BuprePLAST Patch Monograph

Composition

Each transdermal patch contains
Buprenorphine.....5mg / 10 mg
Excipients..... q.s.

Zuventus Healthcare Ltd

Preface

> ***"Pain is inevitable; suffering is optional"***
> - Old Buddhist saying

Pain is a universal phenomenon afflicting millions of individuals across the world and is in fact one of the commonest symptoms for which a patient seeks medical attention. The prevalence of pain interestingly is much higher than many common diseases like cancer, heart disease, diabetes put together. Pain may result from several reasons such as an underlying disease, a chronic health condition, or sometimes due to unknown reasons.

Uncontrolled pain can have several physical and psychological ill-effects hence it is imperative to address it satisfactorily. The costs associated with pain are extremely high, both to the healthcare system and to society at large. Not only do individuals with pain have a greater rate of utilization of the healthcare system, but their productivity is substantially diminished.

Management strategies for pain include pain-relieving medications, physical therapies and complementary therapies (such as acupuncture and massage). Analgesics are broadly divided into two classes, that is, Opioid and non-opioid drugs.

The opioids are emerging as the primary option for cancer pain treatment as approximately 70% of cancer patients and 85% of those suffering from cancer-related pain eventually require management with opioids. The use of opioids is also increasing for treatment of chronic non-malignant pain with established benefits in inflammatory, ischemic, visceral, musculoskeletal, and neuropathic pain. Transdermal formulations have been recognized as an effective, convenient delivery method that encourages patient compliance.

- Buprenorphine, a potent opioid analgesic that acts primarily as a partial agonist at the μ-opioid receptor, was synthesized from thebaine in 1966. Buprenorphine has been used in clinical practice for over 30 years, but the interest in the drug increased after introducing transdermal products. In 1978, Dr Donald R. Jasinski of the US Addiction Research Center described buprenorphine as

A substance with a unique pharmacology with immediately obvious therapeutic applications as an analgesic of low abuse potential

More than 30 years of subsequent clinical data support this statement. The role of buprenorphine continues to be unique among opioid analgesics, particularly in light of the global chronic pain epidemic and an important opioid in the 'tool box' of analgesics.

Contents

Summary

- Uncontrolled pain can have several physical and psychological ill-effects hence it is imperative to address it satisfactorily. Pain is a multidimensional and complex experience that has physical, social, spiritual and psychological aspects.
- According to a study by the World Health Organization, individuals who live with persistent pain are four times more likely than those without pain to suffer from depression or anxiety, and more than twice as likely to have difficulty working. In 1996, the American Pain Society (APS) introduced the phrase “pain as the 5th vital sign.”
- Opioids can be used in cancerous pain and also in the treatment of chronic pain of noncancer origin and are particularly important in the treatment of chronic pain where nonopioid analgesics have proved to be of insufficient effect.

Characteristics of an Ideal transdermal opioid

- Small molecular weight
- High lipophilicity
- High efficacy to compensate for limited absorption
- Low melting temperature
- Relatively short half–life
- Low daily dose
- System dosing providing absorption from a relatively small area
- Matrix patches in which a total amount of a drug is localized homogenously in an adhesion layer

Natural features listed above ease the crossing of a drug through the skin and are possessed by Buprenorphine

Buprenorphine

- Buprenorphine has been used in clinical practice for over 30 years, but the interest in the drug increased after introducing transdermal products.
- Buprenorphine is a semi–synthetic derivative of thebaine. Buprenorphine’s high lipid and water solubilities, low molecular weight (467 kDa) and structural configuration allow the drug to penetrate tissues and body compartments readily. Thus, buprenorphine is readily absorbed from whatever body compartment into whichever it is introduced.

Receptor binding Profile:

- The buprenorphine receptor binding profile is unique in that it binds to all three major opioid receptors (mu, kappa, delta), with much less affinity to the orphan-like receptor (ORL-1).

- Buprenorphine has mixed agonist/antagonist properties – it is a partial agonist at μ-opioid receptors, which appears to be responsible for its analgesic activity, an antagonist at κ-opioid receptors, and a weak agonist at δ-opioid receptors. Binding to and dissociation from the μ-receptor is slow and, thus, the effects of buprenorphine are slow in onset and long in duration.

Pharmacokinetic Profile:

- Buprenorphine has unique pharmacology and markedly distinct profile vs other opioids.
- Primarily excreted in feces and does not accumulate in the body, clearance is independent of renal function and is not removed by dialysis, making it a preferred analgesic in renal failure.
- Clearance is also not influenced by mild to moderate liver failure.

Safety Profile:

Safety of buprenorphine is much superior over the marketed opioids –

- Ceiling effect on respiratory depression but not for analgesia,; much lower risk vs other opioids;
- Lower constipation risk vs other opioids;
- Safest opioid for CNS, immune-suppression issues;
- Anti-hyperalgesic profile and low tolerance issues;
- Low clearance through renal path; no clinically relevant changes in patients with renal impairment;
- Safer option for seniors; minimal drug–drug interactions and minimal influence on pk.
- Lower propensity for opioid abuse or addiction than typical full opioid agonists and its transdermal matrix makes it difficult to extract the substance for nonmedical use
- Buprenorphine continues to be used as an effective treatment for opioid addiction during induction, stabilization, and maintenance phases.

Transdermal Advantage:

Transdermal application (TDS) of buprenorphine meets all the requirements for successful treatment of chronic pain and offers the following significant advantages over oral or parenteral routes of administration:

- Slow and continuous release into the systemic circulation.
- Constant serum levels over prolonged periods of time and noninvasive administration.
- Steady and continuous dose of buprenorphine over a period of up to seven days which confers the convenience of once-weekly dosing.

- Provides convenient administration, making it an optimal delivery route for elderly patients and for those with dysphagia and other gastrointestinal maladies.
- Avoids the discomfort associated with multiple intra- muscular injections and a patient's unwillingness to swallow oral preparations.
- Low concentrations of drugs and small fluctuations of their concentration in the blood serum guarantee long–lasting analgesia with a lower number of adverse effects, especially nausea, vomiting, and constipation.
- Opioid formulations with extended-release (ER) and tamper-resistant properties offer the advantage of achieving analgesia while minimizing risks for opioid abuse or addiction.
- The stability of analgesia, dosage flexibility, ease of application and marginal side-effect profile of BTDS may result in increased patient compliance.

Efficacy and safety:

- BTDB has demonstrated good efficacy and an acceptable tolerability profile in patients with chronic non-malignant pain in randomized controlled trials.
- Pain intensity and sleep disturbance were considerably reduced and patients experienced improved physical function and quality of life after treatment. TDB was tolerated by the majority of the patients in these studies.
- TDB was noted to be non-inferior to other opioid analgesics in reducing pain. Apart from application site reactions that were typical of transdermal delivery systems, TDB has an AE profile that is comparable with the other opioid analgesics.

Given its superior safety and efficacy profile, buprenorphine can now be considered as a first line therapy for the treatment of a wide range of chronic pain conditions.

Pain

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” According to the Joint Commission International, Margo McCaffrey’s definition of pain is the gold standard for patient treatment in clinical practice. McCaffrey defines pain as “whatever the experiencing person says it is, existing whenever he or she says it does.”[1]

The function of pain is to protect the body by making the organism aware of damaging events and to promote healing by causing sensitivity to movement or other stimuli that may delay recovery.[2] Pain is noxious, which makes it a powerful protective force: indeed the inability to feel pain is associated with a shortened life expectancy. After injury, pain encourages us to adopt behaviours that help the healing process; for example, resting the painful part of the body.[3]

Pain is one of the most common reasons for visit to a general physician. Pain may result from several reasons such as an underlying disease, a chronic health condition, or sometimes due to unknown reasons.[4]

Epidemiology

The prevalence of pain interestingly is much higher than many common diseases like cancer, heart disease, diabetes put together and is a huge burden for the healthcare economy.[4] Approximately 30% of the world's population suffers from pain.[5] A survey conducted by the World Health Organization (WHO) in 15 centers across Asia, Africa, Europe, and United States of America demonstrated the prevalence of chronic pain in 5 % to 33% of the population.[6]

A study conducted by Saxena AK et al, showed huge burden of chronic pain in India with prevalence rate of 19.3%, which translates into 180–200 million adults having chronic pain. The prevalence may increase significantly during next two decades, negatively impacting the global health status, man-hours, and overall economy of the nation.[5]

Pain as the 5th vital sign

In 1996, the American Pain Society (APS) introduced the phrase “pain as the 5th vital sign.” This initiative emphasises that pain assessment is as important as assessment of the standard four vital signs and that clinicians need to take action when patients report pain.[4]

Classification of pain

According to the World Health Organization (WHO), anatomic, etiologic, duration, and pathophysiological are the most commonly used classification systems.

- **The Anatomic Pain:**
  Describes the specific region or area of the body that is perceived to be experiencing pain.[1]
- **The etiologic pain:**

Describes the causative factor of pain. Etiologic classification of pain can be subdivided into malignant versus non-malignant.[1]

- **The pain intensity:**
  Can be measured through visual, numerical, rating, and/or descriptor scales. The national institute of pain control recognizes the wong-baker faces pain scale, the 0 to 10 numeric pain rating scale, the verbal pain intensity scale, the neuropathic pain scale, the descriptor differential scale, and the visual analog scale.[1]
- **The duration of pain**:
  Represents the duration of time the patient experiences pain. The 2 primary duration classifications are acute and chronic pain.
  - **Acute pain** is often related to acute injury or trauma, and acts as a warning system in the body. Acute pain plays a vital role in providing warning signals that something is wrong and is in need of further examination. It is self-limiting and resolves over days to weeks, but it can persist longer as healing occurs.
  - **Chronic pain** is currently defined as continuous or intermittent pain that continues after anticipated time for healing of tissues. Chronic (persistent) pain represents long-term pain, 3 months or longer, and is commonly associated with various disease processes, including psychological conditions. Chronic pain can be viewed as its own disease than as a symptom of another health problem.
    Common sources of chronic pain:
    Cancer pain, Arthritis, Headache, Low back pain, Human immunodeficiency virus, Neuropathic pain disorders[1,7]

- **Neurophysiological mechanism of pain:[7]**
  It has been categorized as nociceptive and nonnociceptive pain.

a. Nociceptive pain[7]

Nociceptive pain is presumed to be maintained by continual tissue injury, it results from the activation or sensitization of nociceptors in the periphery, which transduce noxious stimulus into electrochemical impulse. These impulses are then transmitted to the spinal cord and higher rostral centers in the central nervous system. Nociceptive pain is sub-divided into somatic and the visceral pain.

Somatic pain

Results from excitation and sensitization of nociceptors in tissues, such as bone, peripheral soft tissue, joints, and muscles. Somatic pain is characterized, as well localized typographically. It is intermittent or constant and is described as aching, stabbing, gnawing, or throbbing. There are five physiological processes involved in the somatic nociception.

i. **Transduction:** noxious stimuli (mechanical, chemical, and thermal) act on peripheral nociceptors and are converted into electrical activity, hence, culminating in an action potential. This is carried as a nerve impulse.

ii. **Conduction:** nerve impulse travels through the length of the first order neurons to reach the synapse with the second order neuron.

iii. **Transmission:** synaptic transfer of information takes place at the synapse between the first and the second order neurons in the dorsal horn of the spinal cord.

iv. **Perception:** the actual conscious experience of the pain, both sensory (localization, character, and discrimination) and affective (emotional) aspect.

v. **Modulation:** pain experience is not a direct and proportionate mechanical response to the noxious stimuli. A multitude of factors modulate the stimulus–response pathway.

