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ABOUT COVER

Editor-in-Chief of *World Journal of Clinical Cases*, Bao-Gan Peng, MD, PhD, is Professor and Director of the Department of Orthopedics at The Third Medical Center of PLA General Hospital. Professor Peng's research interest is spinal surgery. His career work has generated a multitude of new academic viewpoints and theories, and more than 200 academic papers, published both at home and abroad. In practice, he has systematically elucidated the pathogenesis of discogenic low back pain and established a new minimally invasive treatment method: The intradiscal methylene blue injection. He also revealed and characterized a new pathogenesis of Schmorl's nodes, which is a now a famous concept. Finally, he was the first to discover that ingrowth of Ruffini corpuscles into degenerative cervical disc is related to dizziness of cervical origin. (L-Editor: Filipodia)

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Expert consensus of the Chinese Association for the Study of Pain on pain treatment with the transdermal patch

Ke Ma, Wei Jiang, Yun-Xia Wang, Lin Wang, Yan Lv, Jin-Feng Liu, Rong-Guo Liu, Hui Liu, Li-Zu Xiao, Dong-Ping Du, Li-Juan Lu, Xiao-Qiu Yang, Ling-Jie Xia, Dong Huang, Zhi-Jian Fu, Bao-Gan Peng, Yan-Qing Liu

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Abstract

Chronic pain lasting more than 3 mo, or even several years can lead to disability. Treating chronic pain safely and effectively is a critical challenge faced by clinicians. Because administration of analgesics through oral, intravenous or intramuscular routes is not satisfactory, research toward percutaneous delivery has gained interest. The transdermal patch is one such percutaneous delivery system that can deliver drugs through the skin and capillaries at a certain rate to achieve a systemic or local therapeutic effect in the affected area. It has many advantages including ease of administration and hepatic first pass metabolism avoidance as well as controlling drug delivery, which reduces the dose frequency and side effects. If not required, then the patch can be removed from the skin immediately. The scopolamine patch was the first transdermal patch to be approved for the treatment of motion sickness by the Food and Drug Administration in 1979. From then on, the transdermal patch has been widely used to treat many diseases. To date, no guidelines or consensus are available on the use of analgesic drugs through transdermal delivery. The pain branch of the Chinese Medical Association, after meeting and discussing with experts and based on clinical evidence, developed a consensus for promoting and regulating standard use of transdermal patches containing analgesic drugs.

Key Words: Transdermal drug delivery systems; Pain; Transdermal patches; Topical; Nonsteroidal anti-inflammatory drugs; Analgesics

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Core Tip: Currently no international guidelines or consensus are available on the treatment of pain using transdermal patches. With the help of experts and based on recent clinical evidence, the pain branch of the Chinese Medical Association formulated China's expert consensus on "transdermal pain treatment in China," while considering China's national conditions with a view to regulate and promote the standardized use of the transdermal patch containing analgesic drugs.

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INTRODUCTION

According to the International Association for the Study on Pain, "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Chronic pain refers to pain lasting or

recurring for more than 3 mo^[1]. Chronic low back pain is one of the leading causes of disability in the Chinese population^[2,3]. Hence, treating chronic pain safely and effectively is one of the important clinical problems. In recent years, the research and development of new drugs for chronic pain *via* oral, intravenous and intramuscular delivery are not satisfactory, but transdermal delivery of analgesic drugs has made great progress^[4].

Currently, no international guidelines or consensus are available on the use of transdermal analgesic drugs. Therefore, this article summarizes China's expert consensus on "transdermal pain treatment in China," with a view to regulate and promote the standardized use of the transdermal patch containing analgesic drugs. The consensus was formulated by the pain branch of the Chinese Medical Association with the help of experts and using recent clinical evidence.

