

ORIGINAL ARTICLE

Understanding transdermal buprenorphine and a practical guide to its use for chronic cancer and non-cancer pain management

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ABSTRACT

Transdermal buprenorphine (TDB) has demonstrated effectiveness in treating a range of chronic pain conditions, including cancer pain, nociceptive pain, and neuropathic pain and has a favorable safety profile. Worldwide, clinical experience of its use is relatively limited. There is considerable misunderstanding about the pharmacology, mechanism of action, and safety of buprenorphine. There is also limited guidance on the appropriate use of TDB for chronic pain management. This article presents an overview of TDB and also provides practical recommendations for its use as part of a multifaceted strategy in chronic cancer and non-cancer pain.

INTRODUCTION

Optimal pain management requires a multidisciplinary and multimodal strategy tailored to the individual needs of patients to relieve pain and suffering and improve the quality of life of those living with chronic pain.¹ Opioids form part of the comprehensive approach that encompasses pharmacological and non-pharmacological interventions to provide optimal care for patients with chronic pain.^{2,3} Opioids are the mainstay of analgesic treatment for moderate to severe cancer pain.^{4,5} The World Health Organization (WHO) guidelines for treatment of cancer-related pain suggest using weak opioids for relieving mild to moderate pain (step II) and strong opioids for moderate to severe pain (step III).⁶ More recently, guidelines by the European Society for Medical Oncology and the European Association for Palliative Care propose using low doses of strong opioids as an alternative to weak opioids to achieve more effective relief in patients experiencing mild to moderate cancer pain.^{4,5} In contrast, opioids are only considered for chronic non-cancer pain when

non-opioid analgesics and adjuvant therapies are unsatisfactory in relieving pain.^{2,7}

Although opioids can be effective in relieving chronic pain, they are also associated with potential harms, including opioid-related adverse effects and adverse outcomes associated with abuse.^{2-4,7} The main goal of opioid treatment in chronic cancer and non-cancer pain management is to achieve an optimal level of analgesia with minimal adverse effects and avoidance of medication misuse.^{2,3,7} Patients should be regularly monitored and treatment regimens must be reviewed and modified to meet the specific goals of each individual patient.^{2,3,7} There is marked inter-individual variation in the response to different opioids and hence no single opioid is inherently superior to other opioids, for all patients and in all circumstances.² Physicians need to consider the range of available opioid medications and formulations and tailor the treatment to meet the needs of each individual patient. Opioid switching can be considered if pain persists despite adequate dose titration or unmanageable adverse events (AEs) continue to occur.^{2,3,7}

Buprenorphine is a strong opioid, and transdermal buprenorphine (TDB) is effective in treating a range of chronic pain conditions of moderate to severe intensity and has a favorable safety profile.⁸⁻¹⁰ However, there is considerable misunderstanding about the pharmacology, mechanism of action, and safety of buprenorphine, which may have limited the appropriate and rational use of TDB for chronic pain management. An international panel of experts was drawn from the specialties of medical oncology, palliative medicine, and pain medicine to discuss the role of TDB in chronic pain management and share their clinical experiences. This article, developed from the engagement, aims to improve the understanding of TDB and provide practical guidance on the appropriate use of TDB as part of a multifaceted strategy for chronic cancer and non-cancer pain management.

UNDERSTANDING TRANSDERMAL BUPRENORPHINE

Pharmacology of buprenorphine

Buprenorphine is a strong opioid analgesic with agonistic activity at the μ -opioid receptor and opioid receptor-like receptor 1 (ORL1) receptor and antagonistic activity at the κ - and δ -opioid receptors.¹¹ Buprenorphine has a high affinity for the μ -opioid receptor and dissociates slowly from the receptor, resulting in a long duration of analgesia.¹² The slow dissociation also results in milder withdrawal symptoms with buprenorphine than other μ -opioid agonists, such as morphine and methadone.¹³ Its antagonist activity at the κ -opioid receptors further contributes to its suitability for use in opioid abuse deterrence and maintenance therapies.¹⁴ In addition, buprenorphine exhibits a unique pronounced and long-lasting anti-hyperalgesic effect, which may contribute to its potential to relieve neuropathic pain.¹⁵ Buprenorphine displays a dose-dependent effect on analgesia but a ceiling effect on respiratory depression at higher doses which contributes to its favorable safety profile.¹⁶

In the body, buprenorphine is bound to mostly α - and β -globulins and is metabolized in the liver through cytochrome CYP3A4 to norbuprenorphine, which has minimal analgesic activity.¹⁷ Buprenorphine is excreted primarily in the feces and does not accumulate in patients with compromised renal function.¹⁸⁻²³ Buprenorphine is available in sublingual, parenteral, and transdermal formulations.²⁴