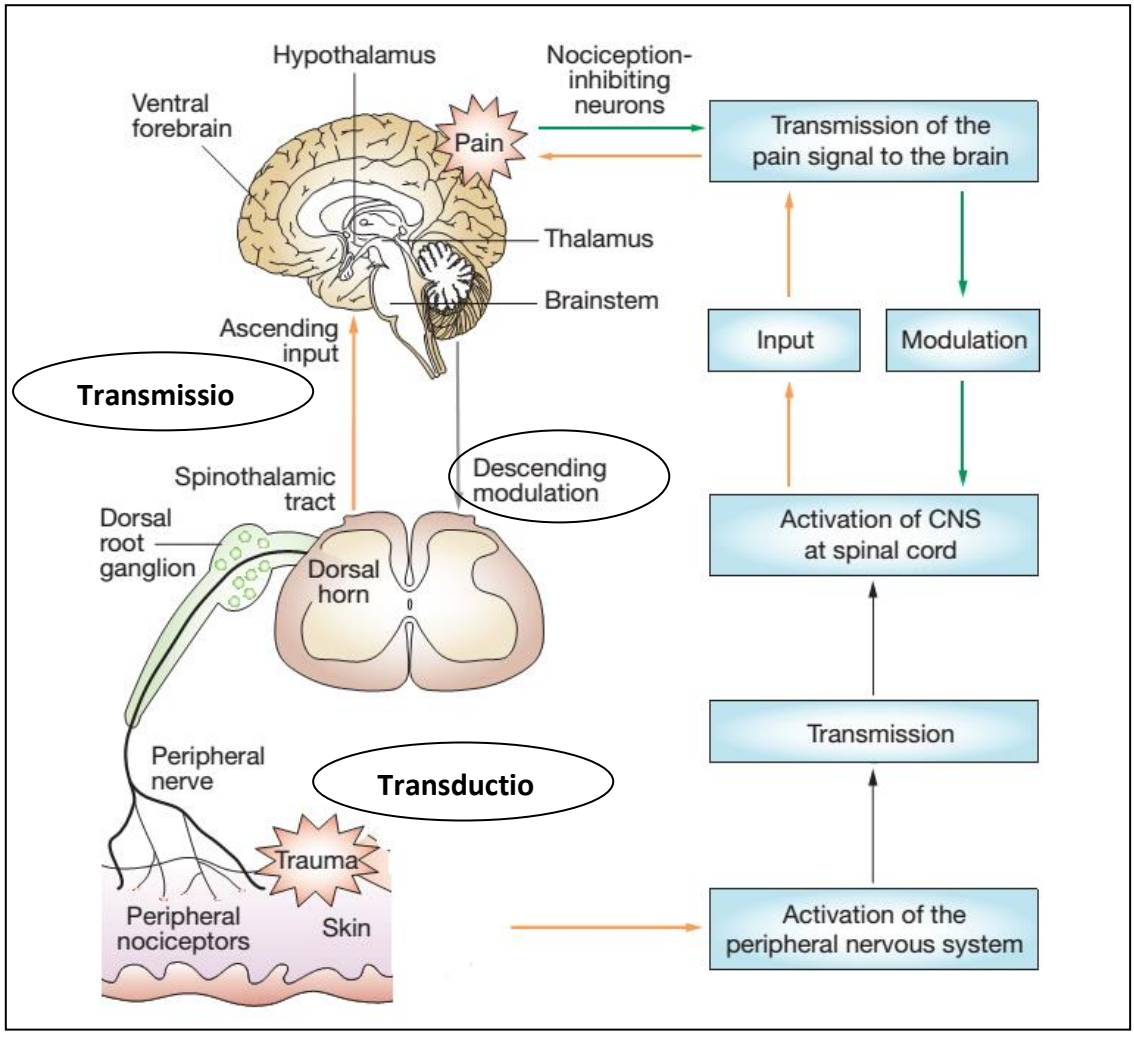

Figure 1: The basic route of pain transmission upon noxious stimuli in ascending and descending order, and the illustration of synaptic transmission in synaptic cleft[8]

Visceral pain

Visceral pain has five important characteristics:

i. Visceral organs are not sensitive to pain.
ii. It is not always linked to visceral injury (cutting the intestine cause no pain, but stretching of the bladder cause pain).
iii. It is diffuse and poorly localized.
iv. It is referred to other locations.
v. It is accompanied by motor and autonomic reflexes such as nausea and vomiting.

b. Non-nociceptive pain[7]

Non-nociceptive pain can be sub-divided into neuropathic and idiopathic pain.

Neuropathic pain

Neuropathic pain can result from injury to neural structures within the peripheral and central nervous system. It is believed to be caused by aberrant somatosensory processing in the central and the peripheral nervous system. Neuropathic pain is usually sharp and burning. There are three subset of neuropathic pain.

i. Peripherally mediated involve the peripheral nerves, brachial plexus.
ii. Central pain syndrome involves the nervous system.
iii. Sympathetically mediated pain that can be generated centrally and peripherally, like RSD symptoms.

Idiopathic pain

Idiopathic pain is used interchangeably with the psychogenic pain. Idiopathic pain is more appropriate as it implies broad spectrum of poorly understood pain states such as myofascial pain syndrome and somatization pain disorder.

Consequences of the pain

Uncontrolled pain can have several physical and psychological ill-effects hence it is imperative to address it satisfactorily.[4] Pain is a multidimensional and complex experience that has physical, social, spiritual and psychological aspects.[9] According to a study by the World Health Organization, individuals who live with persistent pain are four times more likely than those without pain to suffer from depression or anxiety, and more than twice as likely to have difficulty working.[10]

The costs associated with pain are extremely high, both to the healthcare system and to society at large. Not only do individuals with pain have a greater rate of utilization of the healthcare system, but their productivity is substantially diminished.[11]

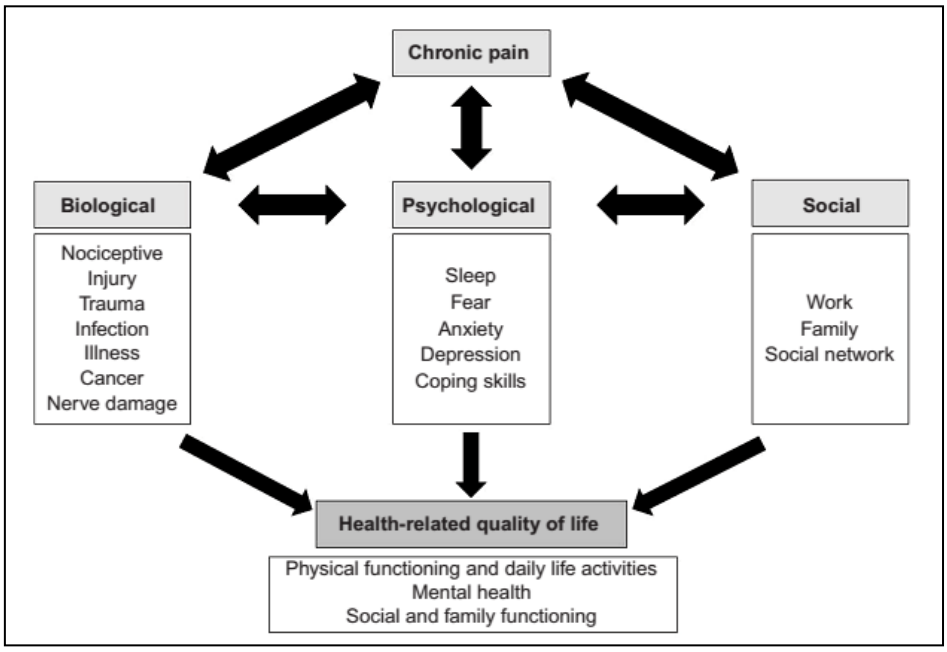

Figure 2: Biopsychosocial model of pain and consequences on the quality of life[12]

Management of Pain

Five identified dimensions contribute to pain management. The dimensions have physiological, sensory, affective or cognitive, and sociocultural components unique for each patient that should be considered.

- Prompt recognition and treatment of pain
- Involvement of patients in the pain management plan
- Improvement of treatment patterns
- Reassessment and adjustment of the pain management plan as needed and
- Monitoring processes and outcomes of pain management[13]

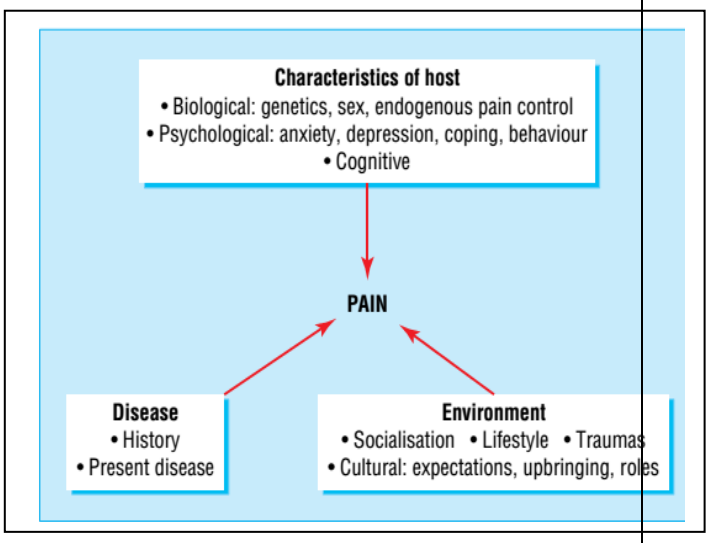

Figure 3: Biopsychosocial factors that interact and modulate the experience of pain[14]

Management strategies for pain include pain-relieving medications, physical therapies and complementary therapies (such as acupuncture and massage).

Analgesics are broadly divided into two classes, that is, Opioid and non-opioid drugs. Opioids are generally reserved for relieve of severe pain and are usually provided under supervision and strict control because of tendency to dependence and abuse. On the other hand non-opioid analgesics are freely available to patients and they provide remedies for mild to moderate pain.[15]

Nonopioid Analgesic Agents

Acetaminophen, Aspirin, and NSAIDs, Antidepressant Agents, Local anesthetics, Antiepileptic Medications, α Agonists

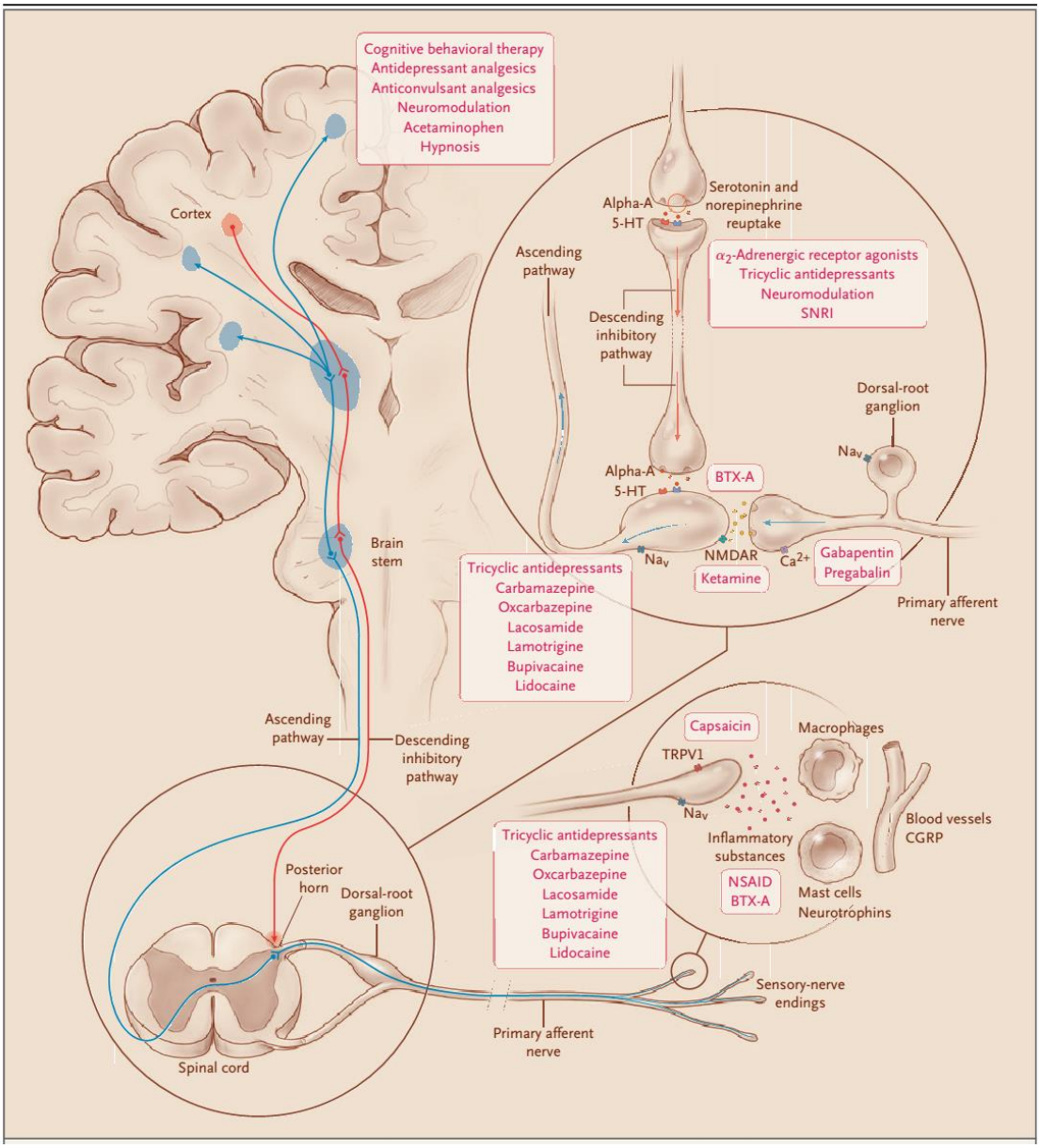

Fig 4: Sites of Action of Various Methods of Pain Management

Opioids

- The first undisputed reference to opium is found in the writings of Theophrastus in the third century B.C. Arab physicians were well-versed in the uses of opium; Arab traders introduced the drug to the Orient, where it was employed mainly for the control of dysentery. By 1680, Sydenham was lauding opium: "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."
- In 1806, Frederich Sertürner, a pharmacist's assistant, reported the isolation by crystallization of a pure substance in opium that he named morphine, after Morpheus, the Greek god of dreams.
- Until the early 1970s, the effects of morphine, heroin, and other opioids as anti-nociceptive and addictive agents, were well described, but mechanisms mediating the interaction of the opioid alkaloids with biological systems were unknown.[16]
- Opioids are used in the treatment of chronic pain of cancer & noncancer origin and are particularly important in the treatment of chronic pain where nonopioid analgesics have proved to be of insufficient effect.
- The best-known opioid is morphine, which is the naturally occuring principal alkaloid in opium. However, in the past, the use of opioids has been curtailed through concerns about misuse, tolerance, addiction, respiratory depression and other side effects such as nausea, vomiting, constipation and drowsiness.[16]

