Focused Review

Breakthrough Pain in Chronic Non-Cancer Pain: Fact, Fiction, or Abuse

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Treatment of chronic non-cancer pain with opioid therapy has escalated in recent years, resulting in exploding therapeutic use and misuse of prescription opioids and multiple adverse drug events. Breakthrough pain is defined as a transient exacerbation of pain experienced by individuals who have relatively stable and adequately controlled baseline cancer pain. Further, the definition of breakthrough pain, prevalence, characteristics, implications, and treatment modalities have been extensively described for chronic cancer pain. However, the literature for breakthrough pain in chronic non-cancer pain including its terminology, prevalence, relevance, characteristics, and treatments, have been poorly described and continue to be debated.

The philosophy of breakthrough pain in chronic non-cancer pain raises multiple issues leading almost all patients to be on high dose long-acting opioids, followed by supplementing with short-acting drugs, instead of treating the patients with only short-acting drugs as required. Consequently, the subject of breakthrough pain in chronic non-cancer pain is looked at with suspicion due to the lack of evidence and inherent bias associated with its evaluation, followed by escalating use and abuse of opioids.

Multiple issues related to the concept of breakthrough pain in chronic non-cancer pain evolve around extensive use, overuse, misuse, and abuse of opioids. In the era of eliminating opioids or significantly curtailing their use to only appropriate indications, the concept of breakthrough pain raises multiple questions without any scientific evidence.

This review illustrates that there is no significant evidence for any type of breakthrough pain in chronic non-cancer pain based on available literature, methodology utilized, and response to opioids in chronic non-cancer pain. The advocacy for increased usage of opioids in the treatment of chronic pain dates back to the liberalization of laws governing opioid prescription for the treatment of chronic non-cancer pain by state medical boards in the late 1990s, and is exploding with new pain management standards for inpatient and outpatient medical care implemented by the Joint Commission on Accreditation of Health Care Organizations in 2000, and the advocacy by many physicians and organizations for increased use of opioids.

This comprehensive review critically evaluates the available evidence of breakthrough pain in chronic non-cancer pain including its existence, prevalence, and managing symptoms which are described as breakthrough pain or episodic pain.

Key words: Breakthrough pain, opioids, chronic non-cancer pain, opioid abuse, opioid misuse, addiction, opioid hyperalgesia, interventional techniques

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Treatment of chronic non-cancer pain with chronic opioid therapy has escalated in recent years, resulting in escalating therapeutic use and misuse of prescription opioids, multiple adverse drug events, inappropriate opioid therapy, and escalating costs of adherence monitoring (1-38). Added to the existing problems of escalating and inappropriate opioid therapy, breakthrough pain has emerged as an issue in chronic non-cancer pain (39-42). Conjecture (breakthrough pain in cancer pain) and personal philosophy of the undertreatment of pain and continuous total pain relief at any cost (43-57), multiple organizations promoting opioid use (52,53), guidelines (3,4,6,15,20,21,58), accreditation standards (59-64), advocacy efforts, and enormous publicity of pain as a fifth vital sign (59-64) have contributed to the overall increased use of medications for breakthrough pain in chronic non-cancer pain (39-46,52-65), rather than for proven efficacy of opioid therapy (3,4,6,12,15,17,34,58,66-73).

The philosophy of breakthrough pain in chronic non-cancer pain raises multiple issues, leading almost all patients to be on high dose long-acting opioids, followed by supplementing with short-acting drugs. In essence, short acting drugs may be the only thing the patient may have needed, specifically with low doses (34,74). Thus, the subject of breakthrough pain in chronic non-cancer pain is looked at with suspicion due to the lack of evidence and inherent bias associated with its evaluation, followed by escalating use and abuse of opioids.

The definition of breakthrough pain, prevalence, characteristics, implications, and treatment modalities have been extensively described for chronic cancer pain (43,44,46,75). However, the literature for breakthrough pain in non-cancer pain, including its terminology, prevalence, relevance, characteristics, and treatment, has been scant and various aspects of breakthrough pain in non-cancer pain has been controversial (39-57,75-96).

This comprehensive review is undertaken to assess the literature for breakthrough pain in chronic non-cancer pain, and various aspects of breakthrough pain in chronic non-cancer pain.

