Single-dose fentanyl sublingual spray for breakthrough cancer pain

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Abstract: Breakthrough cancer pain (BTCP) is defined as a transient exacerbation of pain that arises in patients with otherwise controlled persistent pain. BTCP typically has a rapid onset and relatively short duration, but it causes a significant amount of physical and psychological distress for patients. Several rapid-onset fentanyl formulations have been introduced in the USA to replace traditional oral opioids for the treatment of BTCP: a transmucosal lozenge, a sublingual orally disintegrating tablet, a buccal tablet, a buccal soluble film, a pectin nasal spray and, the newest formulation to enter the market, a sublingual spray. This article reviews the six rapid-onset formulations of fentanyl approved in the USA for the management of BTCP with emphasis on describing the published literature on fentanyl sublingual spray. The different fentanyl formulations vary in pharmacokinetic properties and ease of use, but all have a rapid onset and a relatively short duration of analgesia. Fentanyl sublingual spray has demonstrated absorption within 5 minutes of administration, with fentanyl plasma concentrations increasing over the first 30 minutes and remaining elevated for 60–90 minutes in pharmacokinetic studies in healthy subjects. Fentanyl sublingual spray shows linear dose proportionality, and changes in the temperature or acidity of the oral cavity do not alter its pharmacokinetic properties. In patients with BTCP, statistically significant pain relief is measurable at 5 minutes after administration of fentanyl sublingual spray, when compared with placebo, with significant pain relief lasting at least 60 minutes after administration. Adverse events are typical of opioid treatment and are considered mild to moderate in intensity. In summary, fentanyl sublingual spray provides rapid onset of analgesia and is a tolerable and effective treatment for BTCP.

Keywords: breakthrough pain, cancer, fentanyl, rapid-onset opioid, sublingual, fentanyl sublingual spray

Introduction

Moderate to severe pain is common among patients with cancer and remains a significant challenge to practitioners, despite advances in pain management and the widespread adoption of the World Health Organization (WHO) guidelines for cancer pain management. The WHO 3-step “ladder” approach to cancer treatment includes the use of opioids with fixed, around-the-clock dosing in patients who do not respond to non-opioid analgesics. However, breakthrough cancer pain (BTCP) is a common problem that is currently only minimally addressed by the WHO pain relief ladder.

BTCP has been defined as “a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy.” It is distinguished from continuous background pain that is relatively well managed with opioids. BTCP episodes are generally moderate to severe in intensity, reach...
peak intensity in approximately 3 minutes, and generally last ≤30 minutes.5–7

Estimates of the incidence and prevalence of BTCP vary, although BTCP is more common among patients with advanced disease.5 Results of a survey of adult inpatients referred for evaluation and treatment to a cancer pain management service showed that of 63 patients who achieved stable opioid dosing and reported pain of moderate or less intensity, 41 (65%) experienced at least one episode of BTCP in the preceding 24 hours, with a median of four episodes.5 Of 51 episodes of BTCP, the maximum intensity occurred within 3 minutes of onset in 22 (43%) episodes, and the median duration was 30 minutes.5 Another study of 245 patients admitted for hospice care showed that 218 patients (89%) experienced BTCP, with approximately 88% of those patients experiencing more than one episode per day and 84% of episodes producing moderate, severe, or excruciating pain. The majority (73%) of BTCP episodes lasted ≤30 minutes, with 26% lasting just 10 minutes or less.7

BTCP is associated with a high level of patient dissatisfaction with treatment and also has a negative impact on patients’ lives.6–8 Impairments in sleep, concentration, emotional well-being, interpersonal relationships, everyday function, and work performance are common in patients with BTCP.6,8,9 For example, for some patients, the simple act of turning in bed can trigger an episode of BTCP and thereby interfere with sleep.7 For other patients, even gentle hugs can bring on excruciating BTCP, thus preventing physical contact with others and straining personal relationships.8

This review will focus on current management strategies for BTCP, with a focus on the newest formulation of rapid-onset fentanyl: namely, fentanyl sublingual spray.