Opioid receptors

- Opioid analgesics act on 3 major classes of receptors: μ, δ and κ receptors.
- Each of these classes of receptors has its representative endogenous ligand (eg, endorphin for the m receptor and dynorphin for the k receptor).
- These classes of opioid receptors are widely distributed throughout the central and peripheral nervous system as well as other systems such as the gastrointestinal tract.
- On the basis of their pharmacodynamic profiles, opioid analgesics can also be classified as a full agonist at opioid receptors (eg, morphine, fentanyl) or an agonist-antagonist such as buprenorphine.[17]

	Site of Action	Effects
Mu	Systemic	Analgesia, euphoria, constipation, respiratory depression
	Peripheral	Analgesia, constipation, reduced inflammation
Delta	Systemic	Analgesia, convulsions, anxiolysis
	Peripheral	Analgesia, constipation
Kappa	Systemic	Analgesia, diuresis, dysphor
	Peripheral	Analgesia, reduced inflammation

Figure 5: Opioid receptors[19]

WHO Analgesic Step Ladder

- The World Health Organization's (WHO) pain relief ladder describes a hierarchy of pharmacologic interventions to treat cancer-related pain of increasing intensity.
- In a first step, nonopioids are given, then, if necessary, mild opioids, then more potent opioids until the patient's pain is significantly reduced.[19]

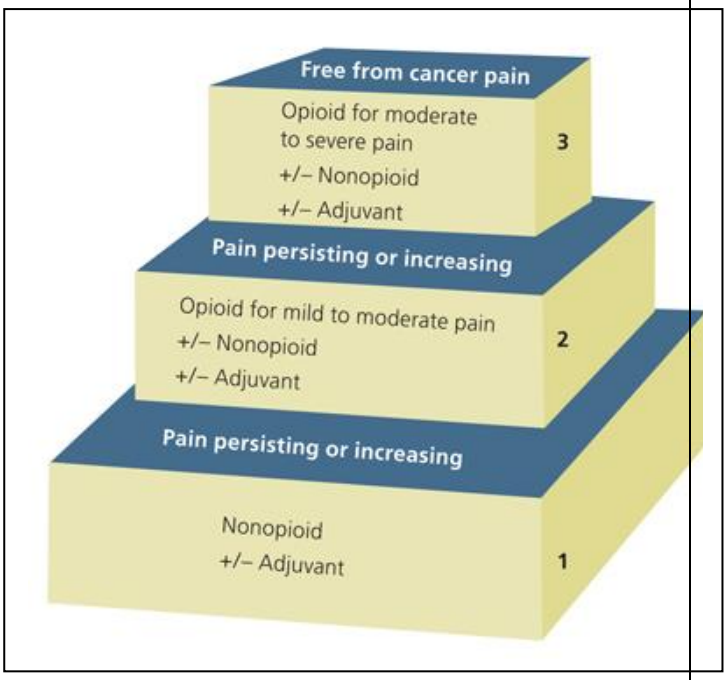

Figure 6: WHO Pain Relief Ladder

- The comprehensive treatment of pain is multidimodal, with pharmacotherapy playing a key role.
- An effective therapy for pain depends on the intensity and type of pain, the patients' age, comorbidities, and appropriate choice of analgesic, its dose and route of administration.
- Opioids are the oldest and most potent drugs for the treatment of severe acute and cancer pain.[19,20]

Guide to prescription of opioids for chronic non-malignant pain

Contract with patient

- One prescriber
- Amount to be dispensed
- No additional prescriptions
- Consequences of breaking contract

Monitoring

- Titration of doses
- Use of short acting opioids
- Use of injectable opioids at home
- Prescription of more than one opioid
- Assessment at intervals of 6-9 weeks[14]

When to avoid

- Alcohol problems
- Drug problems
- Other treatments not tried first
- If in doubt

Aims

- Focus on improved function not pain relief
- Use of long acting opioids
- Make prescriptions tamper proof[14]

Limitations of current opioid therapy

- **Constant demand for more efficacious and safer treatment options**
  - Despite rising opioid prescriptions, many patients feel nonsatisfactory response to treatment options.
  - In addition, long-term use of opioid therapy leads to the development of tolerance and hyperalgesia limiting their clinical utility in controlling chronic pain.
  - Chronic use of opioids also accounts for other side effects such as respiratory depression, constipation, dependence, and abuse potential. With a growing senior population (projected to be approximately 25% by 2020 in major countries), there is constant demand for more efficacious and safer treatment options for patients.[21]

- **Advantages of the transdermal drug delivery system**
  - Avoids the discomfort associated with multiple intra- muscular injections and a patient's unwillingness to swallow oral preparations.
  - The use of the transdermal route allows for the avoidance of problems associated with a disturbed absorption of a drug from the gastrointestinal (GI) tract or other GI problems (i.e., swallowing difficulties, nausea, vomiting), as well as the elimination of the first pass effect through the liver.
  - Avoids issues associated with hepatic first-pass metabolism, poor absorption from the gastrointestinal tract and low or variable interpatient bioavailability.
  - Low concentrations of drugs and small fluctuations of their concentration in the blood serum guarantee long–lasting analgesia with a lower number of adverse effects, especially nausea, vomiting, and constipation.
  - The transdermal form of drugs provides simplicity and convenience of administration, increases compliance, and improves patients' quality of life.[22]

Characteristics of an Ideal transdermal opioid

- Small molecular weight
- High lipophilicity
- High efficacy to compensate for limited absorption
- Low melting temperature
- Relatively short half–life
- Low daily dose
- System dosing providing absorption from a relatively small area
- Matrix patches in which a total amount of a drug is localized homogenously in an adhesion layer

The above technology ensures regulation of the release of an opioid based on a gradient concentration between a patch and the skin. The damage of a patch does not evoke an uncontrolled release of an active substance and enables the division of a patch into smaller parts in order to administer a lower dose of a drug, which is especially relevant in older patients.[20]

Natural features listed above ease the crossing of a drug through the skin and are possessed by Buprenorphine

Buprenorphine

Buprenorphine (Figure 7) is a semi synthetic derivative of an opiate alkaloid thebaine that is isolated from the poppy *Papaver somniferum*. Buprenorphine is a hydrophobic molecule and carries a complex chemical structure with multiple chiral centers.[21]

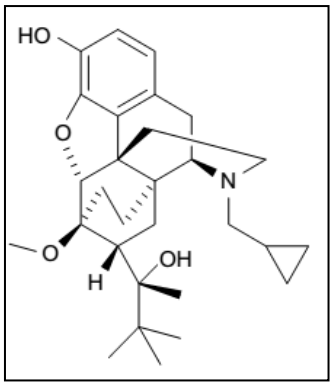

Figure 7: Structures of buprenorphine

Buprenorphine was synthesized from thebaine in 1966, and, approximately 12 years later, Donald Jasinski of the US Addiction Research Centre, issued the following statement:

"In conclusion, buprenorphine has a unique pharmacology with immediately obvious therapeutic applications as an analgesic of low abuse potential"[23,24]

Pharmacology

Pharmacodynamics

Buprenorphine's high lipid and water solubilities, low molecular weight (467 kDa) and structural configuration allow the drug to penetrate tissues and body compartments readily. Thus, buprenorphine is readily absorbed from whatever body compartment into whichever it is introduced.[19]

Receptor binding

- Buprenorphine has a distinct profile, significantly different from morphine, codeine, fentanyl, or methadone.[21]
- The buprenorphine receptor binding profile is unique in that it binds with high affinity to all three major opioid receptor classes (mu, kappa, delta), and with lower affinity to the orphan-like receptor (ORL-1), the receptor for orphanin FQ/nociceptin.[24]
- **μ- receptor:** It is a potent but partial agonist of μ-opioid receptor, showing a high affinity but low intrinsic activity (Figure 9). High potency and slow off rate (half-life of association/ dissociation is 2–5 hours) help buprenorphine displace other μ-agonists such as morphine, methadone from receptors and overcome opioid dependence issues. Buprenorphine is approximately 25–100 times more potent than morphine.
- The slow dissociation from μ-receptor also accounts for its prolonged therapeutic effect to treat opioid dependence as well as pain.

Opioid receptor	Ki (nM)	Agonist/antagonist
μ	1.5	Partial agonist
δ	6.1	Antagonist
κ	2.5	Antagonist
Nociceptin or ORL1	77.4	Agonist

Abbreviation: ORL1, opioid receptor-like 1.

Figure 8: Buprenorphine – binding affinity (Ki, nM) for opioid receptors[21]

- **κ-receptor:** Buprenorphine is a potent κ-receptor antagonist. The inverse agonist activity at the kappa receptor may explain buprenorphine-associated antihyperalgesic activity, as hyperalgesia is likely the result of dynorphin upregulation. It is also a reason why there is less sedation and dysphoria with buprenorphine. Finally, kappa receptor antagonism is associated with antidepressant activity, which may be one reason why buprenorphine has been found to reduce depression and suicide ideation.[21,24]

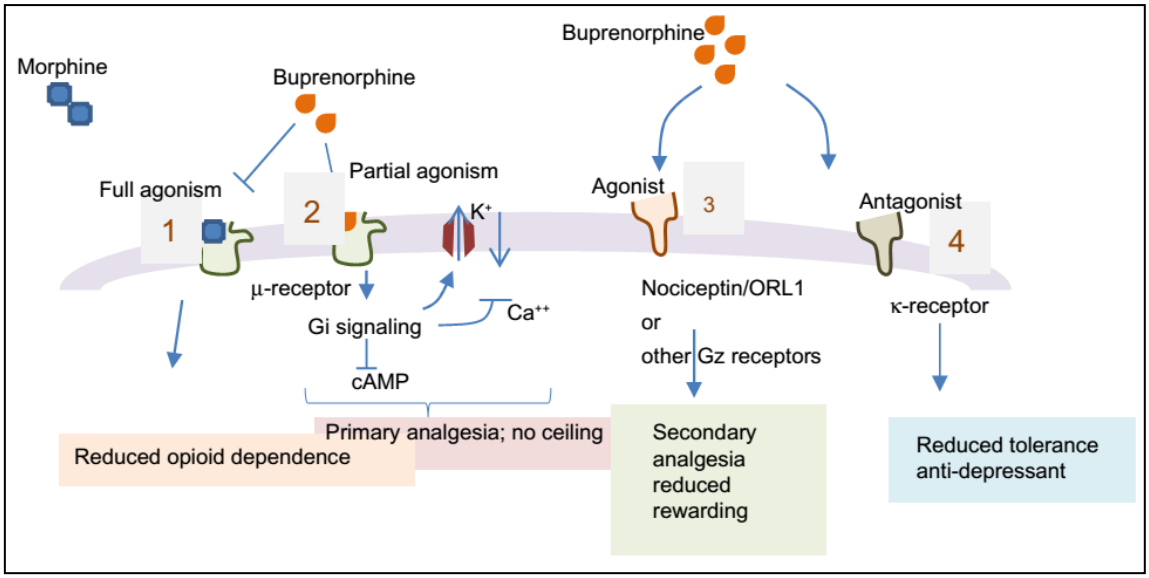

Figure 9: Implications of buprenorphine interactions with opioid receptors[21]

(**1**) It can displace or block morphine binding to μ-receptor thus contributes to reduced opioid dependence.

(**2**) Buprenorphine agonist activity on μ receptor is the primary contributing factor to its analgesic signaling events.

(**3**) Buprenorphine interacts with nociceptin/ORL1 with much lower affinity and thus is unlikely to contribute to analgesic effects at therapeutic doses.

(**4**) Buprenorphine is a potent antagonist of κ-opioid receptor and this interaction could contribute to reduced tolerance and antidepressant like activity.[21]
Abbreviation: ORL1, opioid receptor-like 1.

Pharmacokinetics

When administered orally, buprenorphine undergoes extensive first-pass metabolism and its oral bioavailability is insufficient to achieve analgesic drug concentrations.[19]

Absorption

Following Buprenorphine patch application, buprenorphine diffuses from the patch through the skin. In clinical pharmacology studies, the median time for Buprenorphine patch 10 microgram/hour to deliver detectable buprenorphine concentrations (25 picograms/ml) was approximately 17 hours. Analysis of residual buprenorphine in patches after 7-day use shows 15% of the original load delivered. A study of bioavailability, relative to intravenous administration, confirms that this amount is systemically absorbed. Buprenorphine concentrations remain relatively constant during the 7-day patch application.

The 7-day low-dose transdermal buprenorphine patch has T_{max} of 72 h. There is a 70% variance in peak to trough plasma concentrations over the 1-week period, and there are consistent dose to plasma concentrations with each patch if placed properly.

Over a 3-week period, the 10 µg/h dose produces a minimum plasma concentration that ranges between 108 and 112 pg/mL. The drug half-life after removing the patch is reported to be between 12 and 36 h. Absolute bioavailability of the low-dose transdermal buprenorphine patch is 15% compared with parenteral injection.[24,26]

Distribution:

Buprenorphine is approximately 96% bound to plasma proteins.[26]

Metabolism

Buprenorphine is metabolized by the gut wall and liver. In the human liver, it is metabolized predominantly to buprenorphine-3-glucuronide and partly oxidized to a Ndealkylated product, N-dealkylbuprenorphine (norbuprenorphine), in a reaction mediated by cytochrome P450 3A4. Ndealkylbuprenorphine also undergoes glucuroconjugation and can be found in the plasma, but has a low brain penetration.