1.0 Methodology

The methodology utilized here follows a systematic review process derived from evidence-based systematic review and meta-analysis of randomized trials and observational studies (97-105), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (106,107), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observational studies (108), Cochrane guidelines (66), and APS guidelines (4).

However, due to the lack of evidence of randomized trials available or even appropriately conducted observational studies available, quality assessment was not carried out.

Literature Search

A comprehensive search of the literature was conducted for the period 1996 through June 2010. Databases for the search included PubMed, EMBASE, Cochrane reviews, and clinicaltrials.gov. The search also included cross-referencing of bibliographies from notable primary and review articles, abstracts from scientific meetings and peer-reviewed non-indexed journals.

2.0 Definitions

The definition and nomenclature of breakthrough pain is completely based on cancer pain and translated to chronic non-cancer pain. In addition, not all definitions included controlled chronic pain to less than moderate baseline pain. Finally, breakthrough pain does not define the pain during opioid titration. Thus, it suffers from the same issues as chronic pain which is treated as acute pain either postoperative or traumatic in origin and chronic cancer pain. Further, it is critical that breakthrough pain be differentiated from persistent pain and other increased needs for opioids including abuse, dependency, and diversion.

Interestingly enough, chronic pain itself is beset with controversy, starting with its own definition. For some chronic pain conditions, it is defined as, "pain that exists beyond an expected timeframe for healing" and for other conditions, it is recognized that "healing may never occur" (109). Bonica (110) defined chronic pain as, "pain which persists a month beyond the usual course of an acute disease or a reasonable time for any injury to heal that is associated with chronic pathologic processes that causes a continuous pain or pain at intervals for months or years." In many cases, chronic pain is understood as persistent pain that is not amenable to routine pain control methods.

Chronic pain has been defined based on the mandate of the Ontario government, as, "pain that persists 6 months after an injury and beyond the usual recovery time of a comparable injury; this pain may continue in the presence or absence of demonstrable pathology" (111).

The American Society of Interventional Pain Physicians (ASIPP) defined chronic pain as, "pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years, that may continue in the presence or absence of demonstrable pathology; may not be amenable to routine pain control methods; and healing may never occur" (109).

Further, there is another paradigm known as chronic pain syndrome. Chronic pain syndrome has been defined as a complex pain condition with physical, psychological, emotional, and social components (112,113). While both chronic pain and chronic pain syndrome can be defined in terms of duration and persistence of the sensation of pain in the presence or absence of psychological and emotional competence, chronic pain syndrome as opposed to chronic pain, has the added components of certain recognizable psychological, and socioeconomic influences with characteristic psychological and sociological behavioral patterns inherent and chronic pain syndrome that distinguishes the 2 conditions (112).

Many of the issues related to chronic pain syndrome may even fall into what is described as prevalence or indications for breakthrough pain in chronic non-cancer pain. Three or more characteristics have been described to be required for the diagnosis of chronic pain syndrome (114) of which some of them include the characteristics of breakthrough pain as follows:.

1) Use of prescription drugs beyond the recommended duration and/or abuse or dependence on prescription drugs or other substances;
2) Secondary physical deconditioning due to misuse and/or fear-avoidance of physical activity due to pain;
3) Withdrawal from social milieu including work, recreation, or other social contacts;
4) Development of psychosocial sequelae after the initial incident, including anxiety, fear-avoidance, depression, or non-organic illness behaviors.

Thus, characteristics described for breakthrough pain meet 4 of the 6 characteristics of chronic pain syndrome, making it extremely difficulty to differentiate.

Portenoy and Hagen (45) in 1990 defined breakthrough pain as a transitory increase in pain to greater than moderate intensity (that is, to an intensity of severe or excruciating), which occurred on a baseline pain of moderate intensity or less (that is, no pain or pain of mild or moderate intensity). They defined baseline pain as that reported by the patient as the average pain intensity experienced for 12 or more hours during the 24-hours prior to the interview.

An international survey of cancer pain characteristics indicated that breakthrough pain's definition varied from country to country (81,85). Breakthrough pain is translated to "severe episodic pain" in Italy, "paroxysmal painful bouts" in France, "interrupting or penetrating pain" in Spain (76), as a sign of end of dose failure during dose titration for pain management in England (83), and as a transient increase in pain intensity over background pain in the United States (79). Breakthrough pain is an English term with no literal translation in many languages, including Spanish and Italian, among others (82,86). Further, to avoid confusion, some experts have advocated the use of broader terms like episodic pain or transient pain in place of breakthrough pain, whereas some have listed the types of breakthrough pain depending on its predictability and precipitating factors (85).