Differential profile of buprenorphine

Available research on buprenorphine conducted in a variety of settings in pre-clinical and clinical studies suggest that buprenorphine may have a differential profile from other opioids, although further studies in the chronic pain setting are required to confirm some of these observations^{12,17}: (1) In contrast to other μ -opioid agonists, buprenorphine has been shown to exhibit a pronounced anti-hyperalgesic effect that may contribute to its effectiveness in reducing neuropathic pain, when other opioids fail to produce a response.^{15,25,26} (2) Compared with morphine, methadone, or fentanyl, buprenorphine was associated with a ceiling effect for respiratory depression at higher doses in animal and human studies, suggesting a lower risk of respiratory depression than these opioids.^{16,27,28} (3) In contrast to methadone, buprenorphine had little or no effect on the corrected QT (QTc) interval, even in high doses used in maintenance therapies.^{29,30} (4) While chronic use of opioids has been reported to influence the hypothalamic-pituitary-gonadal axis, buprenorphine appeared less likely to suppress the gonadal axis or gonadal hormone levels than other μ -opioid agonists.³¹⁻³³ (5) When evaluated in a retrospective study involving patients with cancer and non-cancer pain, buprenorphine in transdermal formulation appeared to produce less analgesic tolerance when compared with transdermal fentanyl.³⁴ (6) While all opioids may alter cognition and psychomotor function, patients on buprenorphine were found to exhibit less impairment than those receiving methadone or morphine when tested on their driving ability during maintenance treatment.^{35,36} (7) Compared with sustained-release morphine, buprenorphine in transdermal formulation was associated with significantly less constipation in cancer patients receiving treatment for chronic pain.^{37,38} (8) In contrast to morphine and fentanyl, buprenorphine did not exhibit an adverse effect on the immune system in animal studies or in patients treated for opioid dependence.³⁹⁻⁴¹ (9) In contrast to most opioids, such as morphine, fentanyl, codeine, and tramadol, buprenorphine does not accumulate in patients with reduced renal function and is not removed by hemodialysis. Hence, it can be used in elderly patients or patients with renal disease, without the need for specific dose adjustments.^{20,23,42,43}

Transdermal buprenorphine

The low molecular mass, high lipid solubility, and high potency of buprenorphine make it suited for transdermal administration. Buprenorphine can be homogeneously embedded in a solid polymer matrix patch which is applied to the skin.⁴⁴ TDB is available in low-dose patches with 7-day dosing schedule (marketed as Butrans[®], Norspan[®], Sovenor[®], or Restiva[®] in different countries with slight differences in available dose strengths, approved indications, and maximum approved dose) or high-dose patches with 3-4-day dosing schedules (Transtec[®]).^{43,45-51} The low-dose patches and high-dose patches are available in different dose strengths, delivering

buprenorphine at a steady rate ranging from 5 to 20 µg/h for up to 7 days and 35 to 70 µg/h for up to 4 days, respectively.^{43,45-51} The maximum approved dose for TDB may vary according to the country, in a range of 20 µg/h in the United States to 140 µg/h in Europe, Latin America, and some Asian countries.^{46,50} The pharmacological properties of both low-dose and high-dose patches, along with their approved indications and doses are summarized in Table 1.

Clinical studies have demonstrated the effectiveness of TDB in treating a range of painful conditions including cancer pain, nociceptive pain, and neuropathic pain in patients who were opioid naïve and in those who switched to TDB from a step II or step III opioid.^{8,10,52-58} Better sleep, improved physical

Table 1. Properties of low-dose and high-dose TDB patches

Properties	Low-dose TDB patch (Butrans [®])*	High-dose TDB patch (Transtec [®])				
Pharmacodynamics	<ul style="list-style-type: none"> • A strong opioid analgesic with agonistic activity at the µ-opioid receptor and opioid receptor-like receptor 1 (ORL1) receptor and antagonistic activity at the κ- and δ-opioid receptors • No dose-dependent ceiling to its analgesic effect • Dose-dependent ceiling effect on respiratory depression 					
Pharmacokinetic data ²⁴	<ul style="list-style-type: none"> • Protein binding: 96 percent • Metabolism: Liver • Does not accumulate in patients with renal impairment • Not removed by hemodialysis 					
<i>Onset of action (hours)</i>	18-24	11-21				
<i>Time to peak plasma concentration (hours)</i>	72	60				
<i>Plasma half-life (hours)</i>	13-35	25-36				
<i>Duration of action (days)</i>	7	4				
Indications ^{45,50}	Treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia	Treatment of moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics				
Dose ^{46,51}						
<i>Dose strength (average buprenorphine release rate) (µg/h)</i>	5	10	20	35	52.5	70
<i>Buprenorphine content (mg/patch)</i>	5	10	20	20	30	40
<i>Matrix surface area (cm²)</i>	6.25	12.5	25	25	37.5	50
Administration ^{45,50}	7-day dosing schedule			3-4 day dosing schedule [†]		
No dosage adjustment is required in patients with renal disease, mild to moderate liver disease or elderly patients						
Abbreviation: TDB, transdermal buprenorphine.						
*Also marketed as Norspan [®] , Sovenor [®] , or Restiva [®] in different countries. The dose strengths, approved indications, and maximum approved dose vary between countries. ⁴⁵⁻⁴⁹ For more information, please refer to the local prescribing information.						
†For convenience, the high-dose patch can be changed twice-weekly at regular intervals on fixed days of the week (eg, always on Monday morning and Thursday evening).						