Biliary excretion has a major role in the elimination of buprenorphine. Radioactive-labelled drug was excreted mainly in the feces – 71% after 15 µg/kg orally and 68% after 2 µg/kg intramuscularly, with 15 and 27%, respectively, appearing in the urine. In humans, buprenorphine remains mainly unchanged in the feces, whereas the urine contains conjugates of the parent compound and norbuprenorphine.[19]

Special Population

- In short-term treatment with buprenorphine, end-stage renal failure does not seem to affect the excretion of the drug. This is in contrast to morphine, for which clearance fell markedly in patients with end-stage renal failure.
- As the expression of CYP3A proteins is significantly reduced in patients with severe chronic liver disease, the metabolism of buprenorphine is suspected to be altered in liver cirrhosis, and dose adjustments may be required in patients with liver insufficiency[19].
- Multiple studies undertaken on elderly patients (age 65 years and above) indicate that PK profile, efficacy results, or adverse events of buprenorphine did not alter with age.[21]

For all opioids except buprenorphine, half-life of the parent drug and its metabolites increased in elderly and those with renal impairment[21]

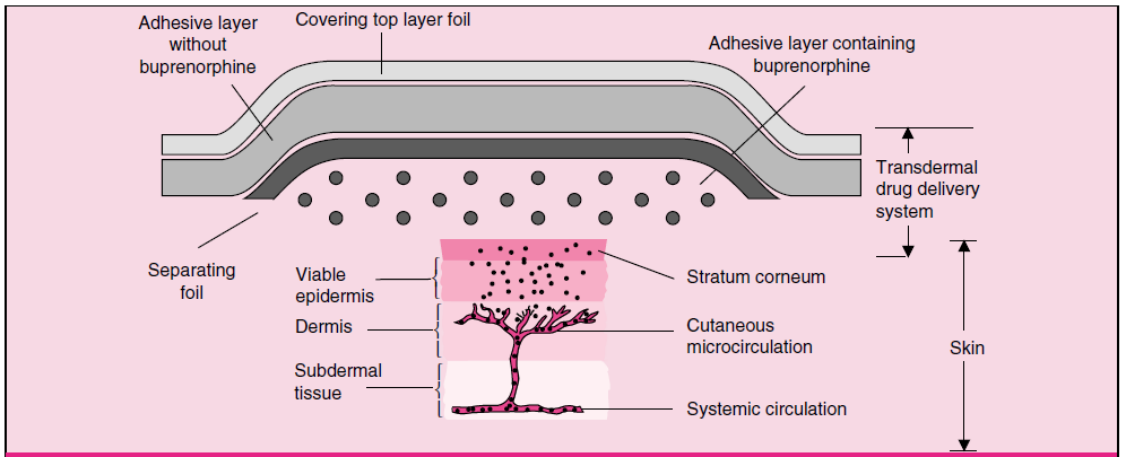

Figure 10: Buprenorphine transdermal patch system

A schematic representation of the matrix transdermal delivery system (not to scale) and the pathway of absorption across the skin. In the matrix system, buprenorphine is incorporated into the polymer matrix, which is located in the adhesive layer. Matrix patch technology allows for continuous slow release of buprenorphine into the systemic system.[22]

Indications

For the treatment of severe opioid responsive pain conditions which are not adequately responding to non-opioid analgesics. For Hospital supply only.

Dosage & Administration

Dosage[26]

BuprePLAST patch should be administered every 7th day. BuprePLAST patch is not suitable for the treatment of acute pain.

Patients aged 18 years and over

The lowest BuprePLAST patch dose (BuprePLAST 5 mcg/hr transdermal patch) should be used as the initial dose. Consideration should be given to the previous opioid history of the patient (see "Drug Interactions") as well as to the current general condition and medical status of the patient.

Titration

During initiation and titration with BuprePLAST, patients should use the usual recommended doses of short acting supplemental analgesics (see “Drug interactions’) as needed until analgesic efficacy with BuprePLAST patch is attained.

The dose should not be increased before 3 days, when the maximum effect of a given dose is established. Subsequent dosage increases may then be titrated based on the need for supplemental pain relief and the patient's analgesic response to the patch.

To increase the dose, a larger patch should replace the patch that is currently being worn, or a combination of patches should be applied in different places to achieve the desired dose. It is recommended that no more than two patches are applied at the same time, regardless of the patch strength. A new patch should not be applied to the same skin site for the subsequent 3-4 weeks. Patients should be carefully and regularly monitored to assess the optimum dose and duration of treatment.

Conversion from opioids

BuprePLAST patch should be used as an alternative to treatment with other opioids. Such patients should be started on the lowest available dose **(BuprePLAST 5 mcg/hr** transdermal patch) and continue taking short-acting supplemental analgesics (see "Drug Interactions") during titration, as required.

Patients under 18 years of age

As buprenorphine patch has not been studied in patients under 18 years of age, the use of BuprePLAST patch in patients below this age is not recommended.

Elderly

No dosage adjustment of BuprePLAST patch is required in elderly patients.

Renal Impairment

No special dose adjustment of BuprePLAST patch is necessary in patients with renal impairment.

Hepatic Impairment

Buprenorphine is metabolised in the liver. The intensity and duration of its action may be affected in patients with impaired liver function. Therefore, patients with hepatic insufficiency should be carefully monitored during treatment with BuprePLAST patch.

Patients with severe hepatic impairment may accumulate buprenorphine during BuprePLAST patch treatment. Consideration of alternate therapy should be considered, and BuprePLAST should be used with caution, if at all, in such patients.

Patch application[26]

- BuprePLAST should be applied to non-irritated, Intact skin of the upper outer arm, upper chest, upper back or side of the chest, but not to any parts of the skin with large scars.

- BuprePLAST patch should be applied to a relatively hairless or nearly hairless skin site. If none are available, the hair at the site should be cut with scissors, not shaven.

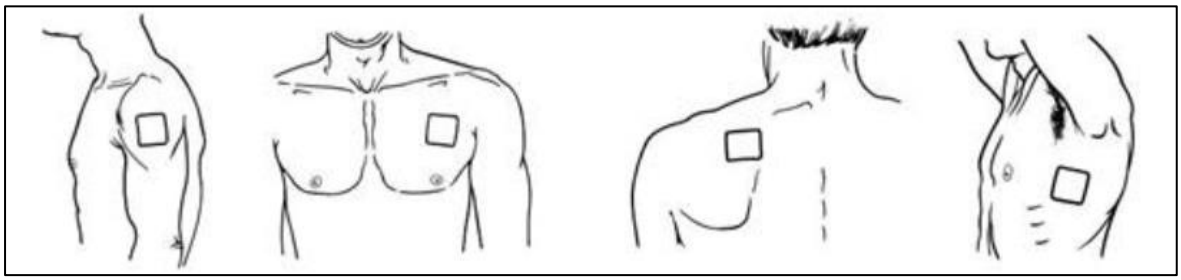

Figure 11: Application sites for BuprePLAST

- If the application site must be cleaned, it should be done with clean water only. Soaps, alcohol, oil, lotions of abrasive devices must not be used. The skin must be dry before the patch is applied.
- BuprePLAST should be applied immediately after removal from the sealed sachet. Following removal of the protective layer, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. If the edges of the patch begin to peel off, the edges may be taped down with suitable skin tape.
- Rotation of application sites is recommended, and a new patch should not be applied to the same skin site for 3-4 weeks.

The patch should be worn continuously for 7 ***days.***

Bathing, showering, or swimming should not affect the patch. If a patch falls off, a new one should be applied.

Duration of administration

BuprePLAST should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with BuprePLAST is necessary in view of the nature and severity to the illness, then careful and regular monitoring should be carried out (If necessary, with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Discontinuation

- After removal of the patch, buprenorphine serum concentrations decrease gradually and thus the analgesic effect is maintained for a certain amount of time. This should be considered when therapy with BuprePLAST is to be followed by other opioids.
- As a general rule, a subsequent opioid should not be administered within 24 hours after removal of the patch. At present, only limited information is available on the starting dose of other opioids administered after discontinuation of the transdermal patch (see "Drug Interactions").

Patients with fever or exposed to external heat

While wearing the patch, patients should be advised to avoid exposing the application site to external heat sources, such as heating pads, electric blankets, heat lamps, sauna, hot tubs, and heated water beds, etc., as an increase in absorption of buprenorphine may occur When treating febrile patients, one should be aware that fever may also increase absorption resulting in increased plasma concentrations of buprenorphine and thereby increased risk of opioid reactions.

Contraindications

- Patients with known hypersensitivity to the active substance buprenorphine or to any of the excipients
- Opioid dependent patients and for narcotic withdrawal treatment
- Conditions in which the respiratory centre and function are severely impaired or may become so
- Patients who are receiving mao inhibitors or have taken them within the last two weeks
- Patients suffering from myasthenia gravis
- Patients suffering from delirium tremens
- Pregnancy[26]

Interactions

Buprenorphine patch must not be used concomitantly with MAOIs or in patients who have received MAOIs within the previous two weeks. *Effect of other active substances on the pharmacokinetics of buprenorphine:*

Buprenorphine is primarily metabolized by glucuronidation and to a lesser extent (about 30%) by CYP3A4 inhibitors may lead to elevated plasma concentrations with intensified efficacy of buprenorphine.

A drug interaction study with the CYP3A4 inhibitor ketoconazole did not produce clinically relevant increases in mean maximum (Cmax) or total (ACU) buprenorphine exposure following buprenorphine patch with ketoconazole as compared to buprenorphine patch alone.

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of buprenorphine patch and enzyme inducers (e.g. Phenobarbital, carbamazepine, phenytoin and rifampicin) could lead to increased clearance which might result in reduced efficacy.

Reductions in hepatic blood flow induced by some general anaesthetics (e.g. halothane) and other medicinal products may result in a decreased rate of hepatic elimination of buprenorphine[26]

Pharmacodynamic interactions:

Buprenorphine patch should be used cautiously with:

Benzodiazepines: This combination can potentiate respiratory depression of central origin with risk of death.

Other central nervous system depressants: Other opioid derivatives (analgesics and antitussives containing e.g. morphine, dextropropoxyphene, codeine, dextromethorphan or noscapine). Certain antidepressants, sedative H1-receptor antagonists, alcohol, anxiolytics, neuroleptics, clonidine and related substances. These combinations increase the CNS depressant activity.

Buprenorphine is a partial mu-receptor agonist but it is described to function as a pure mu receptor agonist at typical analgesic doses. These doses produce buprenorphine exposures comparable to or greater than those produced by buprenorphine patch 5, 10, and 20 mg/hr transdermal patches. In buprenorphine patch clinical studies, where subjects receiving full mu agonist opioids (up to 90 mg oral morphine or oral morphine equivalents per day) were transferred to buprenorphine patch, there were no reports of abstinence syndrome or opioid withdrawal during conversion from entry opioid to buprenorphine patch. [26]

Special warnings and precautions

Buprenorphine patch should be used with particular caution in patients with convulsive disorders, head Injury, shock, a reduced level of consciousness of uncertain origin, intracranial lesions or Increased intracranial pressure, or in patients with severe hepatic impairment.

Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of overdose deaths have occurred when addicts have intravenously abused buprenorphine, usually with benzodiazepines concomitantly. Additional overdose deaths due to ethanol and benzodiazepines in combination with buprenorphine have been reported.

Buprenorphine patch is not recommended for analgesia in the immediate post-operative period or in other situations characterized by a narrow therapeutic index or a rapidly varying analgesic requirement.

Controlled human and animal studies indicate that buprenorphine has a lower dependence liability than pure agonist analgesics. In humans limited euphorigenic effects have been observed with buprenorphine. This may result in some abuse of the product and caution should be exercised when prescribing to patients known to have, or suspected of having, a history of drug abuse. As with all opioids, chronic use of buprenorphine can result in the development of physical dependence. Withdrawal (abstinence syndrome), when it occurs, is generally mild, begins after 2 days and may last up to 2 weeks. Withdrawal symptoms include

agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastrointestinal disorders. [26]

Pregnancy & Lactation

Pregnancy

There are no data from the use of buprenorphine patch in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Towards the end of pregnancy high doses of buprenorphine may induce respiratory depression in the neonate even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the neonate. Therefore, buprenorphine patch is contraindicated during pregnancy.

Lactation

Studies in rats have shown that buprenorphine may inhibit lactation. Excretion of buprenorphine into the milk in rats has been observed. Data on excretion into human milk are not available. Therefore, the use of buprenorphine patch during lactation should be avoided. [26]

Adverse Reactions

Transdermal buprenorphine was usually well tolerated and adverse events reported in clinical trials were generally mild to moderate in severity.

In an open-label study conducted in 114 Asian patients suffering from chronic non-malignant pain, treated with transdermal buprenorphine patch, it was observed that overall, 78.1% patients reported treatment-emergent adverse events (TEAEs), most of which were mild to moderate in intensity (96.5%).

The most common TEAEs reported during the study were nausea (39.5%) and constipation (31.6%), followed by dizziness (27.2%), somnolence (19.3%), vomiting (16.7%), headache (8.8%), pruritus (7.9%), and -application site reactions (6.1%).[27]

Guidelines

European consensus statement

- Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone).