**Opioids for the management of BTCP**

Although traditional oral opioids, such as morphine, have been the mainstay in the treatment of BTCP, their effectiveness is limited by a relatively slow onset of analgesia (often ≥30 minutes), the need for hepatic first-pass metabolism (which reduces bioavailability), the relatively long duration of effect (which increases the risk for adverse events), and variable absorption.10–13 Oral opioids also are not ideal in patients with nausea, vomiting, or dysphagia.11,14,15

Several rapid-onset formulations of fentanyl have been approved by the US Food and Drug Administration (FDA) for the treatment of BTCP. Fentanyl is a synthetic, highly potent, lipophilic μ-opioid agonist that rapidly crosses the blood–brain barrier and has a half-life ranging from 1.6 to 6 hours.13,16 The different fentanyl formulations vary in pharmacokinetic properties and ease of use, but all of them have a rapid onset and a relatively short duration of analgesia.10,17 In comparison with traditional oral opioids, the rapid-onset fentanyl formulations convey a significant advantage in the treatment of BTCP, with a pharmacokinetic profile that more closely matches that of a BTCP episode.10,13,17–18

With the approval of fentanyl sublingual spray by the FDA in January 2012,19 six rapid-onset formulations of fentanyl are now available in the USA – transmucosal lozenge, sublingual orally disintegrating tablet, buccal tablet, buccal soluble film, pectin nasal spray, and sublingual spray (Table 1).13,17–20,29

Randomized, double-blind, placebo-controlled clinical trials in adults with cancer have demonstrated the efficacy of each of these rapid-onset fentanyl formulations in the treatment of BTCP.10,18,26,27,29–31 Adverse events in these trials have been typical for opioids (the most common being nausea, vomiting, headache, dizziness, and somnolence).13,17,26,27

Although all of the rapid-onset fentanyl formulations show efficacy in the treatment of BTCP in opioid-tolerant patients, each formulation has certain advantages and disadvantages. The oral transmucosal fentanyl citrate (OTFC) lozenge requires effort on the part of the patient to control the administration, which results in variability in absorption and the swallowing of a significant amount of drug.13,17,26,27 Any fentanyl swallowed in saliva will undergo hepatic first-pass metabolism, resulting in reduced bioavailability.13,14

In addition, one OTFC unit contains 2 grams of sugar, and prolonged use may increase the risk of dental decay, including dental caries.20,22 Fentanyl buccal tablets have greater bioavailability than OTFC (65% versus 50%), but the tablets

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<td>Oral transmucosal fentanyl citrate</td>
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<td>Fentanyl citrate sublingual tablet</td>
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<td>Fentanyl citrate buccal soluble film</td>
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<td>Fentanyl sublingual spray</td>
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*Onset of analgesia was defined as the earliest time point at which a statistically significant difference in the pain intensity difference score was measured.
still require 14 to 25 minutes to disintegrate completely, and approximately 50% is swallowed in the saliva.20,22 Fentanyl sublingual orally disintegrating tablet disintegrates rapidly and has an overall bioavailability of 54%.10,21 The tablet must remain under the tongue, and patients should avoid swallowing during administration.21 Fentanyl buccal soluble film requires little effort on the part of the patient; little saliva is necessary for absorption, but the film requires up to 30 minutes to completely dissolve and 49% of the dose is swallowed with saliva.10,13,23,27 Fentanyl pectin nasal spray may be useful in patients with nausea and vomiting, whereby oral administration is difficult;13,33 however, some patients are less accepting of intranasal administration, and coexisting nasal problems may complicate use.14,34,35 Fentanyl sublingual spray requires minimal patient effort, and little drug is swallowed in saliva.14,29,36 In a clinical trial, patients indicated that the sublingual spray formulation is convenient and easy to use.29 Fentanyl sublingual spray provides a useful alternative to fentanyl intranasal spray for patients with nasal problems or those who dislike the intranasal route of administration, although it should be used with caution in patients with grade ≥2 mucositis unless the benefits outweigh the potential risk from possible increased exposure.25

Several cancer treatment guidelines discuss options for the management of BTCP that include the use of rapid-onset opioids. The National Comprehensive Cancer Network recommends rapid-onset opioids when exacerbations of pain are not due to inadequate around-the-clock dosing.37 The European Society for Medical Oncology recommends use of opioids with a rapid onset and short duration of action.38 The European Association for Palliative Care recommends oral immediate-release opioids or transmucosal fentanyl and acknowledges that the latter are preferable in some cases due to their rapid onset and shorter duration of effect.39

