

A Health Economic Model of Breakthrough Pain

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Breakthrough pain (BTP) is an abrupt onset, transitory flare of pain occurring in the context of managed, chronic, baseline cancer pain. BTP builds to a moderate or severe intensity, usually peaking within 3 to 5 minutes after onset; episodes last approximately 30 minutes. To distinguish it from inadequate background analgesia, BTP is usually defined as 4 or fewer episodes in a 24-hour period.²

BTP prevalence estimates among cancer patients vary from 24% to 95%, depending on the definition of BTP and the setting from which the study sample was drawn. A 63% prevalence of BTP has been observed in patients admitted to hospice with nonmalignant terminal disease.³ This paper focuses on cancer-related BTP—the most frequently studied BTP scenario with the widest portfolio of US Food and Drug Administration–approved or developing pharmacologic interventions.

Background

Pharmacologic and Nonpharmacologic Management of BTP. A solid body of literature establishes the importance of BTP, as well as detailing strategies for its management; however, despite this available information, undertreatment remains a common phenomenon. In a study of guideline-based pain management versus standard care, Du Pen et al demonstrated that a substantial reason for undertreatment of cancer pain in general is underdosing of rescue medication for BTP.⁴ Strategies for managing cancer-related BTP include nonopioid medications (eg, nonsteroidal anti-inflammatory drugs, acetaminophen), short-acting opioids (eg, codeine, hydrocodone, morphine, oxycodone, hydromorphone, fentanyl), and nonpharmacologic strategies (eg, ice, heat, guided imagery). Oral short-acting opioid formulations are most effective for preemptive management of BTP in patients who suffer predictable moderate-to-severe episodes and who do not respond to nonopioid or nonpharmacologic strategies. Rapid-onset transmucosal lipophilic opioids are recommended for patients with unpredictable moderate-to-severe incident or idiopathic BTP.⁵ Other strategies, such as radiotherapy, neurosurgical procedures, acupuncture,^{6,7} intrathecal and epidural infusions, neurolytic blocks, and yoga, can factor importantly into the management of cancer pain in general, and improvement in BTP is a corollary outcome in these clinical scenarios.

Abstract

Although the literature adequately addresses the biologic basis, epidemiology, and management of breakthrough pain (BTP), it does not yet describe the full impact of this troubling, widespread phenomenon. The risks of a scanty understanding of BTP impact are failure to take preventive measures, underdiagnosis, undertreatment, and inappropriate management. Studies to date of the impact of BTP have followed pharmacoeconomic approaches. Building on prior efforts, this paper develops a more comprehensive health economic model that encompasses the full spectrum of costs, outcomes, risks and benefits associated with BTP and its management. The authors provide a rubric within which stakeholders—including providers, institutional leaders, administrators, and policy-makers—can systematically balance the myriad potential effects of different treatment scenarios to guide decision-making. The paper then extends this model to the population level, providing a template for health economic analysis of alternate strategies for managing BTP, and delineating steps for accomplishing the analysis.

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For author information and disclosures, see end of text.

■ **Table 1.** Difference in Methodology of Pharmacoeconomic Approaches*

Approach	Measurement of Benefit/Outcome	End Point of Analysis
Cost-benefit analysis	Always valued in monetary units (eg, amount the patient is willing to pay to avoid pain)	Net benefit (benefits minus costs) or benefit-cost ratio (benefits/costs)
Cost-effectiveness analysis	Measured in similar natural units (eg, life-years gained)	Cost per unit (eg, cost per life-year gained)
Cost-utility analysis	Valued based on individual preference-based units (eg, quality-adjusted life-years [QALYs])	Cost per unit (eg, cost per QALY)
Cost-minimization analysis	Assumed equivalent, regardless of unit	Compare cost of strategy X vs strategy Y

*Adapted from Reference 10.

Impact of BTP

BTP exacts a significant toll on patients, their families, caregivers, and social networks; the health-care system; and society at large. These consequences are physical, emotional, spiritual, social, and financial in nature. BTP in cancer patients is reported to be associated with decreased functional status, increased levels of anxiety and depression, greater dissatisfaction with opioid treatment, and poorer medical outcomes.^{8,9} Studies to date, however, have not yet taken a comprehensive approach to delineating the impact of BTP on patients, providers and institutions, and society. Additional work is needed to describe and enumerate the full aspects of suffering caused by BTP; a critical first step will be the development of instruments that are sensitive and specific to quality-of-life (QOL) domains differentially affected by BTP.⁹

Purpose

The primary purposes of this paper are as follows: (1) to summarize the costs and benefits associated with BTP and its treatment, as described to date in the cancer population; (2) to present a framework that clinicians can use to guide their decision-making for patients with BTP; and (3) to provide a model for health economic analysis, on a population level, of alternate strategies for the management of BTP, and to delineate steps for accomplishing the analysis. We begin by drawing on the pharmacoeconomic approach, which entails systematic quantification of the costs, risks, and benefits of medical interventions.¹⁰