Svendsen et al (42), in a comprehensive review, provided a graphic display of breakthrough pain with 3 categories which included: 1) stimulus independent = spontaneous; 2) stimulus dependent = precipitated/evoked; 3) related to analgesic regimen = "end of dose" failure.

Further, stimulus dependent was also divided into volitional and nonvolitional; volitional includes pain evoked by normally nonpainful stimuli such as allodynia with stimuli such as touch, normal movements, sitting, standing, walking, coughing, moderate cold or warm, or hyperalgesia such as pin prick or painful heat or warmth. In contrast, nonvolitional includes distention of hollow viscera with sensitization of mechanoreceptors, ischaemia, and metabolic causes.

Zeppetella and Ribeiro (79,84) explained that breakthrough pain is usually related to background pain and is typically of rapid onset, severe in intensity, and generally self limiting with an average duration of 30 minutes.

In contrast, other authors argue that this definition is too narrow and must be elaborated and include various other situations (115-117). Thus, it has been described that transient increased pain and intensity may also be seen in patents without adequate analgesic control of baseline pain (115,117). Further, it has been stated that the best definition of breakthrough pain is "any acute transient pain that flares over baseline" (116).

Roth (118) defined breakthrough pain in patients with osteoarthritis treated with non-steroidal anti-in-

flammatory drugs as an increase in pain that required supplemental analgesics. However, this does not meet other criteria of opioid treatment and other conditions. Further, the term incident pain has been used mostly in postoperative pain as pain occurring other than at rest, such as during ambulation, coughing, or deep breathing (119).

Thus, there is at present no unanimous definition of breakthrough pain in malignant pain. Consequently, the terms breakthrough pain and incident pain have rarely been used in non-malignant conditions. End of dose pain, which is commonly used in cancer pain may be more common in chronic non-cancer pain based on subjectivity. However, it does not meet the criteria for breakthrough pain. Further, pain associated without precipitating factors or spontaneous breakthrough pain, which is not predictable, may not fit the criteria for diagnosis in chronic non-cancer pain.

Consequently, Svendsen et al (42) postulated that since there is no unanimous definition of breakthrough pain, either in malignant or in non-malignant diseases, tentatively defined breakthrough pain as episodic flares of pain on a treated or untreated baseline pain. This is considered as a broad definition which enables the demonstration of possible similarities across various pain conditions. Further, they recognized that there are painful conditions with episodic flares of pain without any baseline pain such as acute recurrent pain seen in migraine attacks and trigeminal neuralgia. Thus, those pain conditions were not considered in this definition.

In summary, the definition of breakthrough pain varies based on the reviewers, their concepts, and requirements. This would make it extremely difficult for one to administer a definition for chronic non-cancer pain, considering the numerous disadvantages and lack of proof of the effectiveness of opioids in managing chronic non-cancer pain on a long-term basis.

3.0 Characteristics Of Breakthrough Pain

Even in cancer pain, it has been stated that it is critical that breakthrough pain be differentiated from persistent pain and other increased needs for opioids including abuse, dependency, and diversion. Breakthrough pain in cancer pain can have a profound impact on both the patient's and the caregiver's quality of life (43,80,86). Patients with breakthrough pain in cancer are often less satisfied with their analgesic therapy, they have a decreased functioning because of their pain, and may also experience social and psychosocial consequences such as increased levels of anxiety and depression (43,84).

There is no unanimous agreement upon the assessment of breakthrough pain in cancer patients. Some authors argue that the term breakthrough pain can only be used when baseline pain is controlled by analgesics. Coluzzi (89) defined breakthrough pain as "a transitory flare-up of pain superimposed on an otherwise stable pain pattern in patients treated with opioids." McQuay and Jadad (90) suggested that breakthrough pain was pain breaking through an existing analgesic regimen and a subtype of "incident pain," which was defined as episodic increases in pain intensity.

Portenoy et al (39), in a study of prevalence and characteristics of breakthrough pain in opioid treated patients with chronic non-cancer pain, described that breakthrough pain might be similar to cancer-related breakthrough pain.