function and quality of life, and a reduced need for rescue therapy were also reported with TDB treatment.^{8,54,57,59} Apart from transient local skin reactions that were typical of transdermal delivery systems, TDB demonstrated an AE profile that is similar to other opioid analgesics,^{8,53,54,57,58} although there is limited evidence to suggest a lower rate of constipation than morphine.^{37,38} In addition, TDB was effective in providing adequate pain relief in elderly patients and patients with renal impairment, with no additional safety concerns.^{9,59}

Addressing misconceptions about buprenorphine

TDB has demonstrated effectiveness and safety in managing a variety of pain types in both cancer and non-cancer populations.^{8,10,52-58} However, there are several misconceptions about the pharmacology, mechanism of action, and safety of buprenorphine, which hinder progress in utilizing the full therapeutic potential of TDB in the treatment of cancer and non-cancer pain.⁶⁰⁻⁶² It is important to address misconceptions about buprenorphine to allow treatment decision to be informed by clinical evaluation rather than by preconceived notions.

Analgesia and respiratory depression profile. Because buprenorphine is commonly referred to as a partial μ -opioid receptor agonist, it is often misunderstood as producing less analgesia than full μ -opioid receptor agonists, such as morphine or fentanyl.⁶¹ Unfounded concerns regarding a ceiling effect of buprenorphine for analgesia, informed by pre-clinical study data, further hinder the appropriate use of TDB in the treatment of chronic pain.¹² However, buprenorphine has been shown to produce the same level of analgesic efficacy as full μ agonists and have a ceiling effect for respiratory depression, but not for analgesia in humans.^{16,27,60,61,63} The unique ceiling effect for respiratory depression reduces the risk of this potentially fatal AE and confers a favorable safety profile to buprenorphine.^{16,27}

Combining or switching with opioids. There is a misconception that buprenorphine has an antagonist effect on other μ -opioid agonists due to its high binding affinity for the μ -opioid receptor.⁶⁰ Therefore, it is perceived that buprenorphine will interfere with the activity of other μ agonists when combining or rotating with these agonists. There are also concerns that it may precipitate withdrawal

symptoms if used concurrently with other μ agonists. However, clinical studies of buprenorphine showed that it is possible to use a μ agonist for breakthrough pain or to switch either way between buprenorphine and a μ agonist without compromising analgesia.⁶⁴⁻⁶⁶ The results of these studies demonstrate the flexibility of using buprenorphine for achieving optimal pain relief.

Data on QTc interval. The maximum approved dose for TDB is 140 $\mu\text{g/h}$ in Europe, Latin America, and some Asian countries.⁵⁰ However, only doses up to 20 $\mu\text{g/h}$ are approved in the United States because of concerns for QTc interval prolongation based on the results of a clinical trial which demonstrated modest prolongation of the QTc interval at a dose of 40 $\mu\text{g/h}$ in healthy subjects.⁴⁶ Other studies also reported mild increase in QTc interval in patients receiving buprenorphine treatment.^{29,67} However, these reported increases were below the clinically relevant range.^{29,46,67} In addition, analysis of spontaneously reported AEs in the Food and Drug Administration (FDA) and WHO databases did not reveal any potential signal of increased risk for cardiac arrhythmia for both low-dose and high-dose TDB patches in real-world use.⁶² As with any other opioids, clinical judgment should be used when initiating TDB in patients who may be at a greater risk of QTc prolongation due to congenital factors or concurrent use of other drugs that may affect QTc interval.

Role of transdermal buprenorphine in chronic cancer and non-cancer pain management

Transdermal opioids are recommended as the treatment of choice for patients who are unable swallow or have poor tolerance or compliance to oral medications.^{4,5,18,68} They are suitable for patients who have stable and predictable opioid requirements.^{2,4} Transdermal opioids confer several advantages over conventional oral or parenteral opioid formulations. Transdermal opioids are noninvasive and avoid the effects of first-pass metabolism.⁶⁹ They provide sustained release of opioids which results in constant opioid levels in the plasma, thus avoiding excessive peaks and troughs typical of conventional formulations which can lead to increased AEs and unstable analgesia.⁶⁹ Indeed, a randomized controlled study comparing TDB with sublingual buprenorphine in patients with osteoarthritis showed that the transdermal formulation was associated with fewer AEs

than the sublingual formulation.⁷⁰ In addition, the extended analgesia duration of transdermal opioids results in reduced dosing frequency and is useful in reducing pill burden and improving patient compliance and acceptability.⁵¹