OVERVIEW OF TRANSDERMAL DRUG DELIVERY SYSTEM

In the transdermal drug delivery system (TDDS), the drug enters systemic circulation through the skin and capillaries at a certain rate to achieve a systemic or local therapeutic effect^[5,6]. TDDS in the broad sense includes all topically administered formulations such as ointment, patch, cataplasm, aerosol, coating, *etc.*, whereas TDDS in the narrow sense refers to the transdermal patch^[7]. The history of transdermal drug delivery dates back thousands of years. In ancient China, leaves and grass stalks were used to smear the skin and wounds. More than 1500 prescriptions are available in the treatise on external treatment of emergency Guangsheng in the Ming and Qing dynasties^[8]. In the modern era, the scopolamine patch for the treatment of motion sickness was the first transdermal patch to be approved by the Food and Drug Administration (FDA) in 1979. From then on, the transdermal patch has been widely used to treat many diseases^[9].

CLINICAL CHARACTERISTICS OF TDDS

Advantages of TDDS

Compared with other routes of administration, transdermal administration has many advantages, as summarized in [Table 1](#)^[10,11].

Absorption and factors influencing skin absorption

Traditionally, transdermal drugs are absorbed by passive diffusion. The stratum corneum, the outermost layer of the skin, is the main rate-limiting barrier for transdermal drug transport. Factors affecting transdermal absorption include physicochemical properties (molecular weight, solubility, partition coefficient and dissociation constant, PKA), carrier properties and skin conditions ([Table 2](#))^[10,12]. The rate and extent of drug absorption through skin can be calculated using the following formula:

$$\log P = -2.7 + 0.71 \times \log K_o/w - 0.0061 \times M$$

Where, K_o/w = oil-water partition coefficient and M = molecular weight^[9-11].

Systemic and local effects of TDDS

In TDDS for systemic delivery, the drug from TDDS gets transported to the subcutaneous capillaries through the skin without accumulating in the dermis. Once the drug reaches systemic circulation, it exhibits its therapeutic action. Examples of such TDDS include fentanyl transdermal patch, buprenorphine transdermal patch and scopolamine transdermal patch^[10,13].

In TDDS, the drug is transported to the subcutaneous tissue through the skin and then to the deeper tissue to exert local action. Some of the TDDS for local action include nonsteroidal anti-inflammatory drugs (NSAIDs) transdermal patch, capsaicin patch and lidocaine patch^[10,13].

Structure and development of the transdermal patch

According to the characteristics of its dosage form, the transdermal patch can be roughly divided into three generations ([Table 3](#)). The first generation of transdermal patch is the most representative transdermal patch^[14].

The structure of a TDDS includes four layers: (1) an impermeable backing layer to protect the system from invasion of external substances and to prevent the loss of

Table 1 Advantages of transdermal drug delivery system administration

Advantages
Simple administration and improved patient compliance
Avoids hepatic first pass metabolism
Avoids direct interaction of drugs with food or other drugs in the gastrointestinal tract, which may affect drug absorption
Helps in controlled drug delivery and reduces frequency of dosing
Reduces dosage and side effects
Can be removed from the skin surface immediately
Has physical form, characteristics and identification marks so that it can be easily and quickly identified in an emergency (such as when the patient is unresponsive, unconscious or comatose)

Table 2 Factors influencing drug percutaneous absorption^[10,12]

Influencing factor	Effect on transdermal drug absorption
Drug concentration	Generally, the amount of drug absorbed per unit area per unit time increases with the increase in TDDS drug concentration
Drug distribution coefficient	Drugs with both water-soluble and fat-soluble properties can be effectively absorbed through the skin. The water-soluble properties of drugs determine the concentration of the drug at the absorption site and the partition coefficient affects the rate of drug transport at the absorption site
Drug molecular weight	The ideal relative molecular weight for transdermal administration is 400 Da or less
Carrier factor	The main effects of carriers on percutaneous absorption include solubility of drugs in carriers and change of drug distribution coefficient by carrier
Site of application and time	The larger the application area (TDDS) and the longer the application time, the more the drugs are absorbed
Skin conditions	Hydration of skin helps increase percutaneous absorption. TDDS can form a closed water barrier with evaporating sweat to increase the hydration degree of the skin. It can be applied to the thin cuticle, with better absorption through the skin. When the skin is damaged, the drug will directly enter the subcutaneous tissue and capillaries, which may affect the properties of TDDS

TDDS: Transdermal drug delivery system.