In contrast, it may be the opposite in chronic non-cancer pain where addictive behaviors or abuse behaviors may incorporate complaints of breakthrough pain. The Alberta Breakthrough Pain Assessment Tool for cancer patients has been validated in cancer pain (87). The same assessment tool has been somewhat modified and attempted to be utilized in chronic non-cancer pain, but it has never been validated.

There are multiple descriptions for cancer pain that continue to be debated and vary from country to country, condition to condition. However, in contrast to cancer pain, there is no definition which is even accepted by some groups or arrived at by a consensus by a group of unbiased specialists for breakthrough pain in non-cancer pain. Thus, there are no characteristics of breakthrough pain in chronic non-cancer pain.

4.0 Prevalence Of Breakthrough Pain

The underlying mechanism of breakthrough pain in cancer pain may be nociceptive, neuropathic, or mixed in cancer pain (85). Nociceptive pain may be somatic due to involvement of structures like bone or muscle; or visceral if due to involvement of underlying solid or hollow viscous. Neuropathic pains are due to involvement of peripheral or central afferent neural pathways. The incidence of various types of pain has been described as nociceptive in 38% to 53%, neuropathic in 10% to 54%, and mixed pain in about 20% to 52% of patients in cancer pain (85).

The above described paradigm may not fit in chronic non-cancer pain, even though prevalence of chronic non-cancer pain has been reported. A pro-

spective survey of 43 patients with advanced illnesses other than cancer reported a prevalence of 63%, with characteristics similar to those of breakthrough pain in cancer (120). Portenoy et al (39) evaluated the prevalence of breakthrough pain utilizing the same criteria as cancer pain. They also showed that the prevalence of 74% in the non-cancer group exceeded the prevalence of 64% (45) and 51% (46) in the cancer surveys, but the median frequency of 2 pains per day was slightly less with 4 per day (45) and 6 per day (46) recorded among those with cancer. The time to peak intensity (10 minutes or less) and the median duration (one hour or less) were similar across samples, and approximately two-thirds of all pains could be related to an identifiable precipitant, especially end of dose failure in one-fourth of the pains.

Portenoy et al (39) evaluated 228 patients with diverse types of chronic non-cancer pain from 9 pain programs through a telephone questionnaire with a breakthrough pain assessment algorithm originally designed for cancer patients. They described that 74% of the patients experienced severe to excruciating breakthrough pain. Among those with breakthrough pain, the most common syndrome was low back pain (52%), and the underlying pathophysiologic was variably characterized as somatic (38%), neuropathic (18%), visceral (4%), or mixed (40%). Not surprisingly, they also reported a total of 189 different types of breakthrough pain. They reported the median number of episodes per day was 2 with a median duration of breakthrough pain of 60 minutes, ranging from one to 720 minutes, with most precipitating causes being activity related. However, they also described that onset could never be predicted for 45% of pains and only sometimes predicted for 31% of pains.

Portenoy et al (40), in a 2010 publication, again evaluated breakthrough pain in community-dwelling patients with cancer pain and non-cancer pain. They concluded that the prevalence of breakthrough pain among community-dwelling patients is lower than that found in prior studies of a more selected population. However, breakthrough pain was more prevalent among patients with non-cancer pain than patients with cancer pain, and although there were many similarities, they identified some differences which may be relevant to treatment strategies with a prevalence of breakthrough pain in 33% with cancer pain and 48% with non-cancer pain, without variation of breakthrough pain by a diagnosis, even though neuropathic pain was more common in those with breakthrough pain. The results were similar to their previous publications (39,45,46)

Bennett et al (65) also evaluated the prevalence and characteristics of breakthrough pain in patients receiving opioids for chronic back pain in speciality clinics. They employed 117 patients taking opioids for a primary diagnosis of back pain and receiving care at geographically diverse pain treatment centers. Patients had pain lasting at least 6 months and had controlled "baseline pain." Their results showed that 74% experienced 93 types of breakthrough pain with a median number of breakthrough pain episodes per day of 2, median time to maximum intensity of 10 minutes, and median duration of 55 minutes. They also showed that onset could not be predicted for 46% of pains. Eighty-three percent of the patients used shorter-acting opioids for breakthrough pain, whereas others used NSAIDS, antidepressants, anticonvulsants, skeletal muscle relaxants, intrathecal local anesthetics, and transdermal local anesthetics.