A systematic review on the use of TDB and transdermal fentanyl patches in cancer pain management showed that both formulations appeared to have similar analgesic efficacy and tolerability.⁵¹ However, it was suggested that TDB patches may have a more favorable safety profile than transdermal fentanyl patches owing to potentially lower risk of developing tolerance and buprenorphine's ceiling effect on respiratory depression.^{16,27,34,51} Guidelines recommend TDB as a suitable option for elderly patients or patients with renal disease, including those with end-stage renal disease because the metabolism of buprenorphine is not affected by advanced age, renal impairment, or hemodialysis and it does not require specific dose adjustment in these patients.^{4,23} Considering the good overall efficacy and tolerability of TDB in patients with chronic pain arising from a range of conditions and the convenience of no specific dose adjustment requirement in renal or elderly patients,^{4,8-10,23,52-59} TDB can be considered a rational choice for treating chronic moderate to severe pain in patients who are otherwise not candidates for oral opioids.

GUIDE TO USING TRANSDERMAL BUPRENORPHINE FOR CHRONIC PAIN MANAGEMENT

Although recommendations for using TDB are provided in the manufacturer's prescribing information, there is little guidance regarding switching between TDB and other analgesics and managing breakthrough pain and common AEs when using TDB. Further, both low-dose and high-dose TDB formulations have different licensed indications and the approved maximum dose for low-dose TDB vary between countries. These can be confusing to prescribers. There is a need for more specific recommendations to guide the safe and appropriate use of TDB for managing both chronic cancer and non-cancer pain. This practical guide summarizes relevant published recommendations and the panel's combined clinical experience with TDB to help physicians tailor the pain treatment to cater to the individual needs of their patients. As cancer evolves to a chronic illness with co-morbid conditions, the traditional cancer pain versus non-cancer

pain divide is becoming more blurred. When applying the recommendations in this guide, physicians should consider the circumstances of the individual patients and exercise clinical judgment to make appropriate decisions for their patients. It should be noted that while opioid treatment is the mainstay of pharmacological treatment for chronic cancer pain of moderate to severe intensity, its use for chronic non-cancer pain should be restricted to specific scenarios where non-opioid analgesics and adjuvant therapies have failed, and benefits of opioid treatment are likely to outweigh harm.^{2,4,5,7} In addition, short-term trial of opioid treatment between several weeks and a few months should be used in chronic non-cancer pain.^{2,7} When adapting this guide to their country, physicians must be aware of the applicable local regulations and local guidelines for opioid treatment. Local prescribing information should be consulted for detailed information on approved dose range and indications, contraindications, warnings, drug interactions, use in special patient populations, and patch application.

TDB should be prescribed as part of a multidisciplinary and multimodal strategy, including psychotherapeutic interventions, physical therapies, and so on, to achieve optimal management of both cancer and non-cancer pain.^{2,3,7} To ensure patients receive the maximum benefit of TDB treatment with minimal adverse effects, physicians must identify appropriate candidates for TDB treatment and keep patients under close clinical surveillance.^{2,3,7} Patients should be regularly monitored for treatment efficacy, adverse effects, and any aberrant drug-related behaviors during the course of treatment. The main goal of TDB treatment is to maintain an optimal balance of the associated benefits and risks.^{2,3,7} If the treatment fails to yield the desired goal, the overall management strategy must be reviewed and revised.^{2,3,7}

Suitable candidates for transdermal buprenorphine treatment

TDB is a valuable treatment option for alleviating chronic moderate to severe pain in a wide spectrum of patients. TDB is approved for the treatment of patients who have cancer pain or those who have non-cancer pain inadequately controlled by non-opioids and adjuvant therapies.^{45,46,50} It is a valuable alternative for patients who have experienced intolerable AEs with other opioids or whose pain is not controlled with other opioids. TDB is also an

attractive option for patients with polypharmacy, or patients who are unable to swallow or have poor tolerance or compliance to oral opioids, or prefer noninvasive administration.^{4,5} The favorable safety profile of TDB makes it particularly suitable for patients renal insufficiency or dysfunction, or elderly patients.^{4,5,23} Considering the potential of TDB to improve neuropathic pain,^{10,25,55,56} it may be used in conjunction with adjuvants, such as antidepressants or anticonvulsants, to manage neuropathic pain. As with all transdermal opioids, TDB is not recommended for use in acute pain or unstable pain.⁴

Patient education

When initiating TDB treatment, physicians should work closely with their patients to develop goals for pain management.^{2,3} Physicians should counsel patients on TDB's indications and alternative treatment options, plans for monitoring treatment, potential adverse effects from treatment, and strategies for minimizing the risk of adverse effects and managing the symptoms of AEs.^{2,3} In addition, patients should be informed that it can take up to 3 days after the application of the TDB patch to experience full analgesia. Patients should be advised on the safe use, storage, and disposal of the TDB patches. A brief summary of important information for appropriate application and disposal of TDB patch is provided in Figure 1.