Although each of these guidelines mentions BTCP, none explicitly addresses it. The Science Committee of the Association for Palliative Medicine of Great Britain and Ireland recently formulated guidelines specifically for the treatment of BTCP, although the Committee notes that their recommendations are based on limited evidence and provide only general strategies.40 Nonetheless, their recommendations include the use of opioids as first-line pharmacologic treatment for BTCP, noting that oral immediate-release opioids are not optimal due to their delayed onset and long duration of analgesia and rapid-onset opioid formulations, such as transmucosal (sublingual, buccal, intranasal, pulmonary) formulations, may be more advantageous.40 Clearly, there is a need for new clinical trials on the treatment of BTCP and the development of definitive, evidence-based, treatment guidelines.

BTCP treatment options need to optimize the benefits while minimizing the risks for any particular patient. As with all potent opioids, there is a risk of abuse, addiction, and diversion with fentanyl products. There is little literature on abuse and misuse of the rapid-onset formulations of fentanyl used to treat BTCP, although rates for abuse and addiction to rapid-onset fentanyl that have been reported in longer-term clinical trials of patients with chronic noncancer pain are low.16,41-43 However, abuse and misuse of rapid-onset fentanyl should not be overlooked when treating patients with cancer-related pain. Medical professionals need to consider the challenge of managing cancer pain or pain among survivors over a potentially longer duration, as cancer is no longer considered a terminal disease. Advancements in medical therapy have helped patients with cancer live longer, and survival rates have increased.44 All patients treated with opioids require careful monitoring of signs of misuse. Diversion is an important consideration among patients receiving palliative care in nursing facilities or from caregivers at home.42,45

In an attempt to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors associated with use of opioids, the FDA has instituted a Risk Evaluation and Mitigation Strategy (REMS) for the class of transmucosal immediate-release fentanyl products.46 A similar class-wide REMS has been implemented for all of the extended-release and long-acting opioids used to treat chronic pain.47 These REMS programs were designed to educate prescribers and pharmacists on appropriate patient selection and on providing patients with information on the proper use, storage, and disposal of potent opioids to minimize risks and improve patient outcomes.46,47

Fentanyl sublingual spray for BTCP

Fentanyl sublingual spray (Subsys®, INSYS Therapeutics, Inc, Chandler, AZ, USA) was approved by the FDA in 2012 for the treatment of BTCP in adult patients who are already receiving and who are tolerant to opioids for the management of underlying persistent cancer pain.13,19,25 Fentanyl sublingual spray is available in dosages of 100, 200, 400, 600, 800, 1200, and 1600 µg.25 The 1200 µg dose is provided as packages of two 600 µg units, and the 1600 µg dose is provided as packages of two 800 µg units.

The sublingual route of administration offers several advantages over other routes of administration. First, the sublingual mucosa is highly vascularized and is the most permeable region of the oral mucosa. It contains a relatively
large surface area with a mucosal thickness measuring about 100–200 $\mu$m, compared with 500–800 $\mu$m for the buccal mucosa.\textsuperscript{48,49} Sublingual administration also bypasses hepatic first-pass metabolism, which minimizes variability in bioavailability.\textsuperscript{14,15,48} The sublingual route of administration is particularly useful in patients with nausea, vomiting, or dysphagia.\textsuperscript{15} In terms of patient preference, there is some indication that patients prefer the sublingual route of administration over other routes of administration, such as intranasal or rectal, for treatment of BTCP.\textsuperscript{54} In comparison with most other opioids, fentanyl has a significantly greater degree of sublingual absorption,\textsuperscript{15} with fewer adverse effects such as unpleasant taste, burning, light-headedness, and numbness.\textsuperscript{55}