- A multidisciplinary group of experts in the fields of pharmacology, toxicology, pain management, and anesthesia met in Sofia, Bulgaria in May 2005 during the International Forum on Pain Medicine.

Recommended transdermal buprenorphine as a first-line opioid for chronic pain in elderly patients[25]

Safety profile

The primary side effects of buprenorphine are similar to other μ-opioid agonists (eg, nausea, vomiting, and constipation), but the intensity of these side effects is reduced significantly compared to full agonist.[21]

Respiratory Depression

- Typically, 1%–11% of patients on opioid therapy suffer from respiratory depression that seems to be more pronounced in seniors, obese, or individuals with sleep apnea or neuromuscular disease.
- Buprenorphine has a **ceiling effect on respiratory depression and remains one of the safest opioids to curtail this adverse effect as concluded by a panel of experts reviewing opioid pharmacology.**
- Interestingly, pre-clinical studies showed buprenorphine with much higher safety window than for fentanyl when comparing analgesia and respiratory distress doses.[21]

Buprenorphine is the only opioid demonstrating a ceiling for respiratory depression when used without other CNS depressants[25]

Abuse potential and withdrawal

- Buprenorphine is a partial agonist and has **fewer rewarding effects compared to another μ-agonists and blocks psychological dependence**.[21]

Opioid	GI safety – constipation	CNS – sedation	Respiratory distress	Immuno suppression	Tolerance	Addiction/ dependence	Hyperalgesia
Morphine	++++	++++	++++	++++	+++	Yes	Yes
Oxycodone	++++	++++	++++	–	+++	Yes	
Hydromorphone		++++	++++	–	?	Yes	
Fentanyl TD	++	++++	++++	++++	+++		Yes
Methadone			++++	?	?		
Buprenorphine TD/SL	++	+	++	–	+	Limited	Anti-hyperalgesia

Notes: Incidence and severity of effect is represented as: ++++, high; +++, moderately high; ++, moderate; +, mild; ?, unknown.
Abbreviations: CNS, central nervous system; GI, gastrointestinal; SL, sublingual; TD, transdermal.

Figure 12: Comparison of safety profile of buprenorphine with other opioids

Constipation

- Based on reported data from clinical studies, **buprenorphine exhibits much lower incidence (1%–5%) of constipation than observed with full μ-agonists**.

Unlike other opioids, buprenorphine does not cause spasm of the sphincter of Oddi and may be a preferred choice, along with nonsteroidal anti-inflammatory drugs, in the management of biliary colic and/or pancreatitis[21]

Cognitive and psychomotor effects

- Opioid use can impair cognitive function and driving ability. Addiction to opioids can influence dependability. The addition of alcohol or sedatives may worsen the cognitive and driving ability.
- Comparative studies done report that **buprenorphine may have better visual, psychomotor or cognitive function vs morphine, methadone or fentanyl**.

In many cases, **buprenorphine effect on cognitive and psychomotor function was comparable to placebo[21]**

Immunosuppression

- Opioids seem to trigger unique biochemical communication between brain and the immune system. The reported data suggest that while exogenous opioids suppress the immune system, the endogenous opioids stimulate it.
- The implications of opioid evoked immunosuppression are particularly relevant during the postoperative period when the pain and susceptibility to infection are high; for sufferers of chronic pain who administer opioids for extended periods; and for patients with immunosuppressive disease such as AIDS, transplant patients, and the elderly, who are predisposed to opportunistic infections.
- The potent opioids such as morphine and fentanyl reduce antibody production, reduce natural killer cell activity, and impair the cytokine expression and phagocytic activity of white cells. The immunosuppressive effect is accentuated in presence of corticosteroids or other immunosuppressive drugs. Some immunosuppression in morphine may also emerge through non-μ-receptor mediation as the effect is not reversed by naltrexone.
- **Unlike morphine, buprenorphine does not reduce natural killer-cell function, increase cortisol, reduce adrenocorticotropic hormone levels, or alter norepinephrine or serotonin levels after injection in the brain.** Most of the studies showing lack of immunosuppressive effect of buprenorphine have been conducted in animals and their clinical relevance needs to be established. However, in immunosuppressed patients, opioids (morphine, fentanyl) treatment may be avoided and buprenorphine should be considered in the scheme of options.[21]

Hypogonadism

- Chronic use of μ-receptor agonists has been associated with hypogonadism and fatigue. With time, hypogonadism can lead to osteopenia and loss of muscle mass. Use of morphine and fentanyl is reported to reduce testosterone levels and testosterone replacement therapy is often recommended.

Even at high doses, buprenorphine seems to have minimal effect on sexual hormone levels.[21]

QTc prolongation vs methadone

- Based on reported data, methadone-maintenance treatment has been associated with QTc prolongation (approximately 29% patients) with approximately 5% showing QTc interval of >500 ms. The risk of QTc prolongation seems particularly high at doses of >120 mg.
- **In contrast, buprenorphinemaintenance therapy for opioid dependence does not seem to be associated with QTc prolongation. Torsades de pointes or sudden cardiac deaths occur four times more frequently with methadone than with buprenorphine.**
- **Since the dose needed for analgesic effect is generally lower, it should also improve therapeutic window for cardiac safety.[21]**

Tolerance and hyperalgesia

- The clinical usefulness of opioids is often hampered by the development of tolerance after chronic treatment.
- Although tolerance to the antinociceptive effect of buprenorphine has been demonstrated, **the onset is slower than tolerance to morphine**.
- In a retrospective study involving nearly 900 cancer and noncancer patients **buprenorphine produced less analgesic tolerance than fentanyl**, as measured by an opioid escalation index.[21]

Treatment of opioid dependence

- Buprenorphine's high binding affinity and low intrinsic activity can induce withdrawal in opioid dependent patients that are using full μ-agonists (methadone, heroin, and morphine) by displacing opioids from the receptor.
- To control opioid dependence, buprenorphine treatment is initiated at the appearance of withdrawal symptoms. The patients on opioids are encouraged to abstain from use for until at least 12–24 hours or until the emergence of withdrawal symptoms. The patients are started on a low dose of transdermal or sublingual formulation of buprenorphine. If clinical signs remain controlled, buprenorphine is titrated upwards to individualized dose.
- A Cochrane review of 13 studies concluded "buprenorphine is an effective intervention for the treatment of opioid dependence".[21]

Postmarketing surveillance

- An open noninterventional survey of transdermal buprenorphine has been conducted in Germany. In the survey of **13,179 patients with chronic pain**, 57.4% had musculoskeletal disorders, 28% had cancer, 12.3% had neuropathic pain and 7% had other diseases.
- In the total population, **most patients (70%) rated their pain relief with transdermal buprenorphine to be good or very good** (74.8% of cancer patients, 69.8% of noncancer patients).
- After a stabilization period of 18 days, no change in dosage or additional analgesia occurred up to the end of the documentation period in 68% of patients, suggesting that **development of tolerance was not a problem**.
- **Better sleep was reported by 63.5% of patients**, indicating good analgesic efficacy and improved quality of life.[19]

Summary of Clinical Trials

Effectiveness and tolerability of transdermal buprenorphine patches in Asian patients with moderate to severe chronic musculoskeletal pain

BMC Musculoskelet Disord. 2017; 18: 337.

- This was **an multicenter, prospective,open-label study conducted in Hong Kong, Korea, and the Philippines** between June 2013 and April 2015.
- Eligible patients fulfilled the following criteria: **18 to 80 years of age**; clinical diagnosis of **osteoarthritis, rheumatoid arthritis, low back pain, or joint/muscle pain; chronic non-malignant pain of moderate to severe intensity** (Box-Scale-11 [BS-11] pain score ≥ 4), not adequately controlled with non-opioid analgesics and requiring an opioid for adequate analgesia; and no prior history of opioid treatment.
- Patients started with a 5 µg/h buprenorphine patch and were titrated as necessary to a maximum of 40 µg/h over a 6-week period to achieve optimal pain control. Patients continued treatment with the titrated dose for 11 weeks
- A total of **114 eligible patients** were included in the analysis.
- Following initiation of TDB, there was a **statistically significant improvement in BS-11 score from baseline to visit 3, which was maintained till the end of the study (visit 7) (p < 0.0001 for both).**

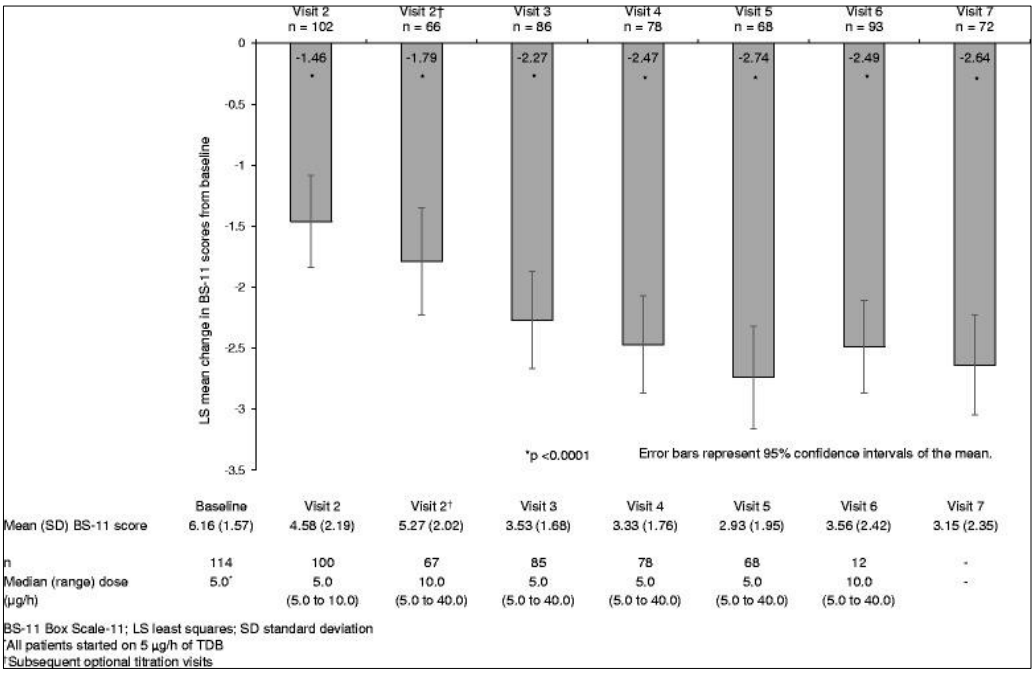

Figure: Change in BS-11 scores from baseline to visit 7

- The proportion of patients who rated **sleep quality as 'good' increased from 14.0% at baseline to 26.9% at visit 6.**
- By visit 6, the mean EQ-5D visual analogue scale (EQ VAS) score increased by 7.7 units. There were also significant improvements in patients' levels of functioning for all

EuroQol Group 5-Dimension Self-Report Questionnaire-3 Level Version Survey dimensions from baseline at visit 6 ($p < 0.05$ for all).

- Seventy-eight percent of patients reported TEAEs and 22.8% of patients discontinued due to TEAEs. **TEAEs were generally mild to moderate in intensity** (96.5%).
- **Treatment with TDB resulted in effective and sustained pain relief over the 11-week treatment period, accompanied by improvements in daily functioning and quality of life.** The tolerability profile was as expected as previous studies of TDB.
- **Results indicate that TDB can be considered a suitable alternative treatment option to control non-malignant musculoskeletal pain.**

Transdermal Buprenorphine in Non-Oncological Moderate-To-Severe musculoskeletal Chronic Pain

Clin Drug Investig . 2010;30 Suppl 2:31-8.

- **An open-label, prospective, single-centre, 6-month study in 'real world' outpatient setting to evaluate the efficacy and tolerability of transdermal buprenorphine (TDS) in the long-term management of non-oncological, chronic, moderate-to-severe musculoskeletal pain.**
- Patients initially received buprenorphine TDS 11.7 microg/h (one-third of 35 microg/h patch) every 72 hours. If required, patients could be up-titrated to 17.5 microg/h (one-half of 35 microg/h patch), 23.4 microg/h (two-thirds of 35 microg/h patch) or 35 microg/h. Concomitant antiemetics were allowed.
- We enrolled **146 patients aged 41-94 years**; their baseline mean +/- SD static and dynamic pain VAS scores were 6.87 +/- 1.89 and 7.70 +/- 1.74, respectively.
- Buprenorphine TDS initial dosages were 11.7 microg/h (n = 139), 17.5 microg/h (n = 4), 23.4 microg/h (n = 1) and 35 microg/h (n = 2). At 6 months, 89 patients were under treatment; 11% (n = 10) were receiving 11.7 microg/h, 30% (n = 27) 17.5 microg/h, 6% (n = 5) 23.4 microg/h and 53% (n = 47) 35 microg/h.
- Patients achieved a nonsignificant reduction in pain at rest and in movement; mean +/- SD static and dynamic pain VAS scores decreased to 1.56 +/- 2.05 and 3.54 +/- 2.02, respectively.
- **The quality of life improved as shown by significant ($p < 0.01$) increases from baseline in all items relating to physical and mental health on the Short-Form 36 health survey**. Patients experienced recovery of daily and social activities according to the significant ($p < 0.01$) increase in Karnofsky Performance Status sub-item scores. Twenty-three patients discontinued treatment because of adverse events, which were mainly gastrointestinal or CNS-related.

