Breakthrough Pain in Cancer Patients: Characteristics, Prevalence, and Treatment

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As indicated in this review by Patt and Ellison, the literature pertaining to the association between transitory acute pains and chronic cancer-related pain is limited and plagued by nomenclatural problems. Nonetheless, the clinical relevance of these so-called breakthrough pains is apparent to those who treat cancer patients.

Moreover, the existing empiric evidence is sufficient to conclude that the phenomenon is prevalent, highly variable, and likely to complicate the outcome of routine opioid-based pharmacotherapy. Further research and education into the nature and treatment of breakthrough pain will occur as novel therapeutic approaches become commercially available in the near future.

Patt and Ellison’s comprehensive review describes our current understanding of breakthrough pain and the consensus regarding its management. Several issues deserve special emphasis.

Definition of Breakthrough Pain--A Paradox

The clinical relevance of breakthrough pain is suggested by the widespread acceptance of "rescue" dosing as a part of routine analgesic therapy. Techniques for the use of this supplemental treatment during fixed-schedule opioid administration evolved in the complete absence of randomized, controlled trials supporting the approach.

The acceptance of rescue dosing by clinicians and patients alike indicates that most cancer patients readily understand the difference between baseline pain and breakthrough pain, and that physicians and patients can translate this understanding into a therapeutic approach that appears to address a substantial clinical problem. Thus, the definition of breakthrough pain is characterized by a paradox: Although problematic to investigators who seek to characterize and measure this heterogeneous subtype of pain in the medically ill, the nature of the phenomenon appears to be intuitively obvious to most patients and physicians.

Development of a Valid Measurement Approach

Systematic efforts to explore the characteristics, impact, and treatment of breakthrough pain require the development of a valid measurement approach. One assessment approach has been proposed for use in epidemiologic surveys. Although this approach has not been independently validated, it has yielded informative data in two surveys and Portenoy RK et al, unpublished data] and could be considered a starting point for the development of better systems. This assessment uses standardized questions to categorize patients into three groups:

1. Those with uncontrolled baseline pain
2. Those with controlled baseline pain and no breakthrough pain
3. Those with both controlled baseline pain and breakthrough pain

The first question distinguishes patients with chronic baseline pain from those with either no clinically significant pain or pain that is recurrent. Patients are asked whether pain has been present for more than half the time that they were awake during the prior week, or whether they used a fixed-schedule opioid regimen on more than half the days during that period. Patients who answer affirmatively are considered to have chronic baseline pain.

A second question distinguishes "controlled" from "uncontrolled" baseline pain. Using a four-point
verbal rating scale, patients are asked to characterize the usual intensity of the baseline pain, ie, the intensity experienced for more than half the time that pain is present. The responses range from "absent," if the analgesic regimen is highly effective, to "usually severe." Patients whose baseline pain is usually absent, mild, or moderate are considered to have controlled baseline pain. Patients who have controlled, chronic baseline pain may be asked whether they have experienced one or more episodes of severe or excruciating pain during the past day. An affirmative response to this question distinguishes patients with both controlled baseline pain and breakthrough pain, and allows follow-up questions that specifically focus on the characteristics and impact of breakthrough pains. As described by Patt and Ellison, the characteristics that appear to be important in clinical practice include the types of breakthrough pain, their temporal features (frequency, onset, and duration), etiology and inferred pathophysiology, precipitating events (including the relationship to the fixed opioid dose), predictability, impact, and factors that reduce either frequency or intensity (including both prescribed therapies and maneuvers discovered by the patient).

**Breakthrough Pain, Opioid Responsiveness, and Outcomes**

Patt and Ellison describe the results of surveys that suggest an association between the experience of breakthrough pain and relatively poor opioid responsiveness. Breakthrough pain could be an indicator of a more severe pain syndrome overall, which is characterized by a reduced response of the baseline pain to optimally administered opioid therapy. Alternatively, only the breakthrough pain itself may be difficult to relieve and thereby reduce the likelihood of a favorable response. Regardless, clinicians must recognize that the presence of breakthrough pain may indicate a challenging pain syndrome and require special attention.

Recent data also suggest that the presence of breakthrough pain may be associated with adverse outcomes related to both physical and psychosocial functioning. A survey of 178 cancer patients noted that patients with breakthrough pains reported significantly greater impairment on validated measures of pain-related functional interference and mood than those without these pains.[Portenoy RK et al, unpublished data] Although additional studies are needed to clarify this association, the data underscore the importance of breakthrough pain as an issue in clinical practice.

**Available Therapeutic Approaches**

Patt and Ellison describe the many therapeutic approaches available for breakthrough pain. They appropriately emphasize the importance of the assessment in selecting treatments. In some cases, breakthrough pain can be ameliorated by treatment of an underlying cause. This treatment can be directed against a structural problem (such as radiotherapy to a bone metastasis) or a physiologic process (such as the effective use of an antitussive to treat cough-induced breakthrough pain).

Patt and Ellison also correctly note that some patients appear to experience fewer or less intense breakthrough pains when the dose of the fixed-schedule opioid regimen is increased. There have been no studies of this approach, but its use is recommended by its simplicity. To help manage breakthrough pain, the dose of the fixed-schedule opioid regimen should be gradually increased until the patient begins to experience treatment-limiting side effects. These side effects, which often occur in the periods between breakthrough pains, define the upper limit of the therapeutic window.

**New Treatments in Development**

Members of the pharmaceutical industry are now engaged in new product development focused on the treatment of breakthrough pain. To date, oral transmucosal fentanyl citrate (Actiq) is the only formulation to be studied systematically. Its efficacy has now been demonstrated in the first randomized, controlled study of the rescue dose.[3] Other controlled trials of this formulation have been completed and further demonstrate the feasibility of such studies. Although the investigation of transitory pains in medically ill outpatients already receiving opioid drugs on a fixed-scheduled basis is clearly challenging, innovative methods can be developed to obtain valid information about the safety and efficacy of novel therapies.

The future will undoubtedly see the development of a variety of new pharmacologic approaches to treat breakthrough pain. Hopefully, studies of the routine approaches described by Patt and Ellison will also be performed and will provide a better scientific foundation for current guidelines advocating the use of short-acting oral or parenteral opioid rescue doses. Combined with systematically collected epidemiologic data, these studies will further improve the recognition of breakthrough pain as an important clinical phenomenon and provide clinicians with a better range of therapeutic approaches with which to manage the problem.

**References:**


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