- ✓ Non-irritated intact skin (preferably on the chest/upper arms)
- ✓ Non-hairy skin (cutoff any hair with scissors, do not shave)
- ✓ If necessary, clean the skin with water only
- ✓ Ensure the skin is dry
- ✓ Apply the patch immediately upon removal from the sachet
- ✓ Ensure the protective layer is removed before application
- ✓ Press the patch firmly in place ensuring good contact and adhesion
- ✓ Patch may be secured with a suitable skin tape if necessary
- ✓ Do not apply more or fewer patches than instructed by the physician
- ✓ Do not cut the patch
- ✓ Patch can be worn during bathing, showering, or swimming
- ✓ Patch should not be exposed excessive heat (eg, sauna, infrared-radiation)
- ✓ Patch should be worn continuously for at least 3 days but no more than 7 days for low-dose patch or 4 days for high-dose patch
- ✓ Write date of application on the patch
- ✓ The new patch should be applied a different skin site (avoid previous site for up to 4 weeks)
- ✓ Remove used patches carefully, fold inward and dispose safely
- ✓ Return unused patches to pharmacy for safe disposal

Figure 1. Important information for appropriate application and disposal of TDB patch for patients.^{45,46,50}

Treatment initiation

Initiate the dosing regimen according to the needs of the individual patient. Considerations should be given to patient's opioid treatment history, type and intensity of patient's pain, and the general condition and medical status of the patient.^{45,46,50} A treatment algorithm based on literature review and the panel's clinical experience in using TDB for managing patients with chronic cancer pain or non-cancer pain is presented in Figure 2. A quick practice guide to using TDB for the treatment of chronic pain is summarized in Figure 3.

Opioid-naive patients should be started on the lowest possible TDB patch dose (5 µg/h). Patients

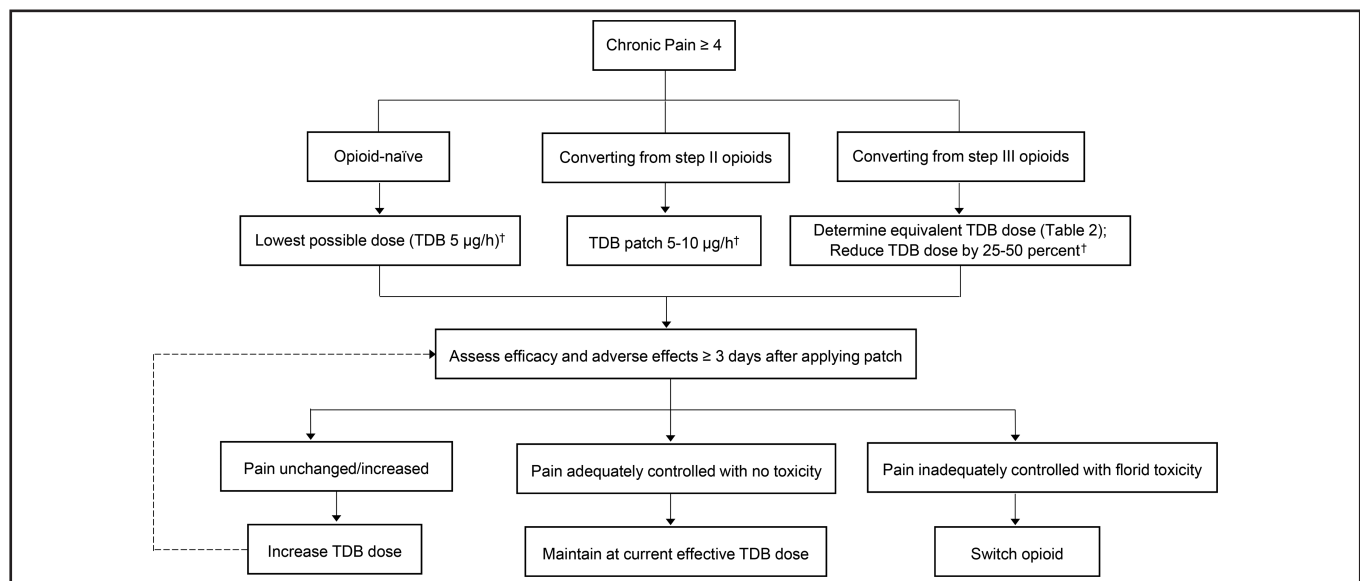


Figure 2. A treatment algorithm for using TDB treatment in patients with chronic moderate to severe cancer pain or chronic moderate to severe non-cancer pain not responding to optimized non-opioid treatment.