Pharmacoeconomic Analysis: The Foundation for a BTP Health Economic Model. Most pharmaco-

economic analyses employ 1 of 4 methods: cost-minimization analysis, cost-effectiveness analysis, cost-benefit analysis, and cost-utility analysis. All of these approaches measure costs in monetary units, but they differ in how they value outcomes¹⁰ (Table 1). Pharmacoeconomic analyses typically categorize costs into 3 basic types—direct, indirect, and intangible. Direct costs include fixed and variable medical costs (eg, hospital capital expenses, costs of medical treatment) and nonmedical costs (eg, transportation to the clinic). Indirect costs encompass the costs of morbidity and mortality because of the illness or health event, and include lost income and time spent in the waiting room. Intangible costs comprise the toll of psychosocial states resulting from the illness or health event, such as suffering, pain, or depression.¹¹

Once costs have been defined, pharmacoeconomic analyses proceed to assign values to cost items and outcomes, determine outcome probabilities, and compare costs with benefits. One such process, presented by Jolicoeur et al, delineates a method for conducting pharmacoeconomic analysis in 10 steps: (1) defining the problem, (2) determining the study’s perspective, (3) determining the alternatives and outcomes, (4) selecting the appropriate pharmacoeconomic method, (5) placing monetary values on the outcomes, (6) identifying study resources, (7) establishing the probabilities of the outcomes, (8) applying decision analysis, (9) discounting costs or performing a sensitivity or incremental cost analysis, and (10) presenting the results, along with any limitations of the study.¹⁰ Other structures may prove equally useful, the critical step in any such analysis being the balancing of costs against benefits. The utility of this step will depend

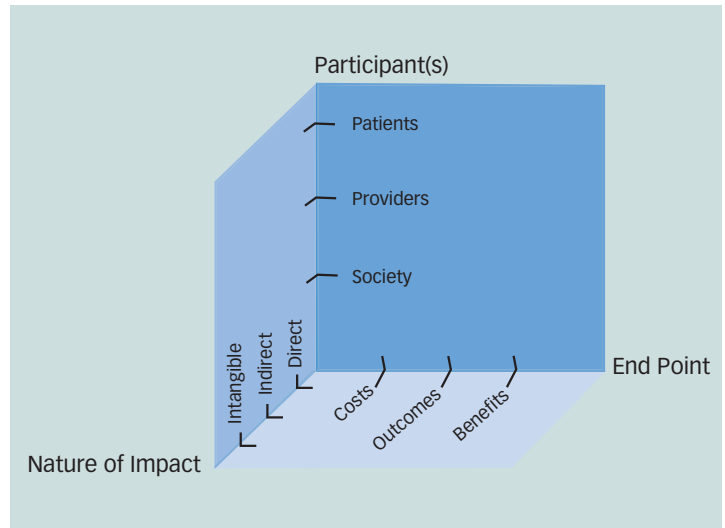
fundamentally on the extent to which both sides of the equation thoroughly capture the impacts of the intervention.

Limitations of Pharmacoeconomic Studies to Date

Most pharmacoeconomic studies in pain have focused on the cost repercussions of chronic pain rather than on BTP. In 1994, the Cancer Pain Panel of the Agency for Healthcare Policy and Research (renamed the Agency for Healthcare Research and Quality; AHRQ) developed a 13-point framework for cost analysis related to cancer pain. This AHRQ framework covers medical costs, cost savings associated with different settings of care, morbidity-related costs, and indirect costs to patients and families and was part of a highly cited monograph on cancer pain management and best practice guidelines (now retired).¹² Extending the AHRQ model, Chandler and Payne classified types of cost impact of unrelieved cancer pain into the following categories: direct medical (hospital personnel, overhead, treatment, complications), direct nonmedical (travel, hotels, meals, lost wages), indirect personal (decreased productivity, QOL), and intangible personal (pain, suffering, demoralization).¹³ In 2003, Fortner et al sought to quantify the costs set out in these 2 models by gathering, directly from patients, data related to the direct and indirect costs of cancer pain.¹⁴ In the same year, Abernethy et al published a clinical decision and economic analysis model of cancer pain management that compared the effectiveness and cost of 3 cancer pain management strategies—guideline-based care that incorporated the AHRQ cancer pain management guidelines, oncology-based care, and usual care.⁶

Overall cancer pain has been the focus of most cancer pain-related pharmacoeconomic studies; the costs of BTP, specifically, remain poorly understood. The lack of a model that depicts the true costs versus benefits of BTP management presents a very real impediment to good clinical practice, hindering consideration of cost-effectiveness and appropriate cost containment. This article builds on prior work in general cancer pain to develop a broader health economic framework that comprehensively captures the costs and other impacts of BTP in 3 key domains. This framework is intended to provide physicians with a guiding tool for clinical decision-making in

■ **Figure 1.** Health Economic Model of Breakthrough Pain



BTP scenarios, thereby averting the underdiagnosis and undertreatment of BTP that are common today. It may also support institutional and national efforts to maximize cost-effectiveness and to allocate resources in a way that best optimizes patients' QOL.