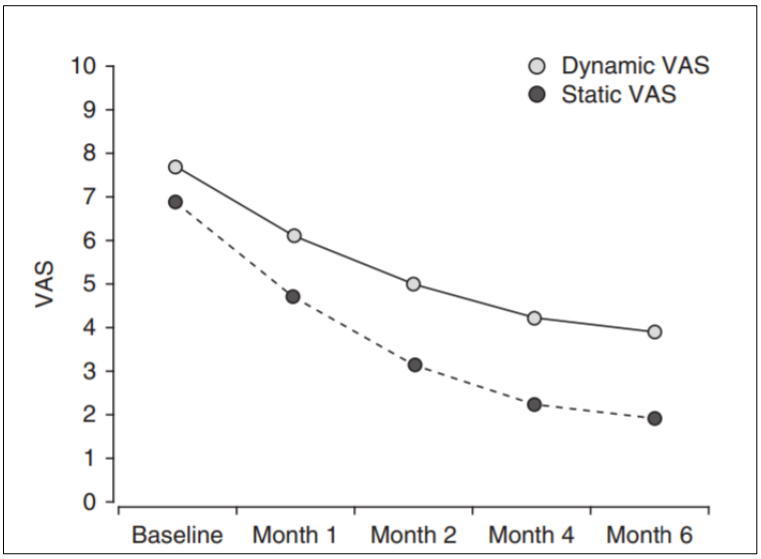

Figure: Changes in pain visual analogue scale (VAS) total score during rest (static VAS) and in movement (dynamic VAS) at baseline (month 0) and during 6 months' treatment with transdermal buprenorphine. The VAS is a 10-point patient-rated scale, where 10 represents the worst possible pain and 0 represents no pain.

- **Low-dose buprenorphine TDS had good analgesic efficacy, and quality of life improved as early as 1 month after treatment initiation. Our results suggest that buprenorphine TDS is a well tolerated long-term analgesic for patients experiencing chronic musculoskeletal pain of moderate-to-severe intensity.**

Effectiveness and Safety of Transdermal Buprenorphine Versus Sustained-release Tramadol in Patients with Moderate to Severe Musculoskeletal Pain

Clin J Pain. 2015 Jul;31(7):612-20.

- An 8-Week, Randomized, Double-Blind, Double-Dummy, Multicenter, Active-controlled, Noninferiority Study. **N=280**
- Eligible patients were randomized (1:1) to receive low-dose 7-day BTDS (5, 10, and 20 µg/h, maximum dosage of 20 µg/h) or sustained-release tramadol tablets (100 mg, maximum dosage of 400 mg/d) over an 8-week double-blind treatment period (3-week titration, 5-week maintenance).
- **Both treatments were associated with a significant reduction in pain by the end of the treatment.** The least squares mean difference of the change from baseline in VAS scores between the BTDS and tramadol groups were 0.45 (95% confidence interval, -0.02 to 0.91), which was within the ±1.5 cm predefined threshold, indicating that the effectiveness of BTDS was not inferior to the effectiveness of sustained-release tramadol tablets.

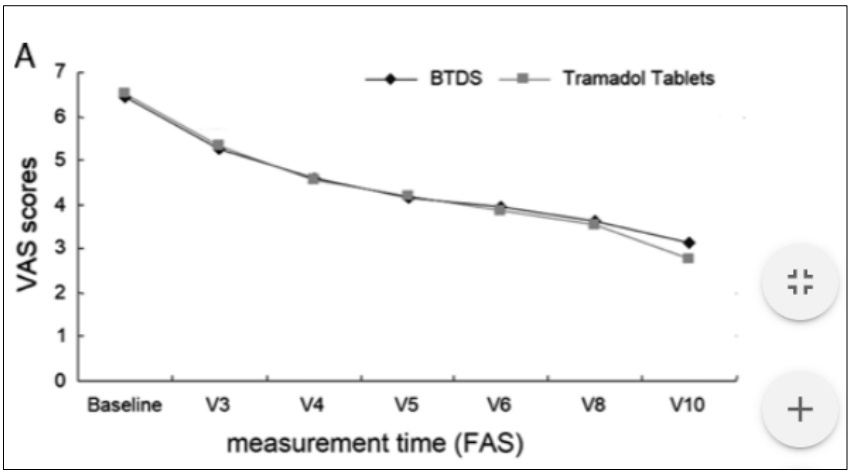

Figure: Changes in visual analogue scale VAS pain score during the study. VAS decreased in both groups, and there was no difference between the 2 treatment groups, both in full analysis set FAS analysis and PPS analysis

- **The incidence of adverse events was comparable between the 2 treatment groups.**
- **Results suggest that BTDS is a good therapeutic option for patients experiencing chronic musculoskeletal pain of moderate to severe intensity that is insufficiently controlled by nonsteroidal anti-inflammatory drugs.**

Buprenorphine Transdermal System Improves Sleep Quality and Reduces Sleep Disturbance in Patients with Moderate-to-Severe Chronic Low Back Pain

Pain Pract . 2016 Mar;16(3):345-58.

- **Two enriched-enrollment, randomized-withdrawal, double-blind, controlled trials examined BTDS treatment for patients with moderate-to-severe chronic low back pain (CLBP).**
- Trial I evaluated BTDS 10 and 20 mcg/hour against a placebo control among opioid-naïve patients. Trial II compared BTDS 20 mcg/hour against a lower-dose control (BTDS 5 mcg/hour) among opioid-experienced patients. The patient-reported Medical Outcomes Study Sleep Scale (MOS-SS) assessed overall sleep quality (Sleep Problems Index [SPI]), Disturbance, and other sleep outcomes.
- Medical Outcomes Study Sleep Scale scores were collected **from 541 (Trial I) and 441 (Trial II) patients prior to randomization and from 369 (Trial I) and 274 (Trial II) patients at week 12.**
- **Patients receiving target treatment showed statistically significantly more improvement in Sleep Problems Index [SPI]and Disturbance scores at 12 weeks than their respective controls (Ps < 0.05).**
- Improvements in SPI and Disturbance for target treatment arms were statistically larger those of the controls by week 4 of the double-blind phase. Pain reduction predicted improvements in sleep outcomes.

- **Buprenorphine Transdermal System improved sleep quality and disturbance for opioid-naïve and opioid-experienced patients with moderate-to-severe CLBP. Benefits of BTDS for these sleep outcomes emerged within 4 weeks and were maintained over the entire 12-week treatment period.**

Buprenorphine Transdermal System for Opioid Therapy in Patients with Chronic Low Back Pain

Pain Res Manag. May-Jun 2010;15(3):169-78.

- **The present randomized, double-blinded, crossover study compared the efficacy and safety of a seven-day buprenorphine transdermal system (BTDS) and placebo in patients with low back pain of moderate or greater severity for at least six weeks. N=53**
- 5 microg/h BTDS or placebo, with acetaminophen 300 mg/codeine 30 mg, one to two tablets every 4 h to 6 h as needed, for rescue analgesia. The dose was titrated to effect weekly, if tolerated, to 10 microg/h and 20 microg/h BTDS. Each treatment phase was four weeks.
- **BTDS resulted in lower mean daily pain scores than in the placebo group (visual analogue scale, P=0.0487; and the ordinal scale, P=0.0358).**
- There were improvements from baseline in pain and disability (Pain Disability Index), Pain and Sleep (visual analogue scale), Quebec Back Pain Disability Scale and Short-Form 36 Health Survey scores for both BTDS and placebo groups, without significant differences between treatments.
- **A total of 82% of patients chose to continue BTDS in a long-term open-label evaluation, in whom improvements in pain intensity, functionality and quality of life were sustained for up to six months without analgesic tolerance.**
- **BTDS (5 microg/h to 20 microg/h) represents a new treatment option for initial opioid therapy in patients with chronic low back pain.**

Efficacy and Safety of Buprenorphine Transdermal System (BTDS) for Chronic Moderate to Severe Low Back Pain

J Pain. 2011 Nov;12(11):1163-73.

- This was an **enriched, multicenter, randomized, double-blind, double-dummy, parallel group, active controlled superiority stud**y designed to compare BTDS 20 or an active control (immediate-release oxycodone capsules 40 mg/day) with BTDS 5 in **1,160 opioid-experienced patients with chronic, moderate to severe low back pain.**
- There were 75 centers in the United States participating in this study.
- Incidences of treatment-emergent adverse events were 56% during the open-label period, and 59, 77, and 73% for the BTDS 5, BTDS 20, and oxycodone 40 mg/day treatment groups

- BTDS 20 was superior to BTDS 5 in providing statistically significant and clinically meaningful pain management in patients previously requiring opioids for moderate to severe, chronic low back pain. Efficacy was maintained over a 12-week double-blind phase. The primary results were statistically significant in favor of BTDS 20, as were 2 secondary efficacy variables (MOS sleep disturbance scale over weeks 4, 8, and 12 and the daily number of tablets of supplemental analgesic medications during the double-blind phase). BTDS was generally well tolerated.

Efficacy and Safety of the Seven-Day Buprenorphine Transdermal System in Opioid-Naïve Patients with Moderate to Severe Chronic Low Back Pain

J Pain Symptom Manage. 2011 Dec;42(6):903-17.

- This article presents the results of a pivotal Phase 3 study that assesses a new treatment for the management of chronic low back pain: a transdermal patch containing the opioid buprenorphine. **In this randomized, placebo-controlled study with an enriched enrollment design,** the buprenorphine transdermal system (BTDS) was found to be efficacious and generally well tolerated in opioid-naïve patients who had moderate to severe chronic low back pain. **N= 1027**
- Patients who tolerated and responded to BTDS (10 or 20 mcg/hour) during an open-label run-in period were randomized to continue BTDS 10 or 20 mcg/hour or receive matching placebo. **Duration 12 weeks**
- **Patients receiving BTDS reported statistically significantly lower pain scores at Week 12 compared with placebo (P=0.010).**
- Sensitivity analyses of the primary efficacy variable and results of the analysis of secondary efficacy variables supported the efficacy of BTDS relative to placebo. During the double-blind phase, the incidence of treatment-emergent adverse events was 55% for the BTDS treatment group and 52% for the placebo treatment group.
- **BTDS was efficacious in the treatment of opioid-naïve patients with moderate to severe chronic low back pain. Most treatment-emergent adverse events observed were consistent with those associated with the use of opioid agonists and transdermal patches.**

Transdermal Buprenorphine Versus Transdermal Fentanyl in the Long-Term Management of Persistent Non-Cancer Pain

Pain Med. 2013 Jan;14(1):75-83.

- **It was a prospective, randomized, longitudinal study over 12 months.**
- The participants were **46 adults** (range 22-80 years.) with nonmalignant persistent pain (mean = 11 years), predominantly with lower back pain. Data were obtained monthly for 12 months.

- Participants were randomly allocated to either buprenorphine or fentanyl patch treatment. Participants were then titrated to optimal doses of medication.
- Nearly one-third of all patients, 41% (8 of 22) of the transdermal buprenorphine (TDB) group and 37.5% (8 of 24) of the transdermal fentanyl (TDF) group stopped treatment due to unacceptable side effects or inadequate pain relief.
- **The remaining participants showed a similar trend in the improvement of pain intensity, physical activity, sleep, and mood throughout the study.**
- Significant relief in the intensity of pain was achieved for the initial 6 months and the effects stabilized in the remainder of the study in both groups.
- **A higher equipotent dose of fentanyl was required for comparable pain relief.**
- Compared with TDF group, the TDB group initially experienced relatively less side effects.
- **Buprenorphine users had significant improvement in mood.**
- Thirty-one percent (5 of 16) of the buprenorphine group and 57% (8 of 14) of the fentanyl users needed additional pain relief medications by the end of 3 months.
- **Twenty percent more patients in the TDB group benefited significantly in symptoms of depression from TDB compared with the TDF group.**

Buprenorphine Transdermal Delivery System in Adults with Persistent Noncancer-Related Pain Syndromes Who Require Opioid Therapy

Clin Ther. 2007 Oct;29(10):2179-93.

- **This was a multicenter, double-blind, parallel-group study in adult subjects (age >/=18 years) with at least a 2-month history of noncancer-related pain** for which they received oral opioid combination agents. **N= 588**
- During a 7- to 21-day open-label run-in phase, all subjects received BTDS, titrated as needed. Subjects who achieved stable pain control and were able to tolerate BTDS in the run-in phase were randomly assigned to continue BTDS at the dose achieved during the run-in phase or to receive placebo for up to 14 days.
- Five hundred eighty-eight subjects entered the open-label run-in phase, and 267 (129 BTDS, 138 placebo) were subsequently randomized to double blind treatment.
- **In the primary efficacy analysis, the proportion of subjects with ineffective treatment was lower with BTDS than with placebo**
- **In the secondary efficacy analyses, the median time from the first dose of double-blind study drug to ineffective treatment was significantly longer with BTDS than with placebo**
- **The mean amount of escape medication used was significantly lower in the BTDS group than in the placebo group**
- **In this population of adult subjects with persistent noncancer-related pain who required opioid therapy, BTDS use was associated with analgesic efficacy and was generally well tolerated.**

Low-Dose Transdermal Buprenorphine with Buprenorphine Sublingual Tablets in Patients with Osteoarthritis Pain

J Pain Symptom Manage. 2010 Aug;40(2):266-78.