†Any previous analgesic medication (with the exception of transdermal opioids) should be given in the same dose during the first 12 hours after converting to TDB and appropriate short-acting supplementary analgesics should be made available during the course of treatment.

<p>Place of TDB for treatment of chronic pain Rational opioid choice for treating chronic moderate to severe pain in patients who are otherwise not candidates for oral opioids.</p> <p>Suitable candidates for TDB treatment</p> <ul style="list-style-type: none">✓ Persistent moderate to severe cancer pain✓ Persistent moderate to severe non-cancer pain, not responding to optimized non-opioid treatment✓ Intolerable AEs with other opioids✓ Inadequately controlled by other opioids✓ Poor compliance to other opioids/prefer noninvasive administration✓ Unable to take or tolerate oral opioids/polypharmacy✓ Renal insufficiency/dysfunction✓ Elderly✓ Neuropathic pain (use in conjunction with antidepressants or anticonvulsants) <p>Contraindications</p> <ul style="list-style-type: none">✓ Acute pain✓ Unstable, fluctuating pain✓ Rapid dose titration required <p>Initiate TDB treatment</p> <p><u>Opioid-naïve patients</u></p> <ul style="list-style-type: none">✓ Start on the lowest possible dose (TDB 5 µg/h) <p><u>Converting from step II opioids</u></p> <ul style="list-style-type: none">✓ Start on TDB 5-10 µg/h <p><u>Converting from step III opioids</u></p> <ul style="list-style-type: none">✓ Determine equivalent total oral morphine dose in past 24 h✓ Determine estimated equivalent TDB dose (Table 2)✓ Reduce TDB dose by 25–50 percent (to account for incomplete cross-tolerance) <p><u>Patients with renal insufficiency/dysfunction or elderly patients</u></p> <ul style="list-style-type: none">✓ No special TDB dose reduction is required <ul style="list-style-type: none">✓ Apply TDB patch concurrently with last dose of any previous analgesic medication during the first 12 hours of application✓ Appropriate short-acting supplementary analgesics should be made available during treatment	<p>Titrate and maintain treatment</p> <ul style="list-style-type: none">✓ Assess treatment and titrate TDB dose ≥72 h after applying patch✓ Take into account the dose of supplementary analgesics used when adjusting the dose✓ Titrate TDB dose until analgesic efficacy is attained with minimal adverse effects✓ Maximum approved dose: 20 µg/h in the US; 140 µg/h in Europe, Latin America, and some Asian countries✓ Regularly monitor patients to assess optimum dose and the continued need for pain treatment.✓ Continually monitor analgesic efficacy, adverse effects, and any aberrant drug-related behaviors over the course of treatment✓ If patient is febrile, monitor for potential increased risk of opioid reactions <p>Manage common AEs</p> <ul style="list-style-type: none">✓ Inform patients potential adverse effects of treatment✓ Laxatives, antiemetics, and topical steroids should be made available during the course of TDB treatment✓ Consider a lower dose of laxative medications as TDB is associated with a lower incidence of constipation than morphine✓ Apply topical steroids a few hours before applying patch or immediately after removing patch to avoid/reduce skin reactions <p>Discontinue treatment</p> <ul style="list-style-type: none">✓ TDB treatment should be discontinued if patients:<ul style="list-style-type: none">- no longer require opioid treatment- did not meet treatment goals- experience intolerable adverse effects or inadequate pain control despite dose increases; or- show signs of opioid misuse, abuse or addiction.✓ A substantial amount of buprenorphine remains in the blood within 24 hours of removing the patch. This should be taken into account when switching to other opioids
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Figure 3. A quick practice guide to using TDB for the treatment of chronic pain.

Local prescribing information should be consulted for detailed information on approved dose range and indications, contraindications, warnings, drug interactions, use in special patient populations, and patch application.

who were previously prescribed a step II opioid are recommended to begin with TDB 5-10 µg/h instead of manufacturer's recommendation of TDB 5 µg/h which may be too low for some patients. For patients who were previously prescribed a step III opioid, the nature of the previous medication, administration, and mean daily dose should be taken into consideration when determining the initial TDB dose.^{46,50} To switch to the TDB patch from another step III opioid, it is best to determine the equivalent total oral morphine dose in the past 24 hours, then calculate the approximate equivalent dose of TDB (Table 2). TDB is reported to be 70-115 times more potent than oral morphine.^{25,72} For convenience, a potency ratio of 100:1 can be used to calculate the equivalent dose of TDB (Table 2).²⁴ It is recommended to further reduce the calculated equivalent dose of TDB by 25-50 percent to account for incomplete cross-tolerance. As there is wide inter-individual variation in the response to different opioids, the calculated doses for TDB provided in Table 2 serve only as a rough guide for switching from other step III opioids to TDB patches. Physicians should exercise discretion and consult local prescribing information when starting TDB treatment.

