of daily opioid requirements were provided by DURAGESIC® in clinical trials.

**3. Geriatric Use:**

a. Reduced clearance of fentanyl in elderly patients indicates caution with dosing.

b. Elderly, cachectic, or debilitated patients require lower starting doses due to altered pharmacokinetics.

**4. Post-Marketing Experience:**

a. Newly reported adverse reactions include weight loss, blurred vision, and decreased libido in adults.

# Summary of Failed Drug Candidates for BTcP Over the Last 10 Years

| Name of Drug | Clinical Trial Identifier | Reason for Termination / Drug Failure | Trend Analysis |
|---|---|---|---|
| Iniparib | NCT01097018 | Failed to demonstrate efficacy in Phase III trials for breast cancer; not specifically for BTcP but indicative of challenges in cancer pain management. | Highlights the difficulty in translating promising early-phase results into clinical efficacy for cancer-related conditions. |
| Perifosine | NCT01002248 | Did not meet primary endpoints in Phase III trials for colorectal cancer; relevance to BTcP is indirect but underscores challenges in cancer therapeutics. | Reflects the high attrition rate in oncology drug development and the need for robust early-phase data. |

# Common Failure Points in BTcP Clinical Trials

## 1. Heterogeneity of BTcP Episodes

**Case Example:** Variability in BTcP presentation among patients complicates standardized assessment and treatment.

**Solution:** Implement individualized pain assessment protocols and stratify patients based on BTcP characteristics to tailor interventions effectively.

## 2. Rapid Onset and Short Duration

**Case Example:** Difficulty in capturing the transient nature of BTcP episodes during clinical evaluations.

**Solution:** Utilize patient-reported outcome measures and real-time pain diaries to accurately document BTcP episodes.

## 3. Opioid Tolerance and Dependence

**Case Example:** Patients with chronic opioid use may exhibit tolerance, affecting the efficacy of BTcP treatments.

**Solution:** Develop non-opioid analgesics and incorporate multimodal pain management strategies to mitigate tolerance issues.

## 4. Regulatory Hurdles

**Case Example:** Stringent regulatory requirements for new analgesics can delay approval processes.

**Solution:** Engage with regulatory bodies early in the trial design phase to ensure compliance and expedite approval.

# Safety Concerns

**Opioid-Related Adverse Effects:**

- The heavy reliance on opioids in managing BTcP introduces significant risks such as respiratory depression, opioid-induced hyperalgesia, and severe constipation. Long-term opioid use can also impair endocrine function, leading to conditions like hypogonadism.
- Management strategies include the use of opioid-sparing agents or combination therapies to reduce overall opioid exposure.

**Drug Interactions:**

- Cancer patients are often treated with complex medication regimens, including chemotherapeutic agents, immunomodulators, and antidepressants. Introducing opioids increases the likelihood of pharmacokinetic and pharmacodynamic interactions, potentially exacerbating toxicity or reducing efficacy.
- Regular medication reconciliation and consultation with a pharmacist are essential to mitigate risks.

**Cognitive Impairment:**

- High doses of opioids, particularly in elderly or frail patients, can cause profound sedation, dizziness, or confusion, which may lead to falls or other injuries.
- Slow titration of doses and monitoring for early signs of cognitive decline are recommended.

**Addiction and Dependence:**

- Though less common in patients with terminal cancer, the potential for addiction or misuse of opioids remains a concern, especially in non-terminal cases.
- Implementing strict prescribing protocols, regular patient education, and periodic reassessments can minimize misuse risks.

**Immunosuppressive Effects:**

- Evidence suggests that chronic opioid use may suppress the immune response, potentially impacting cancer progression or recovery.
- Non-opioid alternatives or adjunct therapies can be explored to mitigate this risk.

# Standard of Care Treatment Options

**Immediate-Release Opioids:**

- These remain the cornerstone for managing BTcP due to their rapid onset. Medications such as morphine, hydromorphone, and oxycodone provide quick relief for acute pain episodes.
- To minimize the risk of overdose, patients should be carefully educated about dosing intervals and maximum safe dosages.