Fentanyl sublingual spray may produce a rapid onset of analgesia in part because the liquid formulation bypasses the need for tablet disintegration and allows for distribution of the active compound throughout the sublingual mucosa, thereby potentially maximizing the rate and extent of absorption.\textsuperscript{29} In addition, fentanyl sublingual spray is composed of the more permeable base form of fentanyl and contains menthol.\textsuperscript{25,50,51} The non-ionized base form of fentanyl favors lipophilicity and absorption through the sublingual membrane, which increases bioavailability.\textsuperscript{20,51} In fact, the base form of fentanyl has demonstrated $\geq 30\%$ bioavailability compared with the fentanyl citrate salt formulation.\textsuperscript{50} Menthol has long been recognized as a highly effective permeation enhancer for a variety of compounds and tissues, including the transmucosal mucosa.\textsuperscript{32–54} Fentanyl sublingual spray has the unique advantage of combining base fentanyl with menthol to achieve fast absorption and superior bioavailability, with minimal variability.\textsuperscript{50,51}

Published clinical trials of fentanyl sublingual spray have evaluated its pharmacokinetic properties in healthy subjects and determined its efficacy and tolerability in opioid-tolerant patients with BTCP.\textsuperscript{29,36,55}

**Pharmacokinetics of fentanyl sublingual spray**

A two-part, Phase I, randomized, five-period crossover trial in healthy adults (aged 18–55 years) was conducted to determine the dose-proportionality of five doses of fentanyl sublingual spray (100, 200, 400, 600, and 800 $\mu$g) under fasted conditions (Part A), and determine the effects of temperature and pH in the oral cavity on the bioavailability of fentanyl after administration of fentanyl sublingual spray 200 $\mu$g (Part B).\textsuperscript{55} A total of 53 subjects (38 female, 15 male) were enrolled in Part A and 14 subjects (3 female, 11 male) were enrolled in Part B. Subjects withdrew due to positive urine drug screen ($n = 2$), positive urine alcohol screen ($n = 1$), and withdrawal of consent ($n = 9$). The mean ± standard deviation (SD) age of subjects was 31 ± 10 years in Part A and 32 ± 10 years in Part B.\textsuperscript{55}

Mean 36-hour plasma fentanyl concentrations across five different doses are shown in Figure 1.\textsuperscript{55} For all doses of fentanyl sublingual spray, mean plasma concentration of fentanyl was detectable within 5 minutes, the first sample point, and was approximately 27.3%, 60.6%, and 86.6% of the mean maximum plasma concentration ($C_{\text{max}}$) within 5, 10, and 20 minutes of administration, respectively. Mean plasma concentration of fentanyl reached a plateau approximately 30 minutes after administration, which was maintained for 60–90 minutes.\textsuperscript{55} Mean $C_{\text{max}}$ increased and median time to maximum plasma concentration ($T_{\text{max}}$) decreased with increasing doses of fentanyl sublingual spray. Linear dose proportionality was demonstrated across the dose range of 100–800 $\mu$g of fentanyl sublingual spray, as determined by linear regression of $C_{\text{max}}$ and area under the concentration–time curve (AUC) from time zero extrapolated to infinity (AUC$\infty$) (Figure 2). Pretreatment of the oral cavity with a cold or hot beverage or a low- or high-pH beverage did not alter the absorption of fentanyl sublingual spray significantly, as determined by assessing $C_{\text{max}}$ and AUC$\infty$ under different temperature and acidity conditions.\textsuperscript{55}

Fentanyl sublingual spray was generally well tolerated. Treatment-emergent adverse events were reported by 31 of 53 subjects (58.5%) in Part A and 9 of 14 subjects (64.3%) in Part B.\textsuperscript{55} The most commonly reported adverse events were nausea ($n = 17$), vomiting/intermittent vomiting ($n = 12$), and somnolence ($n = 8$) in Part A and nausea ($n = 10$), vomiting ($n = 3$), and headache ($n = 3$) in Part B.\textsuperscript{55}

A second pharmacokinetic study was conducted as a single-dose, randomized, open-label, three-way crossover trial in healthy adults (aged 18–55 years) to compare the rate of absorption and systemic bioavailability of fentanyl sublingual spray 400 $\mu$g with OTFC lozenge 400 $\mu$g.\textsuperscript{36} Intravenous fentanyl citrate 100 $\mu$g was used as an independent treatment, and a ±7-day washout period separated treatments. Of 40 enrolled subjects (eight female, 32 male), 29 completed all three treatment periods. Reasons for withdrawal were non-compliance ($n = 8$), violation of entry criteria ($n = 2$), and withdrawn consent ($n = 1$). The mean ± SD age of subjects who completed the study was 35 ± 10 years.\textsuperscript{36}