Using TDB in patients with renal insufficiency/dysfunction or elderly patients. As the pharmacokinetics of buprenorphine remain unchanged in patients with renal disease or elderly patients, no special reduction of TDB dose is required for these patients.^{20,23,46,50}

Converting to a TDB patch. Because it can take about 12-24 hours for the TDB patch to reach minimal effective concentration, any previous analgesic medication (with the exception of transdermal opioids) should be given in the same dose during the first 12 hours after converting to TDB.⁵⁰ Below is a brief guide for conversion from other opioid formulations to a TDB patch. It should be noted that conversion is not limited to these formulations but is dependent on patients' previous analgesic medication. To convert to a TDB patch from⁷³

- **4 hourly oral opioid.** Administer 4 hourly doses of the short-acting opioid for the first 12 hours after applying the TDB patch.
- **12 hourly modified-release oral opioid.** Apply TDB patch and administer the final

Table 2. Estimated equivalent dose of TDB patch for background pain and equivalent rescue dose of oral morphine for breakthrough pain

Oral morphine dose prior to conversion (mg/24 h) ⁷¹	Equivalent TDB dose* (µg/h) ⁷¹	Equivalent oral morphine PRN dose for breakthrough pain [†] (mg) ⁷¹
12	5	2
24	10	5
48	20	10
84	35	15
126	52.5	20
168	70	30

Abbreviations: PRN, pro re nata; TDB, transdermal buprenorphine.

*For convenience, a potency ratio of 100:1 is used to calculate the equivalent dose of TDB. Because of opioid-induced hyperalgesia, it is recommended to further reduce the calculated equivalent dose of TDB by 25-50 percent to account for incomplete cross-tolerance. As the approved maximum dose for TDB vary between countries, physicians should consult the local prescribing information when determining the equivalent TDB dose.

†The rescue doses for as-needed oral morphine is estimated as 1/6 of the total daily opioid dose and rounded up or down to the most convenient available dose. Physicians should also consider non-opioids and non-pharmacological treatment strategies for effective breakthrough pain control.

The estimated doses presented in this table serve as a rough guide only. Actual dosing requires regular assessment and adjustment of treatment regimens to meet the needs of individual patients.

dose of modified-release strong opioid at the same time.

- *24 hourly modified-release oral opioid.* Apply TDB patch 12 hours after administering the final dose of modified-release strong opioid.
- *Opioid via a continuous subcutaneous or intravenous infusion.* Apply TDB patch and continue the infusion for another 12 hours.

Appropriate short-acting supplementary analgesics should be made available during treatment until analgesic efficacy with TDB is attained.^{45,46,50}

Management of breakthrough pain

Breakthrough pain can be managed using appropriate supplementary short-acting analgesics to complement TDB treatment.^{74,75} A short-acting oral

opioid at approximately 1/6 of the total daily opioid dose is traditionally used as needed to relieve breakthrough pain.⁷¹ If the oral route is not suitable for the patients, alternative short-acting formulations, such as nasal, buccal, or sublingual opioid preparations, can be considered.⁷⁴ Physicians should also consider non-opioids and non-pharmacological treatment strategies for effective breakthrough pain control.^{74,75}

A rough guide to the estimated rescue doses for oral opioids is provided in Table 2. Given the diverse nature of breakthrough pain, physicians need to understand the mechanisms of its development and its severity, duration and etiology, and select appropriate strategies to effectively manage breakthrough pain.^{74,75} The required rescue dose and treatment strategies must be adapted to the requirements of the individual patient. If breakthrough pain occurs regularly, then the cause for the increased occurrence needs to be re-evaluated.

Dose titration and maintenance therapy

Patients should be carefully and regularly monitored to assess the optimum dose and the continued need for pain treatment.^{45,46} Analgesic efficacy, adverse effects and any aberrant drug-related behaviors should be monitored over the course of treatment.^{2,3} As TDB has a slow onset of action of about 12-24 hours and it can take up to 72 hours for buprenorphine to reach maximum plasma concentration, evaluation of the analgesic effect should only be made 3 days after applying the patch.^{24,50}

The dose of TDB may be titrated after 3 days of treatment initiation.^{45,46} The dose may be increased by applying either the next TDB patch strength or a combination of patches of the same strength according to local prescribing information and keeping within the maximum approved dose specific for the country; however, it is recommended that no more than two patches is to be applied at the same time.^{45,46,50} The new patch should not be applied to the same skin site for the subsequent 3-4 weeks.^{45,46} The dose of supplementary analgesics administered should be taken into consideration when adjusting the dose.^{45,50} The dose of TDB should be titrated individually until analgesic efficacy is attained with minimal adverse effects. The maximum approved dose for TDB is 20 µg/h in the United States and 140 µg/h in Europe, Latin America, and some Asian countries.^{45,46,50} The low-dose patch can be worn for up to a maximum of 7 days while the high-dose TDB patch can be worn for up to a

maximum of 4 days.^{45,46,50} For convenience, the high-dose patch can be changed twice-weekly at regular intervals on fixed days of the week (eg, always on Monday morning and Thursday evening).^{43,50}

Special precaution for use. The rate of absorption of buprenorphine increases during fever and in the presence of an external heat source.^{45,46,50} Patients should be informed about this and the potential increased risk of opioid reactions.