- **Two hundred forty-six patients with OA pain in the hip(s) and/or knee(s) were enrolled in this randomized, double-blind, parallel-group study**
- Patients were randomized to receive transdermal buprenorphine patches (5, 10, and 20 microg/hour) or sublingual buprenorphine (200 and 400 microg tablets). Their medication was titrated to pain control and they were treated for up to seven weeks.
- **Patients' Box Scale-11 pain scores decreased between entry and assessment in both treatment groups.**
- Use of escape medication was low. In both treatment groups, **sleep disturbance caused by pain decreased between entry and assessment.**
- Patients' **quality of life improved during the study**. **Significantly fewer patients receiving the transdermal buprenorphine patches reported nausea (P=0.035), dizziness (P=0.026), and vomiting (P=0.039).**
- **In conclusion, seven-day, low-dose transdermal buprenorphine patches are as effective as sublingual buprenorphine, with a better tolerability profile.**

Treatment of Chronic Osteoarthritis Pain: Effectivity and Safety of a 7 Day Matrix Patch with a Low Dose Buprenorphine

MMW Fortschr Med. 2008 Jun 26;150 Suppl 2:96-103.

- If pain treatment with NSAIDS and coxibes is no longer indicated, a **constant and user friendly opioid analgesia can be achieved with a low dose buprenorphine patch** being applicated using an interval of 7 days.
- The use of this matrix patch was evaluated in a **multicenter observational study on 4263 patients in clinical practice**.
- During treatment a significant decrease of mean pain intensity on a 11-point scale could be observed from 6.9 points before using the patch to 2.9 points at the end of observation.
- Further effects were a decrease of additional analgetic medication and an improvement of aspects of life quality, e.g. mobility and quality of sleep.
- Only in 4.5% of the patients adverse effects were observed, reflecting the expected range of adverse effects of opioids.
- **Thus it could be demonstrated that the use of the transdermal patch is an effective, user friendly and safe way of chronic pain relief for osteoarthritis patients.**

5-week Study of Buprenorphine Transdermal System in Adults with Osteoarthritis

J Opioid Manag. May-Jun 2010;6(3):193-202.

- This multicenter, parallel-group, 35-day study in adults with osteoarthritis (OA) pain evaluated the analgesic efficacy and safety of buprenorphine transdermal system (BTDS) designed for 7-day wear, at 1 of 3 dose levels (5, 10, or 20 microg/b) or placebo.
- **More BTDS-treated patients experienced treatment success than placebo TDS-treated patients** (44 percent and 32 percent; odds ratio = 1.66, p = 0.036). Fewer patients taking BTDS titrated to the highest dose compared with placebo ($p < 0.05$).
- The most common (> or =5 percent) adverse events reported in BTDS-treated patients were nausea, headache, dizziness, somnolence, application site pruritus, and vomiting.
- **Compared with placebo, BTDS treatment was effective in treating patients with moderate to severe pain due to OA of the knee or hip. BTDS was well-tolerated.**

Efficacy and Safety of Low-Dose Transdermal Buprenorphine Patches (5, 10, and 20 Microg/H) Versus Prolonged-Release Tramadol Tablets (75, 100, 150, and 200 Mg) in Patients with Chronic Osteoarthritis Pain

Clin Ther. 2009 Mar;31(3):503-13.

- **A 12-week, Randomized, Open-Label, Controlled, Parallel-Group Noninferiority Study compared the efficacy and safety of low-dose 7-day buprenorphine patches and prolonged-release tramadol tablets in patients with chronic, moderate to severe osteoarthritis (OA) pain of the hip and/or knee. N= 134**
- Eligible patients were adults with a clinical and radiologic diagnosis of OA of the hip and/or knee and moderate to severe pain, as confirmed by a mean Box Scale 11 (BS-11) score >or=4 while using paracetamol 4000 mg/d for pain during the screening week. Patients were randomized in a 1:1 ratio to receive either low-dose 7-day buprenorphine patches (patch strengths of 5, 10, and 20 microg/h, with a maximum dosage of 20 microg/h) or twice-daily prolonged-release tramadol tablets (tablet strengths of 75, 100, 150, and 200 mg, with a maximum dosage of 400 mg/d) over a 12-week open-label treatment period.
- **Both treatments were associated with a clinically meaningful reduction in pain from baseline to study completion.** The least squares mean change from baseline in BS-11 scores in the 7-day buprenorphine patch and tramadol tablet groups was -2.26 (95% CI, -2.76 to -1.76) and -2.09 (95% CI, -2.61 to -1.58). The efficacy of 7-day buprenorphine patches was noninferior to that of prolonged-release tramadol tablets. The incidence of adverse events (AEs) was comparable in the 2 treatment groups:
- **Most patients (47/67 [70.1%] in the 7-day buprenorphine patch group and 43/61 [70.5%] in the tramadol tablet group) reported that they would prefer a 7-day patch to a twice-daily tablet for future pain treatment.**

- **In these patients with chronic, moderate to severe OA pain of the hip and/or knee, 7-day low-dose buprenorphine patches were an effective and well-tolerated analgesic. The buprenorphine patches were noninferior to prolonged-release tramadol tablets.**

Transdermal Buprenorphine Plus Oral Paracetamol vs an Oral Codeine-Paracetamol Combination for Osteoarthritis of Hip and/or Knee

Osteoarthritis Cartilage. 2011 Aug;19(8):930-8.

- **220 people (aged ≥60 years) with OA hip and/or knee pain** were randomised to treatment with 7-day buprenorphine patches plus oral paracetamol (5-25 µg/h buprenorphine patches plus 1000 mg oral paracetamol q.i.d. (4 times daily); n=110) or co-codamol tablets (two 8/500-two 30/500 mg tablets q.i.d.; n=110).
- **Both treatments significantly reduced patient pain scores.** Patients receiving 7-day buprenorphine patches plus oral paracetamol needed significantly less escape medication (ibuprofen) than those receiving co-codamol tablets (P=0.002; PP population)
- The incidence of adverse events (AEs) was comparable between the groups.
- **7-day buprenorphine patches plus oral paracetamol were non-inferior to co-codamol tablets with respect to analgesic efficacy in older adults with OA pain in the hip/knee.**

Effects of Buprenorphine on QT Intervals in Healthy Subjects

Postgrad Med. 2017 Jan;129(1):69-80.

- **Two randomized, placebo- and positive-controlled, parallel-group, dose-escalating clinical studies evaluated healthy adult subjects randomized to BTDS, placebo, or moxifloxacin in the first study; and to BTDS only, BTDS plus naltrexone, naltrexone alone at the same dose, placebo, or moxifloxacin in the second study.**
- In the first study **(n = 44),** the maximum upper bounds of the 90% confidence interval (CI) for mean placebo-corrected change from baseline in QTcI across 13 time points over 24 h were: 10.0 msec for BTDS 10 (Day 6) and 13.3 msec for BTDS 40 (Day 13); and 17.0 msec (Day 6) and 15.5 msec (Day 13) for moxifloxacin, respectively.
- Similarly, in the second study **(n = 66)**, the upper bound of the 90% CI for mean placebo-corrected change from baseline for QTcI was under 10 msec at all time points for BTDS 10 (maximum upper bound, 5.63 msec), over 10 msec at 5 time points for BTDS 40 (maximum 11.81 msec) and over 10 msec at all 13 time points for BTDS 80 (maximum, 14.14 msec). Naltrexone administered with BTDS eliminated the QTcI prolongation seen with supratherapeutic BTDS doses (BTDS 40, BTDS 80) administered without naltrexone.
- **At the therapeutic dose of 10 mcg/h, BTDS has no clinically significant effect on QTc. At supratherapeutic doses of 40 and 80 mcg/h, BTDS treatment produces prolongation of QTcI similar in magnitude to that produced by a 400 mg dose of moxifloxacin.**

Despite the modest, dose-dependent increase in QtcI noted in these studies, transdermal buprenorphine has not been associated with proarrhythmic effects.

Application of a buprenorphine transdermal patch for the perioperative analgesia in patients who underwent simple lumbar discectomy

Medicine (Baltimore). 2017 May; 96(20): e6844.

- The study was randomized controlled study. **A total of 96 patients** (55 males and 41 females), who underwent simple discectomy under general **anesthesia for treating lumbar disk herniation (LDH),** were enrolled in the study between March 2014 and December 2015.
- The patients were randomly divided into **parecoxib intravenous injection (Group A), oral celecoxib (Group B), and buprenorphine transdermal patch groups (Group C)** (32 patients in each group).
- The degree of patient satisfaction in Group C was higher than that in Groups A and B, with minimal adverse effects.
- The buprenorphine transdermal patch had a better perioperative analgesic effect in patients who underwent simple lumbar discectomy.

	N	Extremely satisfactory	Moderately satisfactory	Unsatisfactory
Group A	32	15	11	6
Group B	32	10	15	7
Group C	32	21	9	2
P		.02*	.28	.19

* A significant difference between Groups C and A, and Groups C and B, respectively ($P < .05$). However, the results did not show a significant difference between Groups A and B ($P > .05$).

Figure: Comparisons of the degree of patient satisfaction between the 3 groups

- **This study indicated that the buprenorphine transdermal patch (preemptive analgesia regimen) could exert the analgesic effect on patients who underwent simple discectomy during the perioperative period, which was beneficial for patients to sustain postoperative physiological and psychological states, and promote functional rehabilitation.**

Efficacy of Transdermal Buprenorphine Patches and Prolonged-Release Tramadol Tablets for Postoperative Pain Control After Spinal Fusion Surgery

Eur Spine J. 2017 Nov;26(11):2961-2968.

- **The present study was a prospective, randomized controlled non-inferiority trial designed to determine the efficacy of buprenorphine TDS for alleviating postoperative pain following patient controlled analgesia (PCA) in persons underwent a single level posterior lumbar interbody fusion surgery through 1:1 allocation. N= 71 patients aged ≥ 20 years**
- Aim was To compare the efficacy of a transdermal buprenorphine patch (5, 10, 15, and 20 μg/h) with that of oral tramadol (150, 200, 250, and 300 mg) for postoperative pain control after single level spinal fusion surgery.
- The primary outcome was the Visual Analog Pain Scale (VAS) score for postoperative back pain at 7 days after surgery. The non-inferior margin of the VAS was set at $\delta = 1.5$ points.
- **The Visual Analog Pain Scale (VAS) score for postoperative back pain at 7 days after surgery in the Buprenorphine group was not inferior compared to the Tramadol group.**
- **The efficacy of buprenorphine patch was not inferior to that of oral tramadol for alleviating postoperative pain in the subacute period from 72 h after surgery, following patient controlled analgesia (PCA) administration.**
- **In addition, adverse events were similar between both groups.**

Efficacy and Safety of Transdermal Buprenorphine Versus Oral Tramadol/Acetaminophen in Patients with Persistent Postoperative Pain After Spinal Surgery

Pain Res Manag. 2017;2017:2071494.

- **Open-label, interventional, randomized multicenter study. Adults with persistent postoperative pain were enrolled. N=87**
- Patients received once-weekly BTDS (n = 47; 5 μg/h titrated to 20 μg/h) or twice-daily TA (n = 40; tramadol 37.5 mg/acetaminophen 325 mg, one tablet titrated to 4 tablets) for 6 weeks.
- At week 6, both groups reported significant pain reduction (both $P < 0.0001$) and improved QoL (both $P < 0.05$).
- **The BTDS group achieved better medication compliance (97.8% versus 91.0%). Incidence of AEs (26.1% versus 20.0%) and adverse drug reactions (20.3% versus 16.9%) were comparable between groups.**
- **For patients with persistent pain following spinal surgery, BTDS is an alternative to TA for reducing pain and supports medication compliance.**

Pharmacokinetics of transdermal buprenorphine patch in the elderly

Eur J Clin Pharmacol. 2013 Feb; 69(2): 143–149.