Compared with OTFC, fentanyl sublingual spray was associated with a higher $C_{\text{max}}$ and greater mean fentanyl plasma concentration from 5 minutes through 6 hours after
administration (Figure 3). In addition, $T_{\text{max}}$ was achieved more rapidly after dosing with fentanyl sublingual spray than with OTFC (median 1.5 hours versus 2.0 hours; $P < 0.05$). Five minutes after administration, mean plasma concentration of fentanyl was 19.0% of $C_{\text{max}}$ for fentanyl sublingual spray and below the lower limit of quantification of the assay (<0.025 ng/mL) for OTFC (Figure 4). Ten minutes after administration, mean plasma concentration of fentanyl was 53.7% of $C_{\text{max}}$ with fentanyl sublingual spray and 6.1% of $C_{\text{max}}$ with OTFC (Figure 4). The systemic bioavailability, calculated using $\text{AUC}_{\infty}$ or $\text{AUC}_{\text{last}}$ from time zero to last quantifiable concentration ($\text{AUC}_{\text{last}}$), was 76% and 72%, respectively, after fentanyl sublingual spray administration compared with 51% and 54%, respectively, after OTFC administration.

Both fentanyl sublingual spray and OTFC were well tolerated, with 15 of 40 subjects (37.5%) reporting adverse events. Only five of 26 reported adverse events were considered to be probably or possibly related to treatment (two reports of glossodynia and one report each of dizziness, headache, and dry throat).

Overall, the results of these studies demonstrate linear dose proportionality of fentanyl sublingual spray across the dose range of 100–800 µg, indicating an increase in the rate of absorption and bioavailability of fentanyl with increasing doses. Fentanyl was detectable in the plasma within 5 minutes after administration, with a sustained elevation in fentanyl plasma concentration starting approximately 30 minutes after administration that was maintained for 60–90 minutes. Alterations in the temperature and acidity of the oral cavity did not affect the pharmacokinetic properties of fentanyl sublingual spray and thus would not alter the effective dosage. Furthermore, fentanyl sublingual spray achieved greater mean plasma concentrations as early as 5 minutes after administration and had greater bioavailability (76% versus 51%) than OTFC lozenge.

**Efficacy and tolerability of fentanyl sublingual spray**

A randomized, multicenter, double-blind, placebo-controlled clinical trial evaluated the efficacy and tolerability of and patient satisfaction with fentanyl sublingual spray in adult (aged ≥18 years) patients with cancer who were opioid-tolerant, and experienced one to four episodes of BTCP daily. A ≥26-day open-label titration phase was
followed by a 26-day double-blind treatment phase, with adverse events evaluated during the trial and for an additional 30 days thereafter. A total of 130 patients (69 female, 61 male) were enrolled in the study, with a mean ± SD age of 56 ± 12 years. Previous medications for BTCP consisted of oral opioids for 93.5% of patients. Thirty-two patients withdrew from the study during the titration phase, and three withdrew during the double-blind phase. The most common reasons for withdrawal were patient decision (n = 16), adverse events (n = 7), and titration failure (n = 3).29 Ninety-eight patients (75.4%) were successfully titrated during the titration phase, and the median effective dose of fentanyl sublingual spray was 800 µg.29 The mean ± standard error (SE) summed pain intensity difference score at 30 minutes after administration (SPID30), the primary efficacy measure, was 640.3 ± 47.8 in patients receiving fentanyl sublingual spray compared with 399.6 ± 40.8 in patients receiving placebo (P < 0.0001).29 Fentanyl sublingual spray was significantly more effective than placebo in reducing pain intensity, as measured by mean pain intensity difference and SPID scores, from 5 minutes through 60 minutes, the last time period assessed (P < 0.05 for all time points) (Figure 5). The mean ± SE total pain relief score at 30 minutes (TOTPAR30), a secondary efficacy measure, was also significantly greater with fentanyl sublingual spray than with placebo (78.3 ± 2.1 versus 61.0 ± 2.2; P < 0.0001).