A Comprehensive Health Economic Model of BTP

Structure of the Model. Our suggested health economic framework overlays the traditional tripartite cost domains (direct, indirect, intangible) with 3 impact domains (patients, providers, society) and 3 end point domains (costs, outcomes, benefits) (Figure 1). The resulting $3 \times 3 \times 3$ rubric offers healthcare researchers, clinicians, institutions, and consumers a rational schematic depiction of BTP costs, that also integrates the potential outcomes and benefits of BTP management, and itemizes these costs, outcomes, and benefits for the full array of stakeholders affected. It offers a tangible mechanism for organizing evidence in clinical decision-making.

The model's first major domain (patients, providers, society) defines the participants affected by BTP and encompasses patients (including family members and caregivers), providers, and society at large. Cancer is experienced within a social context; hence, the consequences of the pain and the corresponding benefits of its amelioration are experienced throughout the patient's immediate social network. On the second level, providers are affected directly in that they bear the resource requirements for management of BTP, accrue many benefits of

improvement in management, or suffer the provider-level stress of treating intractable pain. Third, society at large, which includes payers and employers, experiences the impact of BTP on productivity, finances, psychosocial distress, community engagement, and opportunity costs.

The second major domain of the model (direct, indirect, intangible) denotes the nature of BTP impact. Direct effects are those that have an immediate and unmediated impact. For example, a patient's experience of pain is a direct effect of BTP pain; a medical visit and the cost of a BTP medication are direct, patient-domain impacts of BTP. Downstream effects that occur as mediated consequences of BTP are indirect costs. Examples of indirect consequences are the lost productivity of a caregiver or the impact on a coworker of the patient's absence from work; indirect benefits include secondary gains experienced from increased sympathy for a patient in pain. Finally, intangible aspects are those impacts that are currently beyond our ability to measure. BTP draws from societal energies, resulting in foregone opportunities and advances; these, and the intricacies of human suffering, are currently intangible costs of BTP.

The third domain of the model (costs, outcomes, benefits) structures the end points of analysis. The most recognizable end points are the costs of BTP associated with the BTP itself. Outcomes related to BTP include the results of BTP management, and range from clinical (eg, unrelieved pain, insomnia, increased inflammation) to humanistic (eg, emotional distress, reduced social interaction). Benefits represent those direct, indirect, and intangible positive effects and cost offsets attributable to effective BTP management.

Data to Populate the Model

The cost data necessary to perform a comprehensive health economic assessment of BTP are challenging to obtain. With respect to direct costs, the primary challenge revolves around the necessity to differentiate the costs that are attributable to BTP and that are incurred more than the costs of care for the cancer itself, chronic pain associated with the cancer, and comorbidities unrelated to the BTP. In the case of BTP, direct medical costs might include hospital charges, cost of analgesics and other medications, radiotherapy, surgery, and clinician time; direct nonmedical costs might include the cost of

gas to drive to the clinic, parking during a clinic visit, highway tolls, overnight lodging for family or caregivers, and meals for these individuals while attending to the patient in the hospital. Direct medical costs can be obtained from institutional and clinical accounting systems; however, diagnostic and clinical variables that link the expense to episodes of BTP are nonexistent, making direct accounting for BTP much more problematic than it first appears. Direct nonmedical costs can be calculated once the types of costs are enumerated and the corresponding direct medical event is linked to the BTP episode.

Indirect costs become more difficult to identify in full and, likewise, to compute. Indirect costs for BTP might encompass, for example, lost income as a result of time taken off work for a BTP episode, a spouse's or caregiver's lost income because of time off work, or the expense of extra household help. These costs carry a monetary price tag but are not directly related to the health issue at hand. Many indirect costs can be documented only through the direct report of patients; obtaining this information is becoming more feasible with recent advances in data collection. Specifically, novel information technology allows for the gathering of information directly from patients regarding how they value various costs and outcomes. Patient-reported values can now be integrated into the analysis to create a more comprehensive model of costs and benefits, one that can guide clinicians in their decision-making with a truer depiction of the impact of possible treatment paths.

Intangible costs, which by their nature elude quantifying, have typically been omitted from many pharmacoeconomic studies. For BTP, intangible costs include the patient's pain, suffering, depression, anxiety, loss of sleep, and fatigue, as well as the family's and/or caregiver's distress. Recent developments in clinical/research methodology enable capture of these intangibles in ways not previously possible. New technologies such as the e/Tablet—a wireless notebook-and-pen-style personal computer—have been validated as methods for collecting research-quality, patient-reported outcomes; these data can include scores for intangible costs such as depression, fatigue, anxiety, and QOL.¹⁵

In our model, costs are balanced against the values assigned to benefits of appropriately preventing, managing, or treating BTP. Benefits attributable to BTP are direct and indirect cost savings, symptom

improvement, positive qualitative outcomes, and any improvement in intangible factors above and beyond baseline expectations established for the care and the outcomes of underlying chronic cancer pain.