Thus, the existence of breakthrough pain in chronic non-cancer pain is debated. Portenoy et al (39,45), staunch proponents who defined breakthrough pain initially, have championed the literature of breakthrough pain in opioid-treated patients with chronic non-cancer pain (40). Even then, very little is known about the prevalence and characteristics of breakthrough pain in the population with chronic non-cancer pain. An inherent issue regarding breakthrough pain is the subjective nature of chronic pain, and also the desire of patients to obtain 100% pain relief and be more comfortable. The philosophy that more is better causes multiple issues.

Neither the prevalence nor its mechanism is known in chronic non-cancer pain, thus, it would be difficult to postulate either the mechanism or even existence of breakthrough pain in chronic non-cancer pain.

5.0 Impact of Breakthrough Pain

The impact of breakthrough pain in cancer pain is understandably profound on quality of life. Further, patients with breakthrough pain are often less satisfied with their analgesic therapy, they have decreased functioning because of their pain, and may also experience social and psychosocial consequences, such as increased levels of anxiety and depression (79). Further, in cancer pain, breakthrough can be a poor prognostic indicator (121) and the site of breakthrough pain may predict response to treatment (85).

In contrast to cancer pain which has been well studied, there is no significant evidence in chronic

non-cancer pain of impact and health care burden. Contrary to this, there is substantial evidence of the deleterious effects of opioid therapy for chronic pain without quality of life improvement; a decrease in opioid doses improves pain and function due to multiple reasons including opioid-induced hyperalgesia (1-4,12,15,16,18,26-34,58,66,72,74,122-134).

However, there have been very few studies evaluating impact on function, mood, and quality of life (41,135,136). Taylor et al (135) evaluated the impact of breakthrough pain on quality of life in patients with chronic non-cancer pain. They evaluated 56 adults with chronic non-cancer pain using oral transmucosal fentanyl citrate. Forty-three patients qualified for in-depth analysis. They showed breakthrough pain had significant impact on general activity level and ability to work. They concluded that breakthrough pain appeared to be a clinically important condition in this population and was associated with an adverse impact on quality of life. Abernethy et al (136) presented a health economic model of breakthrough pain. They provided 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. They concluded that breakthrough pain exacted a well-documented toll on quality of life and incurred personal expense. At the societal level, they concluded that breakthrough pain hampered productivity and its costs strained an already overburdened payer system. Portenoy et al (41) also evaluated the impact on function, mood, and quality of life. The results showed that 48%, or 48 of the 99 patients with non-cancer pain, had breakthrough pain. Compared to those without breakthrough pain, patients with breakthrough pain had increased pain interference in function, with increased somatic complaints, pain complaints, depression, decreased quality of life, and increased difficulties with function.

However, all these studies are the result of subjective evaluation with resultant extra opioids. Thus, the validity of any of the studies is debatable.

6.0 Assessment

Assessment of breakthrough pain in chronic non-cancer pain is difficult, even though multiple assessment modalities have been described in cancer pain (43,75,76,79,87,137-142). The usual time from onset to maximum breakthrough pain intensity is 3 minutes and duration is 30 minutes (37,38,45,46,140). Consequently, assessment for response needs to be at short intervals. Most studies measure breakthrough pain intensity by a numeric rating scale or some other scale by gauging changes in pain intensity from baseline at particular intervals, peak pain intensity differences, the sum of pain intensity differences, peak pain relief, and total pain relief over time. The applicability of these principles to chronic non-cancer pain is based only on hypothesis.

7.0 Management of Breakthrough Pain

7.1 Issues

The treatment of chronic pain, therapeutic opioid use and abuse, and the non-medical use of prescription drugs have been topics of intense focus and debate (1-4,12-3458,66-74,143,144). The majority of attraction for the unlimited use of opioids with long-acting and short-acting combinations with emergence of breakthrough pain has been due in some measure to the campaign about the alleged undertreatment of pain (1-3,5,6,34,47-51,58,66-74,145-164), even though the information has been very sparse and derived from mostly cancer pain and postoperative pain. Thus, Americans, constituting only 4.6% of the world's population, have been consuming 80% of the global opioid supply, and 90% of the global hydrocodone supply, as well as two-thirds of the world's illegal drugs (1,5,164,165). Retail sales of commonly used opioid medications, prescriptions for opioids, the amount of opioids per person in the United States, emergency department visits for prescription-controlled drug abuses, unintentional deaths due to prescription-controlled substances, therapeutic opioids, and opioid abuse have been steadily rising (1).