Pain relief scores and TOTPAR scores were significantly higher with fentanyl sublingual spray than with placebo from 5 minutes through 60 minutes (P < 0.0001 for all time points).29

Patient satisfaction was assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM), a validated assessment tool.29,56,57 Treatment satisfaction on all four TSQM domains (effectiveness, side effects, convenience, overall satisfaction) improved from the start of the titration phase (baseline) to the double-blind treatment phase (Figure 6).29 Notably, of the 95 patients who completed the double-blind phase, 90 (94.7%) chose to continue in an open-label extension phase of the trial.29

Seventy-eight patients (60.0%) reported adverse events during the titration phase, and 47 (48.0%) reported adverse events during the double-blind phase.29 The most common adverse events were nausea (n = 17), somnolence (n = 11), dizziness (n = 10), and vomiting (n = 10) during the titration phase and nausea (n = 7), hyperhidrosis (n = 5), and peripheral edema (n = 5) during the double-blind phase.29 Adverse events considered to be probably related to treatment occurred in 33 subjects (25.4%) in the titration phase and two subjects (2.0%) in the double-blind phase.29

The results of this clinical trial demonstrate the efficacy and tolerability of fentanyl sublingual spray for

![Figure 2](https://www.dovepress.com/)

**Figure 2** Relationship between mean fentanyl $C_{\text{max}}$ (A) and $AUC_\infty$ (B) versus dose following administration of single doses of fentanyl sublingual spray (100–800 µg). Linear regression generated slopes ± SE of 1.06 ± 0.016 for $C_{\text{max}}$ and 1.02 ± 0.020 for $AUC_{\infty}$; both with coefficient of determination ($r^2$) = 0.999, demonstrating dose proportional, linear pharmacokinetics. A slope of 1 indicates dose proportionality or linear pharmacokinetics.


**Abbreviations:** $AUC_{\infty}$ area under the concentration–time curve from time zero extrapolated to infinity; $C_{\text{max}}$, maximum plasma concentration; SE, standard error.
Figure 3 Mean ± SE fentanyl plasma concentrations (ng/mL) over time (5 minutes to 36 hours) after a single administration of fentanyl sublingual spray 400 µg, oral transmucosal fentanyl citrate 400 µg, or intravenous fentanyl citrate 100 µg in healthy volunteers.


Abbreviations: IV, intravenous; OTFC, oral transmucosal fentanyl citrate.

Figure 4 Plasma fentanyl concentrations, expressed as a percentage of $C_{\text{max}}$, at 5 and 10 minutes after a single administration of fentanyl sublingual spray (400 µg) or oral transmucosal fentanyl citrate (400 µg) in healthy volunteers.


Abbreviations: $C_{\text{max}}$, maximum plasma concentration; OTFC, oral transmucosal fentanyl citrate.
the treatment of BTCP in opioid-tolerant adult patients. Fentanyl sublingual spray showed significant reduction in pain at 5 minutes after administration, with pain relief lasting at least 60 minutes, the last time point evaluated. Importantly, more than 75% of patients were successfully titrated from their prior BTCP medication to fentanyl sublingual spray, and nearly all were satisfied with treatment during the double-blind phase, as indicated by their opting to continue on therapy. Adverse events were generally mild to moderate.
Conclusion
Effective management of BTCP episodes should be based on current knowledge of how quickly this exacerbation of pain can occur, with the goal of limiting its intensity and duration. Several rapid-onset formulations of fentanyl have demonstrated efficacy and tolerability in the treatment of BTCP in opioid-tolerant patients. Fentanyl sublingual spray, the newest of these products, has the characteristics of an ideal BTCP treatment – it has proven efficacy, rapid onset (with significant measurable effects within 5 minutes of administration), a relatively short duration of action, a tolerable adverse event profile, is easily administered, and may improve overall patient satisfaction with BTCP treatment.

Acknowledgment
Technical editorial and writing assistance was provided by Karamarie Fecho, PhD, for Synchrony Medical Communications, LLC, West Chester, PA, USA. Funding for this support was provided by INSYS Therapeutics, Inc, Chandler, AZ, USA.

Disclosure
Dr Taylor discloses that he has participated on the speakers’ bureau for INSYS Therapeutics, Inc. Dr Taylor has no other conflicts of interest to declare.

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