Application of the Model. To use this framework in a clinically meaningful way, the clinician must pull together all of the diverse costs, benefits, and outcomes associated with the BTP phenomenon; apply currently best-available methods for assigning values to those factors; and present the values in an accessible, functional format that facilitates clinical evaluation of treatment options. We will demonstrate this method below, after briefly describing available evidence to assist in the process.

Current State of Knowledge for Pharmacoeconomics of BTP

Pharmacoeconomic studies have examined the cost-utility and cost-effectiveness of a variety of pain types, including chronic spinal pain,¹⁶ chronic low back pain,¹⁷ neuropathic pain,¹⁸ pain postcraniotomy,¹⁹ and anterior cruciate ligament reconstruction.²⁰ In parallel, BTP itself, as distinct from chronic cancer pain and other nonmalignant pain, has been characterized and described in the literature.^{3,7} It is reasonable to assume that BTP is included in more general studies of cancer pain, and accounts for a significant portion of the variance in, or effect of, pain intensity, character, and impact. Few studies, however, have assessed the cost and benefit elements associated with BTP specifically, and none have presented a pharmacoeconomic framework for or analysis of BTP. The preliminary evidence that does exist uniformly suggests the following: (1) BTP results in financial burden on multiple levels, in addition to significant indirect and intangible costs; and (2) the financial, psychosocial, logistical, and symptom-related impact of BTP for diverse stakeholders may be ameliorated through improved clinical care and effective pharmacologies of BTP.

The current, albeit limited, available pharmacoeconomic data for BTP derive from the studies described below. Results from these studies have been used to populate **Tables 1 through 3**, delineating the impact of BTP in each of the model's domains. An analytic, health economic approach to BTP begins with itemization of, and assignment of value to, the costs on one hand, and the cost offsets and benefi-

cial outcomes on the other. The domains in our model clarify in which the burden of costs falls, and for which the benefit of savings and outcomes accrues. This format will facilitate communications and make information readily accessible to interested parties in decision-making.

Principal Studies Providing Pharmacoeconomic Data for BTP. A multicenter trial studied adult patients who suffered from noncancer pain and who took (1) an opioid medication on a regularly scheduled basis for persistent pain, plus (2) a stable dose of short-acting oral transmucosal fentanyl citrate (OTFC) for BTP for at least 2 weeks.⁹ Patients completed a structured assessment of the impact of BTP on their QOL; this assessment specifically included the dimension of "finances." Patients indicated that 2 of the 4 most frequent negative impacts of BTP were "ability to work (both outside the home and housework)" (93%) and "finances" (81%). These factors ranked alongside QOL constructs such as "enjoyment of life" and "general activity level."

One-hundred forty-four responses to a survey of 373 cancer outpatients attending regularly scheduled oncology visits demonstrated that BTP predicts greater costs in cancer patients.¹⁴ Patient-rated severity of BTP pain was measured by the first item of the Brief Pain Inventory (eg, worst pain in the past 24 hours)²¹; simultaneously, patients completed a questionnaire developed to measure direct and indirect costs of pain incurred during the previous 3 months. Of the 373 cancer patients, 144 (39%) reported experiencing cancer-related pain, and 33 of these (23%) reported BTP. Sixty-nine percent of patients had experienced some type of direct medical cost related to pain; these patients reported direct medical costs averaging \$825 per month. BTP patients had higher direct pain-related costs (mean for patients with BTP \$1080 vs \$750 for patients without BTP) and indirect costs (mean for patients with BTP \$88 vs \$53 for patients without BTP).

The largest study designed to measure the costs of BTP utilized a computerized, semistructured, telephone survey of 1000 community-based cancer patients, 160 of whom had clinically significant BTP requiring pharmacologic treatment.⁸ BTP patients reported more hospitalizations (1.0 hospitalization per year vs 0.4 among cancer patients without BTP), with longer hospital stays per event (7.1 vs 4.1 days).

■ **Table 2.** BTP Costs

	Patient/Caregiver	Provider/Institution	Society/Payer
Direct medical costs	Copayments, deductibles, ¹⁴ out-of-pocket expenses ¹³ for: analgesics, BTP-related office visits, BTP-related emergency department visits, and BTP-related hospitalizations ¹⁴	Provider portion of: \$1550/day average of published costs for hospitalizations for uncontrolled cancer pain ²² \$400/day average cost of emergency department visit ²² \$150 average cost of office visit ²² Costs of analgesic medication for BTP (eg, \$204/mo for transdermal fentanyl, \$381/mo for IV morphine ¹⁴)	Payer portion of: \$1550/day average of published costs for hospitalizations for uncontrolled cancer pain ²² \$400/day average cost of emergency department visit ²² \$150 average cost of office visit ²² Costs of analgesic medication for BTP
Direct nonmedical costs	Transportation to BTP-related medical visits ¹³ ; increase or change in pain medication; child care; household help; pain therapy not covered by insurance; special items for pain (eg, hot water bottle); alternative pain relief methods ²² (eg, massage)	Administrative time for scheduling, billing, and related functions	Third-party administrative load for handling insurance claims
Indirect costs	Educational materials for pain management; counseling, psychotherapy related to pain ²² ; lost earnings or productivity ¹³	Preparation and delivery of medications, ¹⁴ medical procedures, and technologies; preparation and delivery to patients and families/caregivers of cancer pain education	Allocation of medical technology and capacity to BTP vs other needs; higher taxes; higher insurance premiums ¹⁴
Intangible costs	Reduction in quality of life, including: pain, suffering, anxiety, depression; impaired function; stress; strain on family and friends ^{13,14}	Clinician stress; additional burden on clinic operations; clinic or hospital crowding	Ethical “cost” of not adequately caring for patients with pain

BTP indicates breakthrough pain; IV = intravenous.