Along with multiple deleterious effects associated with chronic pain, including disability, the prevalence of chronic pain has been increasing (167). Multiple interventional techniques have been evaluated with evidence to provide improvement in functional status and pain relief in a significant proportion of patients, which should decrease opioid use and avoid the issues related to breakthrough pain (34,74,166,168-206). The deleterious effects of opioids have been described.

It appears that in the modern era, more attention must be focused on adverse consequences, diversion, and misuse rather than undertreatment of pain. Multiple authors have shown escalating therapeutic opioid use (1-3,207-210). Furthermore, what is important are the deleterious effects of early or continued use of opioids (122-134). Importantly, opioid use has been associated with increased disability, medical costs, subsequent surgery, and continued or late opioid use in

chronic pain (1-3,122-134). An epidemiologic study from Denmark (129), where opioids are prescribed liberally for chronic pain, demonstrated worse pain, higher health care utilization, and lower activity levels in opioid treated patients compared to a matched cohort of chronic pain patients not using opioids, suggesting that when opioids are prescribed liberally, even if some patients benefit, the overall population does not. In addition, Eriksen et al (130) also demonstrated worse pain, higher health care utilization, and lower activity levels in opioid-treated patients compared with a matched cohort of chronic pain patients not using opioids. Other studies also have shown that instead of improving functional status, opioid use has been associated with increased disability, medical costs, subsequent surgery, and continued or late opioid use. Further, overall evidence from epidemiological studies regarding function and quality of life with opioids is very weak (1-4,15-18,34,57,66,131,143,144,205).

7.2 Effectiveness of Treatment

There has not been any significant literature studying the effectiveness of treatment of breakthrough pain in chronic non-cancer pain.

A study reported the long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain (92). This was a long-term (18-month), open-label study assessing the safety and tolerability of fentanyl buccal tablets for the treatment of breakthrough pain in 646 opioid-tolerant patients receiving around-the-clock opioids for persistent non-cancer pain. Almost all the patients were included in the dose titration study. By the end of the dose titration, 87% had achieved a successful dose and 14% had discontinued treatment, mainly because of adverse events or lack of efficacy. Overall, only 22% of the patients completed the 18-month maintenance phase of the study. The majority discontinued treatment due to adverse side effects, non-compliance with study medication, very few due to lack of efficacy, and a large number because of one site closure, which contributed to approximately 25% of the discontinuations. Patients were offered as many as 8 doses of fentanyl buccal tablets ranging from 100 to 800 mcg. The successful dose was 800 mcg in 42% of the patients, 600 mcg in 24% of the patients, 400 mcg in 20% of the patients, and 200 mcg in 11% of the patients. Thus, these doses are considered fairly high with poor outcomes. Eighty-eight percent of the patients had one or more adverse events. Overall, this study shows that despite very high doses of fentanyl provided to these patients at their will, it was not highly successful.

A meta-analysis evaluated the impact of opioid rescue medication for breakthrough pain on the efficacy and tolerability of long-acting opioids in patients with chronic non-malignant pain (94) after 48 studies were identified. Results showed that after adjusting for potentially confounding variables (study design and type of opioid), the difference in analgesic efficacy between the "rescue" and the "no-rescue" studies was not significant, with regression coefficients close to 0% and 95% confidence intervals that excluded an effect of more than 18 points on a 0-100 scale in each case. There was also no significant difference between the rescue and the no-rescue studies for the incidence of nausea, constipation, or somnolence in both the unadjusted and adjusted analysis. Consequently, the authors concluded that they found no evidence that rescue medications, short-acting opioids for breakthrough pain, affects analgesic efficacy of long-affecting opioids or the incidence of common opioid-related side effects among chronic non-malignant pain patients. This evaluation shows that there is neither evidence for effectiveness of treatment of breakthrough pain, nor even the prevalence of breakthrough pain.