Table 3 Development of transdermal patch^[14]

Classification	Characteristic
First-generation transdermal patch	The drug should have suitable properties (highly potency, low molecular weight and lipophilic) to solve the problem of low oral bioavailability, to reduce the frequency of drug administration or to achieve stable drug administration
Second-generation transdermal patch	This generation of patch can promote and improve the percutaneous absorption of small molecule drugs by means of a chemical penetration enhancer, ion introduction or ultrasound
Third-generation transdermal patch	These patches help to promote percutaneous absorption of macromolecules, including therapeutic proteins and vaccines

drugs or evaporation of skin moisture; (2) a drug storage or framework system to store and release drugs; (3) a liner that protects the patch during storage, which has to be removed prior to use; and (4) an adhesive layer to keep the patch in contact with the skin^[10]. The adhesive layer can be divided into peripheral type and surface type. Peripheral type refers to applying a circle of pressure-sensitive adhesive on the periphery of the TDDS drug part. In surface type, TDDS is completely covered with finger-sensitive adhesive coating. Of the two types, the surface type of adhesive layer is the most common^[10].

Only two types of TDDS were available before 1990: reservoir type and matrix type. After 1990, the adhesive dispersion type was introduced. In the adhesive dispersion type, the drug is dispersed in the adhesive layer itself; this helps to reduce the layers to two or three^[15]. Since 1999, the FDA has not approved a reservoir type because of the risk of uncontrolled drug release from the reservoir. Most of the existing patches in the

United States market (72%) are of the adhesive dispersion type^[16].

Complications with application of patch

Dose adjustment is the main challenge faced in the use of a transdermal patch because only fixed dosages are commercially available^[17]. In theory, an alternative option to reduce the dose is cutting the patch. However, cutting the patch may result in altering the structure of the patch, which may result in altering drug release, especially controlled release, and the quality of the adhesive layer^[18]. Cutting the microdrug reservoir of the patch can damage the microparticles of the drug, which leads to inaccuracy of dose evaluation^[17,18]. A comparative study on the use of the clonidine patch (Catapres TTS) in sections and as a whole reported difficulty in predicting absorption degree and rate of drug release after cutting the patch, and the incidence of abnormal (too high or too low) blood concentration increased significantly with sections of patch. For most analgesic drugs, it is recommended to refer to the relevant instructions provided by the manufacturer^[19].

Application site of patch: transdermal analgesic drugs can be applied at two application sites. Opioid transdermal patch is generally fixed on the chest, abdomen or upper arm because of its systemic effect. Topical patches with local effects such as topical NSAID patches, 8% capsaicin patch, 5% lidocaine patch and other patches are generally applied to the pain site^[17,18].

COMMON CLINICAL TDDS

Transdermal NSAIDs

NSAIDs act by inhibiting prostaglandin synthesis and reduce persistent hyperalgesia by inhibiting cyclooxygenase activity to play an analgesic and anti-inflammatory role^[20,21]. Compared with NSAIDs administered systemically, topical administration of NSAIDs reach therapeutic concentrations at the pain/inflammation site while maintaining low serum levels and potentially minimizing adverse effects related to high systemic absorption^[20-22].

The advantages of topical NSAID application depend on the ability of the drug to penetrate the skin and reach the site of action. Different NSAIDs have different penetration abilities. Table 4 summarizes the pharmacokinetic properties of different topical NSAIDs^[23-29]. According to studies reported, for a drug to be formulated as a TDDS, it should have ideal properties such as a partition coefficient ($\log P$) of 1 to 4, molecular weight of < 400 Da, lipophilic, highly potent, low melting point and short half-life^[6,30,31]. The peak plasma concentrations of NSAIDs vary greatly, but their concentrations in synovial fluid were much more stable than those in the plasma^[32]. The plasma concentration of NSAIDs through topical delivery is about 1% to 10% of that of systemic administration. However, whether the concentration of NSAIDs in the local tissue of the application site is higher than that of systemic administration remains uncertain^[32]. Most studies show that the concentration of NSAIDs in the deep tissue of the application site (such as the skeletal muscle and synovium) is equivalent to that of systemic administration. In addition, topical administration of NSAIDs in elderly patients may result in increased plasma concentration, which may be due to reduced drug clearance and thin skin^[31,32].