The BTP patients’ total cost per year for reported pain-related hospitalizations was \$1.7 million versus \$192,000 for non-BTP patients. BTP patients also reported more emergency department visits for pain (1.3 vs 0.5 per year), resulting in greater estimated average cost per year for emergency department visits (\$84,000 vs \$19,000). BTP patients reported more outpatient doctor visits per year for pain (4.2 vs 0.6), resulting in a greater cost per year for physician office visits (\$103,000 vs \$7000). BTP patients averaged higher total pain-related costs per year (\$12,000 vs \$2400). Examination of total pain-related costs for the entire sample revealed that BTP patients accounted for 90% of costs, and that these costs were primarily attributable to BTP-related hospitalizations.

In the context of these findings, an additional study suggests that quality improvement in BTP clinical management may reduce BTP-related medical costs. The Zero Acceptance of Pain Quality Improvement Project examined 207 patients before and 211 patients

after the implementation of a pain improvement program focusing on assessment and education of patients with pain in community oncology. Patients completed the Brief Pain Inventory and a survey (similar to that described previously) evaluating direct and indirect costs related to pain. Pre- and post-results showed significant improvement in decreasing pain-related costs, particularly direct costs²²; the preceding study suggests that these costs, and cost savings, are largely attributable to BTP and its management.¹⁴

Preliminary evidence suggests that treatment with short-acting OTFC reduces BTP-related costs. A multicenter study conducted by Taylor et al administered a patient-reported survey to 43 patients who had a mean BTP intensity score of 9 on a 0 to 10 scale.⁹ These patients reported that the areas of their lives most affected by BTP were “general activity level” (93%) and “ability to work, both outside the home and housework” (93%). Among these patients, 37% reported that short-acting fentanyl had

Table 3. BTP Outcomes (due to results of BTP management)

Direct Impact	Patient/Caregiver	Provider/Institution	Society/Payer
Direct medical	Change in patient-borne costs related to BTP outcome ^{13,14}	Change in clinician time; hospitalizations; emergency department utilization	Change in payer obligation due to BTP outcome
Direct nonmedical	Change in expenditures on: transportation ¹³ ; parking; lodging; meals; other items directly related to BTP outcome	Hospital/clinic overhead; administrative costs ¹³	Impact on administrative load for payers
Indirect impact	Impact on income (patient); impact on income (family or caregiver) ¹³ ; additional downstream expense due to change in sleep, ¹⁴ inflammation, other health factors	Impact on efficiency of services and on quality of care; changes made to patient education and support activities	Impact on worker productivity; insurance premiums; taxes ¹⁴
Intangible impact	For patients and caregivers, change in QOL including: anxiety, depression, fatigue, insomnia; impact on social interactions; change in functional status ^{13,14}	Impact on provider stress and workload burden; opportunity costs and allocation of resources	Contribution of patients and caregivers to society; creation/alleviation of scarcity in health resources; opportunity costs

BTP indicates breakthrough pain; QOL, quality of life.

improved their finances “very much” or “somewhat,” and 53% reported that it had improved their ability to work “quite a bit” or “very much.”

Evidence from a retrospective chart review evaluating the efficacy of short-acting fentanyl for management of BTP in an outpatient cancer pain center indicates areas of potential cost savings. Burton et al analyzed records of 39 patients experiencing recent-onset severe pain (7 or higher on a 0-10 scale); in most cases, OTFC obviated the need for hospital admission, an emergency department visit, and parenteral opioids.²³

Application of the Health Economic Model for BTP

Using data from the foregoing studies, we proceed to populate the model framework in **Tables 2 through 4**, with values assigned to costs and benefits as provided in the manuscripts reporting results of those trials. Note that the cost/outcome/benefit elements reported in the literature are footnoted; the many additional elements appearing in these tables warrant inclusion in a comprehensive health economic analysis, and are presented here as suggestions for future inquiry, although they have not yet been published. Suggested elements are not meant to be

exhaustive, but rather this framework is presented as a working template that the clinician, administrator, institution, or policymaker can adapt and complete so as to best inform treatment and policy decisions.