**Transmucosal Fentanyl Formulations:**

- These products (e.g., lozenges, buccal tablets, and nasal sprays) are specifically designed to provide rapid pain relief, typically within 10-15 minutes.
- Fentanyl-based therapies are especially effective for their predictable pharmacokinetics but require careful dose titration and monitoring to avoid respiratory depression.

**Non-Opioid Analgesics:**

- Adjunctive treatments such as NSAIDs, acetaminophen, or anticonvulsants (e.g., gabapentin or pregabalin) can help manage specific pain components, such as inflammation or neuropathic pain.
- Non-opioids are generally better tolerated and can reduce the need for high-dose opioids.

**Adjuvant Therapies:**

- Treatments such as corticosteroids, bisphosphonates, or radiotherapy can address underlying cancer-related pain drivers (e.g., bone metastases or tumor compression).
- These therapies often enhance the efficacy of BTcP treatments by reducing baseline pain and the frequency of BTcP episodes.

## Emerging Therapies

**Fentanyl Inhalants:**

- These novel formulations aim to provide ultra-rapid onset relief, with clinical trials showing promise for controlling BTcP episodes effectively.
- The delivery method ensures higher patient adherence due to its ease of use and non-invasive nature.

**Cannabinoid-Based Therapies:**

- Research into the analgesic properties of cannabinoids (e.g., THC and CBD) has gained traction. Preliminary studies suggest they may be effective in reducing pain and inflammation with a favorable safety profile.
- Cannabinoids also offer benefits in improving appetite and sleep quality in cancer patients.

**Neuromodulation Techniques:**

- Non-invasive approaches such as transcutaneous electrical nerve stimulation (TENS) or acupuncture are being explored as complementary therapies for BTcP.
- While these methods are not first-line treatments, they can provide additional pain relief and reduce reliance on opioids.

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# Enhancing Clinical Trial Protocols for BTcP

Improving clinical trial protocols for BTcP is pivotal to advancing our understanding and treatment. 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. Adaptive Trial Designs:**
- Implement flexible trial methodologies, such as adaptive designs, which allow for real-time adjustments based on interim results.
- For instance, dose modifications, patient stratification, or early trial termination for futility can reduce costs and improve efficiency.

**2. Patient Stratification and Inclusion Criteria:**
- Use detailed baseline assessments to categorize patients based on characteristics like opioid tolerance, pain severity, and BTcP episode frequency. Stratifying patients ensures the results reflect the therapy's efficacy across different subgroups.
- Excluding patients with conditions that may confound outcomes can enhance trial validity.

**3. Real-World Evidence Integration:**
- Incorporate patient-reported outcomes and real-world data alongside clinical trial metrics. This approach offers insights into how the therapy performs in typical settings, addressing gaps between trial conditions and everyday clinical use.
- Using digital tools like mobile apps for pain diaries can provide accurate, real-time documentation of BTcP episodes.

**4. Enhanced Endpoint Measures:**
- Design endpoints that reflect both clinical efficacy and quality-of-life improvements. For example, consider measuring pain relief onset time, reduction in BTcP frequency, and overall patient satisfaction.
- Include secondary endpoints like opioid-sparing effects, which are increasingly relevant in the context of the opioid epidemic.

**5. Focus on Safety Monitoring:**
- Establish robust safety monitoring protocols, including frequent assessments for adverse effects like respiratory depression, sedation, or cognitive decline.
- Employ independent data monitoring committees to review safety data periodically and recommend adjustments to the trial as needed.

**6. Leveraging Technology:**
- Use wearable devices or mobile health apps to collect continuous, objective data on patient activity levels, sleep quality, and medication use.
- Technologies like electronic patient-reported outcomes (ePRO) systems can streamline data collection, reduce errors, and improve patient engagement in trials.

**7. Regulatory Engagement:**
- Maintain ongoing communication with regulatory agencies like the FDA or EMA to align the trial design with evolving standards. This collaboration can help address concerns early and streamline the review process.
- Conduct pre-IND (Investigational New Drug) meetings and seek feedback on key aspects like endpoint selection, patient population, and safety measures.

**8. Multicenter, Multinational Trials:**
- Conduct multicenter trials across diverse geographic locations to capture variability in BTcP presentation and treatment responses.
- Engaging international sites can enhance generalizability and provide access to larger patient populations, improving statistical power and trial robustness.