Fentanyl buccal tablets for relief of breakthrough pain in opioid-treatment patients with chronic low back pain was also studied in a randomized, placebo-controlled study, by Portenoy et al (95), strong proponents of breakthrough pain, sponsored by drug maker Cephalon Inc. As others have reported, breakthrough pain was present in a significant proportion of patients and fentanyl buccal tablets are efficacious and very well tolerated in the treatment of breakthrough pain in opioid-treated patients with chronic low back pain. The study included 16 pain treatment centers in the United States. The titration was achieved by open-labeled titration.

7.3 Treatment

In an era of escalating therapeutic opioid use and abuse, with a lack of evidence for the effectiveness of opioids, in consideration of breakthrough pain, increasing opioid dosages leading to potential adverse consequences appears to be inappropriate.

Three principles have been proposed for the management of breakthrough pain in cancer pain which involve implementation of primary therapies for the underlying etiology of pain, where therapy such as

chemotherapy, radiotherapy, and surgery can modify the pathologic process of the disease and may result in an improvement in both background and breakthrough pain; optimizing around-the-clock medication using the World Health Organization (WHO) ladder to deliver a combination of analgesics and adjuvant analgesics; and specific pharmacological interventions for pain such as supplemental analgesia. In a 2007 Cochrane review of opioids for the management of breakthrough pain in cancer patients (79), the authors concluded that breakthrough pain is a common and debilitating component of pain in patients with cancer. They concluded that oral transmucosal fentanyl citrate was effective in management of breakthrough pain.

In reality, in chronic non-cancer pain, patients request medication for breakthrough pain even if they are on q 6 hour dosage of medications. Further, they request these numerous doses instead of 2 episodes as Portenoy et al (39) have described. In addition, functional status generally does not improve and patients become more dependent and the long-acting drugs become less effective with escalating dosages (1,18,34). Further, patients also prefer short-acting medications better than long-acting ones. Consequently, none of these assessment modalities would be applicable for management of chronic non-cancer pain for so-called breakthrough pain.

The assessment as well as treatment of complaints of breakthrough or episodic pain should follow the same pattern as opioid induced hyperalgesia. A patient must be evaluated clearly for undertreatment, opioid hyperalgesia, increase of pain with new onset pathology, drug diversion, dependency, addiction, abuse, and misuse. The treatment is based on appropriate principles with behavioral modification, exercise programs, interventional techniques, and the addition of non-steroidal anti-inflammatory agents and education.

8.0 Summary

There is no significant evidence of any type of breakthrough pain in chronic non-cancer pain based on available literature, methodology utilized, and response to opioids in chronic non-cancer pain. The advocacy for increased usage of opioids in the treatment of chronic pain dates back to the liberalization of laws governing opioid prescription for the treatment of chronic non-cancer pain by state medical boards in the late 1990s (52), and is exploding with the introduction of new pain management standards for inpatient and outpatient medical care implemented by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in 2000 (59,64), and the advocacy by many physicians and organizations for increased use of opioids (3,4,53-56,120). In addition, the usage of opioids, in general, and the most potent forms of opioids including Schedule II drugs in particular, has dramatically increased (207-209). This dramatic increase has been due to a shift in the regulations largely driven by published, albeit weak, evidence suggesting that opioids could be used safely in selected persons with chronic non-cancer pain (7), by the advocacy of physicians and others who felt constrained by the near absolute prohibition of such before that time (56), and by consensus of professional societies of pain specialists who believe that chronic pain had been previously undertreated (53). Despite the escalating use and abuse of therapeutic opioids (1), nearly 15 to 20 years later, the scientific evidence for the effectiveness of opioids for chronic non-cancer pain remains unclear. Concerns continue regarding efficacy (3,4,6,34); problematic physiologic effects such as hyperalgesia (18), hypogonadism, and sexual dysfunction; and adverse effects – especially the potential for misuse and abuse (57,131) – and the increase in opioid-related deaths (7-11). During the same period, numerous efforts by organizations for appropriate use and exercise of constraints have been misrepresented (3,143,144,205).

9.0 Conclusion

Breakthrough pain in chronic non-cancer pain appears to be a hypothesis without any significant evidence leading to excessive use and abuse of opioids. Thus, patients must be evaluated when they request medication for breakthrough pain or episodic pain and educated along with the application of principles of appropriate pain management therapy with repeat evaluations with investigations of all the causes and application of other modalities including functional interventional techniques and behavioral management.

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