Topical NSAIDs can be used in different diseases such as acute sprain/strain, low back pain, chronic musculoskeletal pain and neuropathic pain^[13,21,22,31-33]. A review showed similar efficacy with topical and oral NSAIDs in the treatment of chronic skeletal muscle pain^[34,35]. When NSAIDs alone are not effective in treating moderate to severe pain or multisite pain, combination therapy with other analgesic drugs helps in effective treatment. When a combination of topical and oral NSAIDs is used, attention should be paid to avoid an overdose^[36-40].

NSAIDs for topical application can be in the form of ointment, gel, gel paste and patch. Some studies compared topical NSAID patches with ointments and gelatin formulations. The results showed that the permeability of patches was better than that of gelatin and ointments. Compared with ointments, patches had better adherence^[41-44].

Adverse effects with topical NSAIDs can be cutaneous and systemic adverse reactions. The incidence of cutaneous adverse reactions is about 1% to 2%, which include erythema, pruritus, irritation, fever or burning sensation and contact dermatitis. Most of the cutaneous adverse reactions were reported to be mild and disappeared after drug withdrawal^[45-47].

Table 4 Pharmacokinetic characteristics of topical nonsteroidal anti-inflammatory drugs patches^[23-29]

	Loxoprofen sodium	Ketoprofen	Diclofenac sodium	Flurbiprofen	Indometacin	Ibuprofen
Log <i>P</i> value	1.97	2.94	4.31	3.81	4.42	3.51
C _{max} in ng/mL	61.20	891.36	0.81	43.00	27.00	556.00
T _{max} in h	82.30	7.60	16.90	20.00	16.00	14.40
T _{1/2} in h	7.8	NA	NA	13.90	11.55	NA

Transdermal opioids

The commonly used opioid transdermal patches in China are the fentanyl transdermal patch and buprenorphine transdermal patch^[13]. Table 5 represents the pharmacology of opioid transdermal patches^[48-52].

Fentanyl transdermal patch

Fentanyl is a strong opioid analgesic. Its analgesic intensity is about 100 times that of morphine, and its transdermal penetration ability is 43 times that of morphine. Because of its ideal properties such as small molecular weight (337 Da), highly lipophilic properties and no biotransformation in the process of transdermal penetration, it was the first analgesic drug formulated as a TDDS^[49]. The fentanyl transdermal patch was approved by the FDA in 1990 for the treatment of chronic pain^[13]. Other than chronic pain, it is also used for neuropathic pain and cancer pain^[50].

Buprenorphine transdermal patch

Buprenorphine, a semisynthetic derivative of dimethylmorphine, is a partial agonist of the μ opioid receptor and antagonist of the κ receptor. The buprenorphine transdermal patch was approved by the FDA in 2010 for pain treatment. It is used for moderate to severe cancer pain, skeletal muscle pain, neuropathological pain, and visceral pain. As with fentanyl, buprenorphine is also not recommended in the treatment of acute and breakthrough pain^[4,13,51,52].

Compared with fentanyl and other opioids, buprenorphine transdermal patch has lower neurotoxicity, especially in the elderly or patients with Alzheimer's disease. Another significant advantage of the transdermal buprenorphine patch is that no dosage adjustment is needed in patients with renal insufficiency^[13].

Opioid transdermal patches can significantly reduce pain and gastrointestinal related adverse effects such as nausea, vomiting and constipation and reduce the proportion of patients discontinuing treatment due to adverse reactions. However, in the treatment of chronic low back pain and knee and hip arthritis opioids (including opioid transdermal patches) were reported to have no significant difference in relieving pain and improving body function, while more adverse reactions were reported when compared with NSAIDs^[53-57].