Case Illustration of Model Application

Megan is a 61-year-old woman with multiple myeloma. She has experienced usual pain rating 2 to 3 on a 0 to 10 scale for the past 5 months, due to a tumor deposit in her right ribs. Three months ago, Megan began experiencing episodes of shooting pain in her ribs lasting 20 to 60 minutes per occasion and rating 9 to 10 in intensity; she has suffered 4 such episodes. Because of these BTP episodes, Megan visited her doctor twice per month for 3 months. Her oncologist adjusted long-acting opioids, short-acting opioids, nonopioid analgesics, and her anticancer treatments; eventually, radiotherapy in combination with adequate long- and short-acting opioids succeeded in relieving her pain. Megan spent approximately 2 hours in round-trip travel for each of her visits to her doctor; she also underwent 5 radiotherapy sessions, each requiring 2 hours in travel time; and she had to quit her part-time job because of the unpredictable pain and the time required for additional clinic visits. Her travel time related to BTP thus totaled 22 hours.

■ **Table 4.** BTP Benefits and Cost Offsets

Direct Cost Savings	Patient/Caregiver	Provider/Institution	Society/Payer
Direct medical	Fewer BTP episodes and less severity of episodes ²³ result in less out-of-pocket costs to the patient/caregiver	Fewer hospitalizations, emergency department visits, office visits ¹⁴ ; less use of parenteral opioids ²³	Fewer reimbursement claims
Direct nonmedical	Fewer related expenses such as transportation to clinic, ¹³ parking	Lower administrative costs (eg, billing, scheduling, arranging urgent visits)	Lower administrative costs
Indirect cost savings	Ability to return to work ⁹ ; less expenditure on downstream supports (eg, education, psychotherapy) ²²	Clinic/hospital space adequate to handle patients' needs; clinic/hospital staffing adequate to handle patients' needs	Improved work capacity and productivity ¹³ ; income taxes paid
Intangible beneficial outcomes	Sleep, pain relief, QOL, emotional well-being, functional status, relief of fatigue ^{13,14}	Smoother operations; greater predictability of patients' needs; efficiency; less staff stress; less clinic and hospital crowding	Perception of healthcare system working to address patient needs; perception of rational, proactive health system

BTP indicates breakthrough pain; QOL, quality of life.

By the time Megan's BTP had abated, with relief defined as usual pain levels of <2 on a scale of 0 to 10 and manageable BTP of fewer than 4 episodes daily at an intensity of <2 on the same scale after 20 minutes, Megan had cycled through 3 different opioids (morphine, oxycodone, fentanyl) for differing lengths of time. She finally ended up on transdermal fentanyl, at a dose of 75 mcg every 72 hours, with short-acting OTFC at a dose of 400 mcg every hour as needed; she self-administered between 2 and 4 doses of the latter drug, daily. Additional management strategies for Megan's BTP included 800 mg of ibuprofen taken 3 times per day, guided imagery with a local counselor, and yoga class 3 times per week. Her total drug costs were \$1730 monthly, experienced by Megan as a monthly copay of \$60. The total radiotherapy cost was \$8000; Megan's personal payments for radiotherapy totaled \$300. The nonpharmacologic costs of yoga and guided imagery amounted to \$164 out of pocket monthly (\$11 per yoga class, \$30 per imagery session). A summary of her treatment costs is in **Table 5**. After achieving analgesia from the combination of opiates, nonopioids, nonpharmacologic strategies, and radiotherapy, Megan attained a good measure of freedom from pain flare-ups. She was able to cut her outpatient office visits in half, return to work at the local middle school, and once again participate in the care of her 2 grandchildren.

Given the current stage and severity of Megan's multiple myeloma, she is expected to live approximately 3 years with currently available therapies; hence, monthly costs would be multiplied by 36 to derive a total cost for managing Megan's BTP. The total cost calculation should factor in an anticipated 2 to 5 further episodes of severe BTP requiring additional attention over baseline. The clinician would consider, alongside this figure, the qualitative (unquantified) costs in terms of negative intangible impacts of her BTP. Balanced against these comprehensive costs would be the quantifiable and qualitative benefits and positive cost offsets of pursuing this aggressive BTP management strategy. This analysis will arm the clinician with a sound basis for decision-making, which will inform his discussion with Megan concerning course of treatment and adherence to regimen.

Building a Population-based Cost-effectiveness Analysis

We have now demonstrated the application, on an individual patient basis, of our health economic framework for analyzing the impact of BTP and its management. This model provides a decision-support tool for clinical practice, taking into fuller account the array of factors associated with the BTP phenomenon, across multiple stakeholders.