- **This was a multiple-dose, open-label, parallel-group study in healthy volunteers split into two age groups (younger, 50–60 years; elderly, ≥75 years) with 37 individuals in each.**
- Study participants received two consecutive 7-day buprenorphine 5 µg/h transdermal patch applications, and blood samples were collected on the week of the second patch application [day 7 (predose), days 8, 9, 10, 12, and 14] to determine PK at steady state.
- **The area under the plasma concentration-time curve at steady state (AUC_{tau}), measured over one dosing interval, was similar for elderly** [mean ± standard deviation (SD) 9,940 pg/h/ml (4,827 pg/h/ml] **and younger** [mean ± SD 11,309 (3,670 pg/h/ml] **individuals**.
- Bioequivalence was not demonstrated between groups, which may be attributable to the relatively high level of variability in individual plasma profiles.
- **No dosage alterations are necessary for PK reasons when treating elderly people with buprenorphine transdermal patches.**

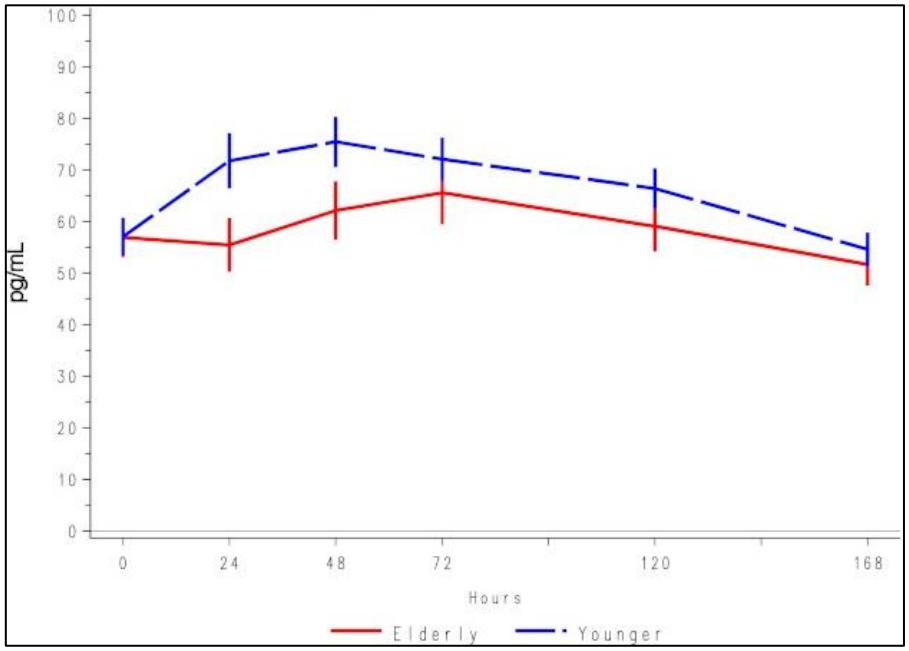

Figure: Mean plasma concentrations for buprenorphine for each group. Data points are mean ± standard error of the mean

Effectiveness and Safety of Transdermal Buprenorphine for Chronic Pain Treatment in the Elderly

Med Clin (Barc). 2007 Feb 17;128(6):204-10.

- A **prospective, uncontrolled observational study that included a 3-month follow-up** of patients starting transdermal buprenorphine was performed.
- Out of **1,188 patients** with known age, 564 were under 65, 337 were between 65 and 75, and 287 were over 75 years. Within these respective age groups, 63.9%, 66.3% and 67.7% of patients showed <<good>> or <<very good>> pain relief; 60.4%, 60.7% and 65.2% showed improvement of sleep quality; and the mean increases of the score of the EuroQol-5D visual analogue scale were 16.0 mm, 15.8 mm and 16.8 mm. Drug-related adverse events were reported in 39.6%, 35.4% and 31.9% of patients, respectively.
- **This study performed in the routine-care setting supports the findings from previous randomised controlled clinical trials of transdermal buprenorphine.**

Transdermal Buprenorphine for the Treatment of Chronic Noncancer Pain in the Oldest Old

J Pain Symptom Manage.2011 Apr;41(4):707-14.

- **Multicenter, prospective, observational study to evaluate the efficacy and safety of the buprenorphine transdermal delivery system (TDS) in elderly patients with chronic noncancer pain.**
- The study included 93 patients (69 women and 24 men); the mean age was 79.7 years, and in most cases, the pain was due to osteoarthritis. Almost three-quarters (74.2%) of the patients had suffered pain for more than 12 months.
- The treatment was buprenorphine TDS, starting from a dose of 17.5 µg/h. Outcomes were assessed using the Mini-Mental State Examination (MMSE), the 17-item Hamilton Depression scale (HAM-D 17), the Neuropsychiatric Inventory, the Barthel Index, the Short-Form Health Survey (SF-12), a verbal numeric rating scale, and the Cumulative Illness Rating Scale (CIRS).
- **Buprenorphine treatment was associated with a decrease in pain severity without negative effects on the central nervous system.**
- On the HAM-D scale, there were reductions in both the psychological and somatic scores. On the MMSE, values at the beginning and end of the study were comparable. Evaluation by SF-12 showed improvements in physical and mental status. CIRS values at baseline and at the end of the study were superimposable, indirectly confirming the tolerability and safety profile of the drug.
- Our experience confirms the analgesic activity and safety of buprenorphine TDS in the elderly. There was an improvement in mood and a partial resumption of activities, with no influence on cognitive and behavioural ability.

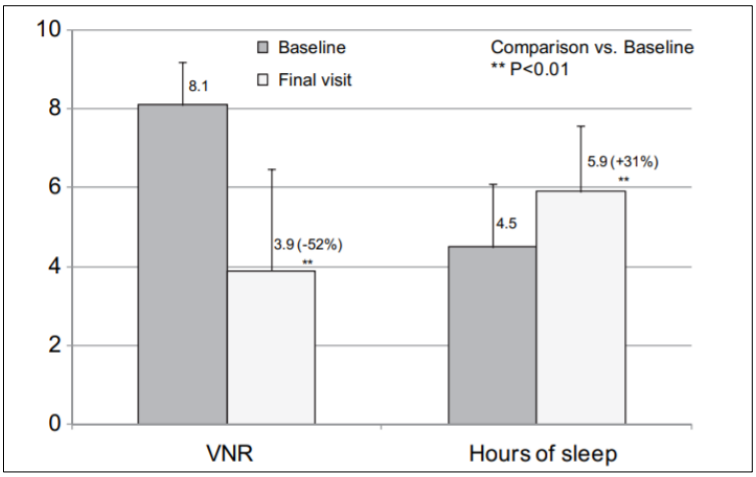

Figure: Reduction of spontaneous pain and increase in hours of sleep in 89 geriatric patients affected from chronic noncancer pain and treated with buprenorphine TDS for three months

Transdermal Buprenorphine Relieves Neuropathic Pain

Diabetes Care. 2016 Sep;39(9):1493-500.

- **This multicenter, randomized, double-blind, placebo-controlled, parallel-group trial enrolled patients with type 1 or type 2 diabetes and stable glycemic control who had been experiencing moderate to severe diabetic peripheral neuropathic pain (DPNP)** for at least 6 months on maximal tolerated conventional therapy.
- Patients were randomly assigned to receive buprenorphine (5 µg/h) or placebo patches. The dose was titrated to effect to a maximum of 40 µg/h.
- One hundred eight-six patients were enrolled, with 93 randomized to either buprenorphine or placebo.
- Among the per-protocol population, buprenorphine group (86.3%) experienced a 30% reduction in average versus baseline pain at week 12 than those in the placebo group (56.6%, P < 0.001).
- **A non-significant trend favoured the buprenorphine group within the intention-to-treat analysis of the same end point (51.7% vs. 41.3%, P = 0.175).**
- **Transdermal buprenorphine is an effective therapy for DPNP and provides another option to manage this challenging painful condition. Nausea and constipation need to be managed proactively to optimize treatment outcomes.**

Low Doses of Transdermal Buprenorphine in Opioid-Naive Patients with Cancer Pain

Clin Ther. 2009 Oct;31(10):2134-8.

- This was a **nonrandomized, open-label, uncontrolled study in consecutive opioid-naive patients with advanced cancer and moderate pain**. TD buprenorphine was initiated at a

dose of 17.5 microg/h (0.4 mg/d), with patch changes every 3 days. Doses were then adjusted according to the clinical response. **N= 39**

- Thirty-nine consecutive patients completed all 4 weeks of the study. Low doses of TD buprenorphine were well tolerated and effective in these opioid-naive patients with cancer pain.
- **Pain control was achieved within a mean of 1.5 days after the start of TD buprenorphine therapy**. **The mean TD buprenorphine dose was significantly increased from baseline beginning at 2 weeks after the start of therapy and had doubled by 4 weeks (P < 0.05).**
- **Pain intensity was significantly decreased from baseline beginning at 1 week and continuing through the remaining weekly evaluations (P < 0.05).**
- **Quality of life improved significantly over the study period (P = 0.007). There were no significant changes in opioid-related symptoms between weekly evaluations.**

Transdermal Buprenorphine in the Treatment of Cancer and Non-Cancer Pain

Pharmacol Rep. 2011;63(4):935-48.

- **This was a multicenter, non-interventional, post-marketing study that aimed to evaluate the analgesic activity, safety of use, safety profile and adverse drug reactions of transdermal buprenorphine (35, 52.5 and 70 µg/h) during the treatment of moderate to severe chronic cancer and non-cancer pain.**
- The study was performed in Poland by 339 doctors. The study involved **4,030 general practice outpatients**, pain therapy center patients, specialist outpatient clinic patients as well as patients treated in inpatients units
- the mean pain intensity assessed using a visual analogue scale (VAS 0–100 mm) gradually decreased from a mean value of 62.5 mm at the baseline visit to the value of 16.5 mm at the final study assessment.
- The pain decrease observed during the first, second and third follow-up visits compared to baseline was statistically significant (p < 0.001).

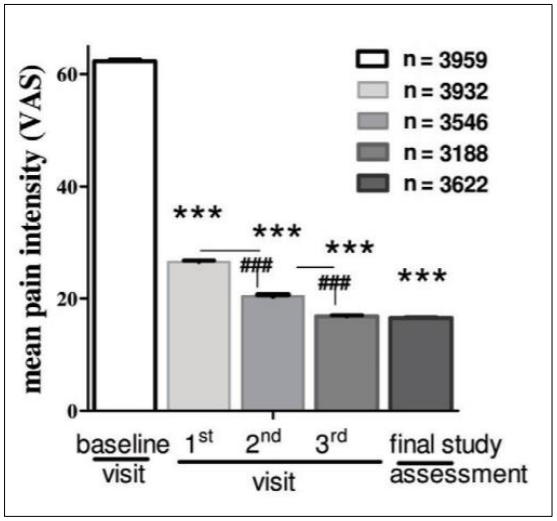

Figure: Mean pain intensity (VAS scale) during follow

t. *** p < 0.001 vs. baseline visit; ### p <0.001 1 vs. 2nd visit and 2nd vs. 3rd visit

- Compared with the baseline visit, at the third follow-up visit, significant improvement in sleep quality was seen in 918 patients (28.0%), improvement in sleep quality was seen in 1,035 (31.5%), slight worsening was seen in 47 (1.4%) and no improvement was seen in 1,187 (36.2%) patients.
- Antiemetic/laxative drugs had been used by 825 (20.5%) patients before starting therapy. These drugs had not been used by 3,149 (79.3%) patients
- In total, 34 cases (0.84%) of non-serious ADRs were reported. The most commonly reported adverse drug reactions were local skin reactions, representing 50% of the non-serious adverse drug reactions reported. The second most common adverse drug reaction was vomiting, a reaction that represented 14.7% of the adverse drug reactions reported.
- **Transdermal buprenorphine can be considered an efficient, safe, well tolerated drug in patients with moderate to severe cancer pain as well as in patients with severe nonmalignant pain that cannot be effectively treated with non-opioid drugs.**

Efficacy and Safety of Transdermal Buprenorphine in the Management of Children with Cancer-Related Pain

Pediatr Blood Cancer . 2013 Mar;60(3):433-7.

- **A single-arm, nonrandomized, 60-day trial open-label evaluation of the efficacy and side-effects profile of buprenorphine TDS in children with cancer-related pain.**
- **Sixteen pediatric patients with moderate to severe cancer-related pain** not satisfactorily controlled with previous non-opioid therapies were enrolled. Transdermal buprenorphine was administered following a 72 hour schedule
- Eleven patients (68.75%) responded to transdermal buprenorphine after 2 weeks of treatment. **Pain intensity measured with Wong-Baker faces pain rating scale (WBS) decreased from 6.25 at baseline to 1.38 at Day +60 (P < 0.001).**
- **All outcome measures of global quality of life (quality of sleep, alimentation, play and activity, speech, and crying) significantly improved over the 60-day study period. Children's evaluations of compliance and tolerability of the drug were always positive over the entire period of treatment. No severe adverse events were recorded.**

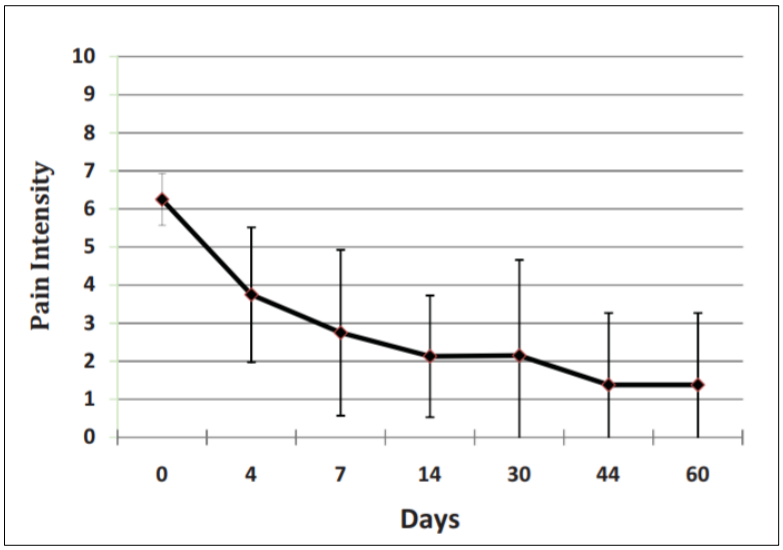

Figure: Reduction of mean pain intensity rated on WBS during the 60-day study period

- **Transdermal buprenorphine was found to represent an efficient, safe and well tolerated approach to the management of children's chronic cancer pain.**

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