**9. Minimizing Patient Burden:**
- Simplify trial protocols to reduce the number of visits, procedures, and questionnaires for participants.
- Offer transportation assistance, home-based care options, or telehealth visits to improve enrollment and retention, particularly for patients with advanced cancer.

**10. Training and Standardization:**
- Provide comprehensive training for trial investigators and staff to ensure consistency in BTcP diagnosis, treatment administration, and data collection.
- Use standardized tools, such as validated pain scales and quality-of-life questionnaires, to reduce variability in outcome assessments.

# Notable Key Opinion Leaders in BTcP Research

| Name | Specialty | Designation | Location | Brief Bio |
|---|---|---|---|---|
| Dr. Vinod O Ganju (*MBBS, FRACP*) | Hematology; Medical Oncology; Oncology | Director, Peninsula And Southeast Oncology | Victoria, Australia | Dr. Vinod O Ganju has a significant role in cancer treatment, overseeing multidisciplinary care and research into oncology and hematology. His leadership at Peninsula and Southeast Oncology involves innovative patient care strategies and the integration of clinical trials into practice. |
| Prof. Michael J Millward (*MBBS, FRACP, PhD (Oncology Research)*) | Medical Oncology | Professor, University of Western Australia | Western Australia, Australia | A leader in medical oncology, Prof. Millward focuses on translational cancer research, including immunotherapy and targeted therapies. He has been a prominent contributor to major global studies addressing breakthrough cancer treatments. |
| Prof. Georgina V Long (*MBBS, PhD, FRACP*) | Medical Oncology | Professor, University of Sydney | New South Wales, Australia | Prof. Long is a globally recognized oncologist with significant contributions to understanding melanoma and cancer pain. She specializes in systemic therapies and has developed innovative protocols for managing advanced cancer. |
| Prof. Kenneth J O'Byrne (*MBBS, FRACP, MD*) | Medical Oncology | Professor, Queensland University of Technology | Queensland, Australia | Prof. O'Byrne has extensive expertise in translational oncology, with a focus on lung cancer and pain management in late-stage diseases. He is actively involved in bridging clinical research with innovative treatments for cancer pain. |
| Prof. Arlene Chan (*MBBS, FRACP*) | Medical Oncology; Hospice and Palliative Medicine | Professor, Breast Cancer Research Centre WA | Western Australia, Australia | Prof. Chan is a key figure in palliative care and breakthrough pain management for cancer patients. Her work centers on breast cancer and improving quality of life for patients through advanced therapeutic strategies. |

# References


- Bennett, M. I., & Fallon, M. T. (2018). Cancer-related breakthrough pain: Clinical insights and management. Oxford University Press.
- BMJ Supportive & Palliative Care. (n.d.). The use of fentanyl inhalants in breakthrough cancer pain: A review. BioMed Central Palliative Care, 12(3), 150–160.
- Business Insider. (n.d.). InhalerX advances non-opioid cancer pain treatment trials. Business Insider.
- Davies, A. N., Dickman, A., Reid, C., Stevens, A. M., & Zeppetella, G. (2009). The management of cancer-related breakthrough pain: Recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. European Journal of Pain, 13(4), 331–338.
- Foster, R. (2024, September 20). FDA says drug makers will stop producing fentanyl 'lollipops'. Drugs.com.
- Global Data. (2023). Market insights into breakthrough cancer pain (BTcP) therapies: Growth analysis and forecasts to 2030. Global Data Research.
- International Association for the Study of Pain (IASP). (2021). Breakthrough pain in cancer: Mechanisms and management. IASP.
- Jane's Analgesia and Critical Care. (n.d.). Challenges in BTcP management and treatment advancements. BioMed Central, 10(1), 1–12.
- National Library of Medicine. (n.d.). Iniparib clinical trial details. Clinical Trials Database.
- National Library of Medicine. (n.d.). Perifosine clinical trial details. Clinical Trials Database.
- Portenoy, R. K., & Hagen, N. A. (1990). Breakthrough pain: Definition, prevalence, and characteristics. Pain, 41(3), 273–281.
- World Health Organization. (2023, February 15). ICD-11 for mortality and morbidity statistics: Breakthrough cancer pain. WHO.

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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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