A next, and important, step in establishing a ra-

Table 5. Megan’s BTP Health Economic Profile

COSTS			
Direct Costs	Patient/Caregiver	Provider/Institution	Society/Payer
Direct medical	Out-of-pocket expense of generic ibuprofen, \$12/mo; analgesic copay \$60/mo*; \$30 copay on outpatient visits for BTP*; \$50 copay for radiology (rib films)*; \$50 copay for each medical oncology and radiotherapy visit*; \$132/mo for yoga classes; \$120/mo for guided imagery*	6 hr oncologist time @ \$150/hr*; 12 hr radiotherapist time @ \$35/hr*	Insurer costs of \$204/mo for transdermal fentanyl and \$1526/mo for OTFC before copay for analgesics, between \$7000 and \$9000 for outpatient visits, radiology, and radiotherapy*
Direct nonmedical	\$56 travel/mo for outpatient visits for BTP*	Clinic overhead for direct medical care	Costs for paperwork processing, customer service calls
Indirect costs	Loss of part-time job earnings of \$1000/mo	45 minutes of human resource time for tertiary support staff in billing records and facilities management; indirect cost portion of clinical overhead	Increase in group plan expenditure and resulting increase in group premium
Intangible costs	Insomnia; psychosomatic toll on husband (develops migraines); inability to attend church due to worry about BTP flare-up	Clinic time devoted to BTP care rather than innovations in disease treatment	Use of limited plan resources diverted away for plan improvement or from investment in coverage for lower-income participants
OUTCOMES, BENEFITS, AND OFFSETS			
Direct Cost Savings	Patient/Caregiver	Provider/Institution	Society/Payer
Direct medical	Reduced outpatient visits by 50%/mo results in \$150 less in copays	Reduced time spent in office visits with patient by 50%	Reduced outpatient expense of 50% (\$300/mo)
Direct nonmedical	Savings in transportation costs, parking, meals while in clinic	Reduction in clinic overhead (eg, incremental addition to facility maintenance, utilities, and others)	Reduction in paperwork and customer service costs
Indirect cost savings	Able to return to her part-time job @ \$800/mo; able to continue self-care at home rather than relying on classes and support group; resumes providing 10 hr/wk childcare for grandchild, saving \$50/mo for grown daughter	Lowered costs due to tertiary staff support of billing, records, claims, and facilities upkeep	Increased revenue for plan; improved figures for group premium
Intangible beneficial outcomes	Husband’s migraines subside; she returns to church; resumes walking for exercise; her sleep improves; anxiety abates	Increased available resources for practice improvement and program development	Increases resources for development of disease management programs and increased supportive care resources
<p>*The copays and cost/hour of providers is a general estimate of what is observed in our local practice. There is a large variance of copays and providers across hospital systems, states, and insurers. The scope of this paper does not include a global assessment of payment practices. Over-the-counter drug information, complementary therapy costs, and actual cost of prescription drugs is readily accessible, and consequently was recorded here. BTP indicates breakthrough pain; OTFC, oral transmucosal fentanyl citrate.</p>			

tional approach to decision-making with regard to BTP is to develop a population-based decision-analytic model that allows extension of the identified potential costs, outcomes, and benefits to broader populations. The advantages of developing a population-based model include the ability to (1) project the burden of cancer-related BTP in large, user-specified populations, and (2) estimate the cost-effectiveness

of employing different pain management strategies in the user-specified cohort. Audiences with a direct interest in these applications will be healthcare policy decision makers, managers of healthcare organizations, pharmacy and therapeutics committees, and active clinicians. The model assumes the perspective of the healthcare organization, such as a clinical practice setting or health insurer.

Figure 2. Application of the Health Economic Model for BTP on a Population Level

- Step 1:** Define the population and its rate of cancer.
- Step 2:** Determine the probability of BTP in the target population.
- Step 3:** Multiply the population's probability of developing BTP by its probability of using a strategy to manage BTP. (Repeat process separately for each management strategy.)
- Steps 1-3 yield the proportion and number, in the defined population, of patients using various strategies to manage BTP.**
- Step 4:** Estimate the efficacy and corresponding cost offsets of each BTP management strategy.
- Step 5:** Assign values to other positive outcomes/benefits of BTP management strategy.
- Step 6:** Estimate the costs of the BTP management strategy.
- Step 7:** Multiply the per-patient cost/outcome/benefit by the number of patients expected to use the BTP management strategy.
- Steps 4-7 yield an aggregate health economic assessment of the BTP management strategy of interest.**
- Step 8:** Calculate ICER for BTP management strategies being compared.
- Step 9:** Perform sensitivity analysis.
- Steps 8 and 9 yield: (a) the increased per-patient expense of more vs less effective BTP management strategies, and (b) an assessment of the range of variance in this figure that might be attributable to differing inputs such as probabilities, cost estimates, and benefit values.**

BTP indicates breakthrough pain; ICER, incremental cost-effectiveness ratio.

Figure 2 depicts the steps involved in applying the population-based model, with the cost/outcome/benefit values delineated in Tables 2 through 4 embedded at Steps 4 to 6.

Model application begins with definition of the population to which the model will be applied. The probability of cancer within the target cohort is defined by the user or estimated from United States cancer prevalence counts published by the National Cancer Institute. Prevalence of specific tumor types and stages of illness within the population should be used, since the rate of BTP will differ by tumor type and stage. Stratification by sociodemographic factors such as sex, race, and age will improve the model's accuracy, since cancer prevalence rates differ by these distributions. The total number of cancer cases by tumor type and stage constitutes the overall burden of cancer in the defined population.