Capsaicin transdermal patch

Capsaicin is a selective transient receptor potential vanilloid receptor, subtype 1 agonist that activates the nociceptive sensory nerve fibers (C- and Ad-fibers) of transient receptor potential vanilloid receptor, subtype 1 in the skin, resulting in enhanced sensitivity to stimuli, burning sensation and erythema. Exposure to a single high dose or repeated exposure to low dose of capsaicin can lead to the non-functioning of nociceptors^[13,58].

Studies reported absorption of 1% capsaicin into the epidermis and dermis after an hour of patch application. The absorption of capsaicin is directly proportional to the surface area and time of application. Skin temperature was also found to have an influence on the absorption of capsaicin. The results of a population pharmacokinetics study showed that peak plasma concentration (1.38 ng/mL) of an 8% capsaicin patch was attained after 1.46 h. Moreover, capsaicin has a high protein-binding capacity (93%-94%). After absorption, it is mainly metabolized in the liver by P450, and the elimination half-life is 1.64 h^[59,60]. The transdermal patch available is 8% capsaicin at a dosing frequency of one patch per day. Capsaicin is used for the treatment of neuropathic pain. Better results were reported with capsaicin than placebo in the treatment of post herpetic neuralgia and diabetic peripheral neuralgia^[61,62].

Table 5 Pharmacology of fentanyl and buprenorphine transdermal patches^[48-52]

	Fentanyl transdermal patch	Buprenorphine transdermal patch
Absorption	Bioavailability, 92%; Plasma protein binding, 79%-87%; Cmax, 2.6 µg/L; Effective time, 12.7-16.6 h; Peak time 38.1 h; AUC, 117 µg/L; H (0-72 h)	Bioavailability, 50%; Plasma protein binding, 96%; Cmax, 305 pg/mL; Onset time 21 h; Peak time, about 60 h; AUC, 20228 pg/mL
Metabolism	Metabolized by CYP3A4 in the liver, and the metabolites are basically inactive	Metabolized by CYP3A4 in the liver
Elimination	The half-life of the transdermal patch is about 17 h (13-22 h)	The half-life of the transdermal patch is 25.3 h
Mechanism	µ opioid receptor agonist	µ opioid receptor partial agonist, δ opioid receptor agonist, weak κ opioid receptor antagonist, ORL-1 agonist
Indication	Moderate to severe chronic pain and intractable pain treated with opioid analgesics	Chronic pain beyond the control of nonopioid analgesics
Dosage form specification	2.1-, 4.2-, 8.4- and 12.6-mg paste; Four specifications, lasting for 72 h	5-, 10- and 20-mg paste. Each paste is used for 7 d
Adverse reactions, > 10%	Nausea, headache, constipation, dry mouth, drowsiness, fuzzy consciousness, powerlessness, sweating	Erythema, pruritus, nausea

AUC: Area under the curve; ORL: Opioid receptor like; TDDS: Transdermal drug delivery system.

Lidocaine transdermal patch

Lidocaine is a voltage-gated sodium channel blocker (mainly Nav1.7 and 1.8). It can reduce the ectopic negative charge, increase the threshold of peripheral ectopic discharge and reduce the pain transmission by stabilizing the membrane potential of neurons on abnormal excitation of Aδ and C fibers to have an analgesic effect. In addition, the lidocaine patch also has an analgesic effect on pain from injurious sources^[13,63].

Transdermal lidocaine majorly penetrates local tissues through the skin, and very little is absorbed into systemic circulation (about 3% ± 2%); hence, adverse reactions related to systemic administration can be avoided. Patients with severe impairment of heart, kidney and liver function should be cautious with lidocaine use. It is contraindicated in pregnant women and patients allergic to local anesthetics^[13,64,65].

The lidocaine patch is generally well tolerated even after long term use. The most common adverse events include erythema, pruritus, rash, burning sensation, dermatitis, edema and other skin reactions. The lidocaine patch is used in the treatment of neuropathic pain, but there is no high-quality evidence to prove its clinical efficacy^[64-69].

Other transdermal patches

The ketamine transdermal patch and dextromethorphan transdermal patch are common nonbarbiturate anesthetics. They are peripheral N-methyl-D-aspartate receptor inhibitors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor inhibitors. They also inhibit voltage-gated Na⁺ and K⁺ channels^[63].