As buprenorphine is mainly a substrate of CYP3A4, physicians should exercise caution if TDB is prescribed concurrently with CYP3A4 inhibitors (eg, clarithromycin, itraconazole, protease inhibitors, etc) or CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, and rifampin), because of the potential to affect buprenorphine levels.^{45,46,50,71}

Management of common adverse events

An important goal of chronic opioid treatment is to maintain a favorable balance of associated benefits and risks.^{2,3,7} Regular evaluation for treatment efficacy, adverse effects, and any aberrant drug-related behaviors should be conducted over the course of treatment.^{2,3} Common adverse effects of TDB treatment include constipation, nausea, vomiting, and application site skin reactions, which are typical of transdermal opioid medications.^{18,8,53,54} Proactive and timely management of associated adverse effects will improve the tolerability of pain treatment and enable patients to receive more effective pain care.^{3,75} It is vital for physicians to communicate the potential adverse effects of TDB treatment and educate patients on the strategies to combat these symptoms.

There is little guidance on managing common adverse effects of TDB treatment in the manufacturer's prescribing information. Based on published recommendations and reports of clinical observations,^{2,5,76,77} it is recommended that laxatives, antiemetics, and topical steroids be made available during the course of TDB treatment. As TDB is associated with a lower incidence of constipation than morphine, consider using a lower dose of laxatives.^{37,38} Alternative options for treating opioid-related constipation, such as peripherally acting μ -opioid receptor antagonists, should be considered in patients who do not show sufficient clinical benefit with conventional laxatives.^{78,79} Antiemetics should be used as required for patients who experienced opioid-related nausea or vomiting.^{5,75} As these symptoms are typically transient,

antiemetics can generally be withdrawn within a few days of starting TDB treatment.⁷⁵ Physicians may consider applying topical steroids a few hours before applying the patch or immediately after removing the patch as per published clinical experience with TDB,^{76,77} to minimize application site skin reactions.

Discontinuation

Discontinuation of TDB treatment should be considered when patients (i) no longer require opioid treatment; (ii) experience no progress toward meeting treatment goals; (iii) experience intolerable adverse effects or inadequate pain control despite dose increases; or (iv) show signs of opioid misuse, abuse or addiction.^{2,3} After removing the TDB patch, buprenorphine serum concentrations will decrease gradually but a substantial amount of buprenorphine remains in the blood following 24 hours after removal. This should be taken into account when treatment with TDB is to be followed by other opioids.^{45,50} Below is a brief guide for conversion from a TDB patch to other opioid formulations. It should be noted that the conversion is not limited to these formulations but should be adjusted to tailor to the clinical situation and to the needs of individual patients. To convert from a TDB patch to⁷³:

- *12 hourly modified-release oral opioid.* Remove the TDB patch and administer the modified-release formulation at least 12 hours after removal of the patch.
- *24 hourly modified-release oral opioid.* Remove the TDB patch and administer the modified-release formulation at least 12 hours after removal of the patch.
- *Opioid via a continuous subcutaneous or intravenous infusion.* Remove the TDB patch and commence the infusion at least 12 hours after removal of the patch.

SUMMARY

Despite increased research on TDB, there are still some misconceptions about the pharmacology, mechanism of action, and safety of buprenorphine. In clinical practice, buprenorphine produces the same level of analgesia as full μ agonists and exhibits a unique ceiling effect for respiratory depression, but

not analgesia. It can be switched or combined with other μ -opioid agonists without compromising analgesia. Buprenorphine has shown a differential profile in terms of gonadal and immunosuppressive effects, cognitive impairment, and hyperalgesia when compared with other specific opioids. TDB has demonstrated good efficacy and tolerability in patients with chronic pain, providing effective analgesia as part of a multifaceted strategy for a wide range of pain indications, including cancer pain, nociceptive pain, and neuropathic pain. It also has the convenience of once-weekly or twice-weekly administration, with no specific dose adjustment requirement in elderly patients or those with compromised renal function, and is a valuable alternative for patients who are not suitable for oral opioids. TDB represents an additional and important treatment option for use as part of a multifaceted and multi-professional approach by competent physicians in carefully selected and supervised patients. With a better understanding of buprenorphine and the development of this practical guide to provide guidance on the safe and appropriate use of TDB for chronic cancer and non-cancer pain management, physicians can adapt this guide to help them use TDB more safely and effectively in their patients.

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