The user then applies the rate of BTP by cancer type and stage, referring to published reports, to the defined cohort. In cases in which data are unavailable or uncertain, prevalence can be estimated using

tumor types with similar invasion patterns likely to cause similar degrees of pain (eg, rate of BTP in gastric cancer can be used to approximate that in esophageal cancer). Cumulative probability of BTP is calculated as the sum of estimates generated for all included subpopulations by tumor type. Assumptions used in estimates should be carefully noted, because this is a fertile area for future research.

Probability of developing BTP is then multiplied by probability of using various strategies to treat the BTP. Strategies used with varying frequencies among cancer subpopulations include analgesics, cancer-pain procedures, complementary and alternative approaches, and anticancer approaches. The efficacy of each strategy is estimated, ideally from published studies. As more research becomes available, new information can be added to the model.

Costs of various BTP management strategies are estimated using the pharmacoeconomic inputs described in this article. Individual costs, outcomes, and benefits would be tallied using direct, indirect, and intangible inputs. Typical daily doses of each medication are calculated using the mean number of morphine equivalents prescribed per day for each short-acting opioid type, per expert guidance. Pharmacy costs are estimated from the payer's formulary costs, or through *Red Book* values for average wholesale price using unit drug costs; generic costs can be used if a generic product is available. For parenteral opioids, Medicare fee schedules are used for medical services and durable medical equipment (DME).

Although this article, and the model description it contains, have focused on pharmacologic interventions, procedural interventions are often used for BTP as well and should be included in both the individual-level and population-based analysis. Per-patient costs by intervention category (eg, surgery) are based on the probability that a particular type of procedure (eg, percutaneous cordotomy) would be used in the intervention category and the summation of procedural costs. Judgments can be solicited from cancer, pain, anesthesiology, surgery, radiotherapy, and psychology specialists about the most common procedures that they perform and the relative frequency of each procedure. Specialists can also provide information about the services (described in terms of the *Current Procedural Terminology* [CPT] codes and/or Diagnostic Related Groups [DRG]) and DME that would be required to complete the

procedure. Each procedure type is built into a scenario based on the required components and the typical period of effectiveness; the total cost of the scenario is then determined using the Medicare CPT or DRG reimbursement for each component. A weighted per-patient cost is generated for each procedure scenario by multiplying the scenario cost with the relative frequency for the scenario; scenario costs are tallied to generate the total per-patient cost within each intervention category. Users can tailor (a) the likelihood that a nonpharmaceutical intervention category is prescribed, and (b) the cost of the intervention, based on their particular healthcare organization.

The product of (a) the probability that the medication or other action (“intervention”) will be required, times (b) the probability that the intervention will be prescribed if it is required, yields the likelihood that the intervention will be used. Multiple assumptions behind this approach need to be explicitly stated. For example, the user should specify whether the probability of patient compliance with a prescribed medication is included, whether a medication or service that is prescribed is purchased within the system, and whether it is assumed that patients who do not require an intervention do not receive it.

When the user is deciding whether to add new services, medications, or BTP management strategies to the patient’s current portfolio, an incremental cost-effectiveness ratio (ICER) can be calculated. The ICER reflects the increased expense incurred to effectively treat one more BTP patient when changing from a less effective cancer pain management strategy (strategy Y) to a more effective strategy (strategy X). The ICER is calculated according to the following formula:

$$\text{ICER} = \frac{\text{cost X} - \text{cost Y}}{\text{effectiveness X} - \text{effectiveness Y}}$$

In all cases, sensitivity analyses should be conducted to evaluate the effect of variations in clinical probabilities and cost estimates on the results. For pharmaceutical and nonpharmaceutical utilization parameters, factors with expected variations likely include the probability ranges and costs as recommended by clinical experts in these areas. One to 2 inputs are varied at a time. Worst-case and best-case scenarios are examined using cumulative changes in

the likelihood an intervention would be used and in the intervention cost. The influences of various probabilities and cost inputs on model outputs can be compared to each other by normalizing the results to a standard unit, according to the following formula:

$$\text{Influence of input} = \frac{\% \text{ change in model output}}{\% \text{ change from baseline model input}}$$

Amplification of this population-based model lies beyond the scope of this article, but represents a valid subject for further research. The ability to generate population-specific estimates of the impact of various BTP management strategies could serve to better inform institutional and policy leaders as they make decisions on healthcare resource allocation, reimbursement policy, and clinical guidelines.

Conclusion

From the patient/caregiver perspective, BTP exacts a well-documented toll on QOL and incurs personal expense. For providers and institutions, treatment of unmanaged BTP substantially raises the costs of care and places undue demands on healthcare resources. On the societal level, BTP hampers productivity and its costs strain an already overburdened payer system. By delineating the full array of factors that, taken together, describe the impact of BTP on patients, providers, and society, a comprehensive health economic model will improve clinical decision-making, optimize outcomes, and enhance satisfaction with the processes of care across all stakeholder levels.

Extension of this model to population-level analyses will help to improve institutional and societal/payer decision-making, thereby minimizing the negative effects of BTP while maximizing potential benefits and offsets of good BTP management. The results will be sound management, in aggregate, of this troubling and widespread phenomenon.

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