Ketamine transdermal patch (25 mg/24 h) is used to relieve postoperative pain. The 4% dextromethorphan hydrochloride is formulated with 4% lidocaine and 10% trolamine salicylate (Permavan) and used to treat pain, but its efficacy and safety have not been determined. At present, neither of the two transdermal patches have been approved for marketing^[70,71].

The bupivacaine transdermal patch is also under development. Compared with the lidocaine patch for 12 h, the bupivacaine patch can be applied once every 3 d and can be used for post herpetic neuralgia treatment. The United States bupivacaine transdermal patch (Eladur) is under investigation^[71].

Rotigotine and amitriptyline are commonly used in the treatment of neuropathic pain. At present, the rotigotine transdermal patch (listed in Europe and the United States in 2007 and in China in 2018) and amitriptyline transdermal patch are available. The rotigotine transdermal patch can improve chronic pain in Parkinson's disease^[72]. However, neither of the drugs has been approved for pain treatment^[73].

Clonidine, a α₂ adrenergic receptor agonist and imidazoline receptor agonist, is used in antihypertension, acute and chronic pain management and sedation. However, the clonidine transdermal patch is currently approved only in the treatment of hypertension. The analgesic effect of the clonidine patch is related to the α₂ receptor in the skin and the imidazoline receptor in the peripheral nerve endings, but clonidine

use in the treatment of neuropathic pain is insufficient^[71,74-77].

CONCLUSION

Based on expert opinions and careful assessment of the existing evidence, the classification and definition of grade evidence were summarized in Tables 6 and 7, while the consensus recommended by experts was summarized in Table 8. This consensus can help clinicians to use transdermal patches in pain management more effectively.

Table 6 Quality classification and definition of grade evidence

Quality level	Definition
High (a)	Very sure that the true effect value is close to the effect value estimation
Medium (b)	There is a moderate degree of confidence in the value of effect; the real effect value may be close to the estimated value, but there is still a possibility that the two are not the same
Low (c)	There is limited confidence in the effect estimates; the true effect values may not be the same as the effect estimates
Very low (d)	There is little confidence in the estimated effect; the true effect value may be quite different from the effect estimate

Table 7 Grade recommended strength classification and definition

Recommended strength	Explanation	Expression method	Expression method
Strong recommendations to support the use of an intervention	The advantages of the intervention measures outweigh the disadvantages	Recommended	1
Weak recommendations to support the use of an intervention	Interventions may have more advantages than disadvantages	Recommended use	2
Weak recommendations against the use of an intervention	Interventions may do more harm than good or the relationship between the advantages and disadvantages is not clear	Not recommended	2
Strong recommendations against the use of an intervention	The disadvantages of the intervention measures are obviously greater than the advantages	Not recommended	1

Table 8 Consensus statement of Chinese experts on pain treatment with transdermal patch

Consensus opinion	Recommended strength level of evidence
The effect of the transdermal patch in pain treatment is clear. It has the advantages of reducing adverse drug reactions and improving patient compliance	1A
NSAID transdermal patch is effective in the treatment of chronic skeletal muscle pain with few side effects, which is recommended as the first choice for the treatment of chronic musculoskeletal pain	1A
NSAIDs can be used as a combination therapy for neuropathic pain	2C
When the efficacy of transdermal NSAIDs alone is not good enough, which can be combined with analgesic drugs of another administration route, such as oral NSAIDs	2B
Opioid transdermal patch is effective in the treatment of chronic pain, but it should not be used as the initial treatment for chronic pain due to addiction and adverse reactions	1B
Opioid transdermal patch should not be used in the treatment of acute or breakthrough pain	1A
When other first-line treatment drugs are ineffective, 8% capsaicin patch can be considered for chronic pain related to peripheral neuropathic pain	1B
When other first-line treatment drugs are ineffective, 5% lidocaine patch can be considered for chronic pain related to peripheral neuropathic pain	2B

NSAID: Nonsteroidal anti-inflammatory drug.

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