Pain management

Personalized topical pain treatment

www.fagron.gr

Fagron
personalizing medicine

Transdermal drug delivery in pain management

The management of pain is perhaps the most obvious area where transdermal administration of commonly used medications can be clinically effective in avoiding suboptimal outcomes

The primary benefit of transdermal administration is most often the avoidance of unpleasant adverse events that either reduce the quality of life, or worse, are at the root of non-compliance.

Although oral NSAIDs are effective in relieving pain and reducing inflammation, their use shows a high incidence of adverse events, notably dose-dependent gastro-intestinal disturbances such as nausea, vomiting, or dyspepsia.

Furthermore, continued use of NSAIDs in particular can be harmful to body systems, because of accumulation in nontarget organs. Prolonged high systemic drug concentrations after oral NSAID therapy may result in potentially serious adverse events such as gastrointestinal ulceration or bleeding, hypertension, and cardiovascular events, acute renal impairment, and hepatotoxicity.[5, 12]

The risk of such effects could be reduced by the use of topical formulations, which can deliver effective analgesic concentrations at the site of inflammation while minimizing systemic concentrations. Lower systemic concentrations after topical administration would also be expected to result in a lower risk of drug–drug interactions resulting from NSAID-mediated displacement of drugs binding to plasma proteins or alterations in drug concentrations due to induction or inhibition of cytochrome P450 enzymes.

We also observe that invasive delivery systems for pain relief medications are often uncomfortable for patients and stressful for caregivers. Patient acceptance and adherence to therapy may be better with topical formulations than with oral and invasive treatment because of the combination of improved tolerability and convenient dosing regimens.[5, 12]

Development of transdermal formulations has been based on this approach to overcoming these significant obstacles to efficacy and compliance.

NSAIDs are mainly used in the treatment of acute, nociceptive pain. Neuropathic pain however, responds poorly to treatment with NSAIDs and is difficult to treat successfully. Neuropathic pain is primarily the result of a neuropathic injury or modulation within the central nervous system and generally is a chronic, long-term disease process. Various types of drug therapy are used to treat neuropathic pain. While none are specifically designed for this purpose, there is some rationale for their use. Examples include: anticonvulsants, NSAIDs, narcotic analgesics, tricyclic antidepressants, ketamine, and clonidine.[24, 25]

Due to the chronic nature of neuropathic pain, and undesirable side effects associated with most of the oral medications available for it, manufacturers and compounding pharmacists have worked on medications to treat neuropathic pain topically. Today, many compounded topical medications are used to treat chronic neuropathic pain effectively. The recent use of multifaceted regimens of topically applied medications has been anecdotally reported as being successful.[1, 4, 7, 13, 16, 24]

In many instances, pain and inflammation are localized to one part of the body. The bioavailability of topical NSAIDs has been reported to be generally less than 5% to 15%, while drug concentration at the site of administration can be 30-fold higher than with oral dose. [38] A plausible explanation might be that topical applied NSAIDs exert their pharmacological effects through localized accumulation at the application site rather than from systemic absorption.

Personalized topical pain treatment

Advantages of transdermal drug delivery

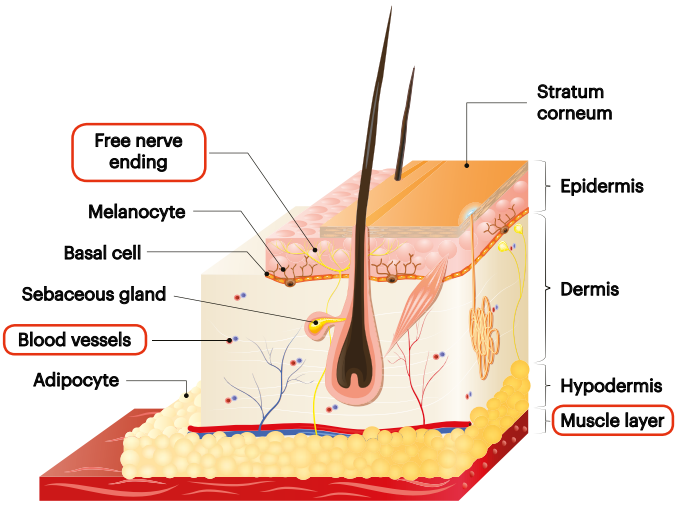
Scientific and clinical evidence over the last 15 years in the United States has shown that topical pain treatment is effective and safe.[3, 27, 28, 32] In a randomized, double-blind clinical study, patients with neuropathic pain treated with a variety of Active Pharmaceutical Ingredients (APIs), experienced significantly greater pain reduction.[28] Patients reported better outcomes in regard to walking ability (P=0.028) and performance of normal work (P<0.001) compared to the placebo group. No serious adverse events were observed.[28]

Transdermal delivery systems are popular because they have the following advantages over conventional drug delivery:

- They can substitute for oral administration of medication when that route is unsuitable, as in case of vomiting and diarrhoea
- They avoid the first-pass effect of the liver that can prematurely metabolize drugs
- They increase elimination half-life and establish high joint Tissue-plasma concentration ratios resulting in prolonged therapeutic effect; thus improving compliance because less frequent dose administration is required
- Drug therapy may be terminated rapidly by removal of the transdermal drug delivery systems from the surface of the skin
- They are non-invasive, avoiding the inconvenience of parenteral therapy and increasing the patient's acceptability
- They allow combination therapy with one dosage; a wide range of drugs with different chemical properties can be included in the transdermal drug delivery system
- Transdermal creams are easy to prepare, transdermal creams can be compounded in a few simple steps
- They can be self-administered, allowing the patient to have self-control over the generally inexpensive therapy [34, 38]

Multimodal treatment approach

Topical pain treatment uses cutaneous delivery of APIs to specifically target the soft tissues and peripheral nerves underlying the site of application.[28] Multiple APIs can be combined into a single preparation, offering the possibility for a customized and multimodal approach, in order to achieve additive effects in the treatment.[17, 27, 32, 33] Fagron developed a unique, easy to use, therapeutic approach that facilitates personalized prescription. Using the five building blocks, the prescriber can tailor the treatment to the patients' specific needs. The below APIs and concentrations can be used individually or combined. Goal of the treatment is to successfully address all specific peripheral component(s) involved to optimize efficacy.



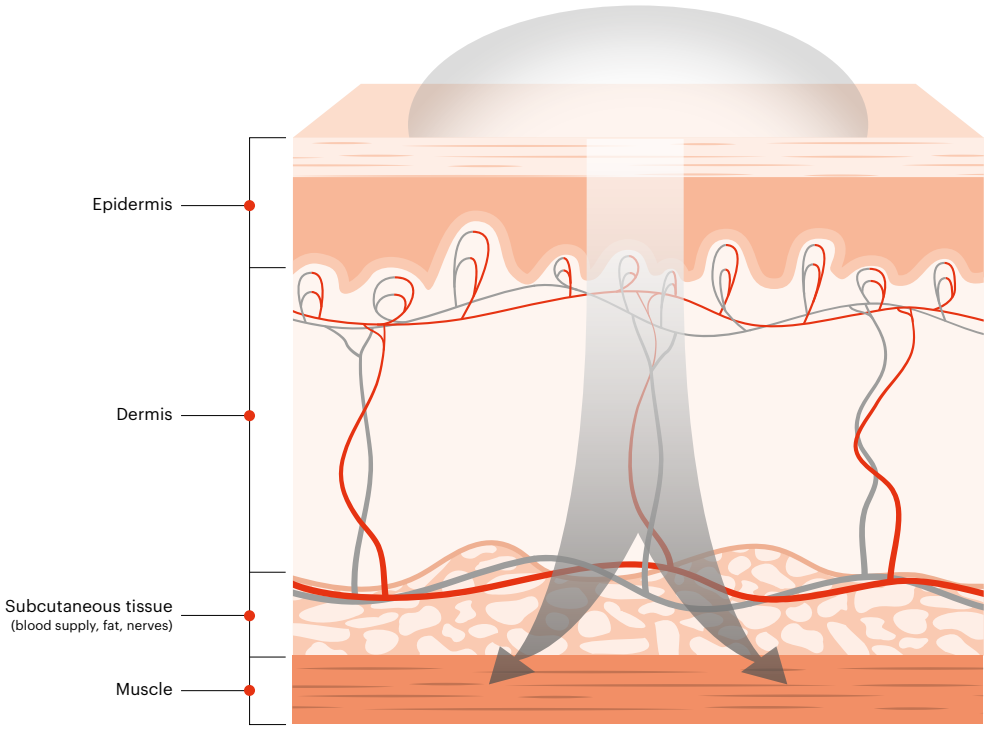
Transdermal drug delivery in pain management

Pain management building block system

	Inflammation	Nerve activation	Nerve impulse generation	Blood circulation	Muscle spams
1st choice	**Ketoprofen** 2 to 20%	**Ketamine HCl** 2 to 15%	**Lidocaine** 2 to 10%	**Nifedipine** 0.3 to 4%	**Baclofen** 2 to 5%
2nd choice	**Dicolofenac sodium** 1 to 5%	**Gabapentin** 4 to 10%	**Amitriptyline HCl** 2 to 5%	**Pentoxifylline** 0.5 to 5%	**Cyclobenzaprine HCl** 1 to 3%

Figure 1 Pain management building block system

Transdermal absorption



Transdermal absorption of a drug leads to direct penetration of the drug through the stratum corneum (SC), which is the outermost layer of the epidermis; a 10 to 15 m thick layer, consisting of dead cells (corneocytes). The lipid content is concentrated in the extracellular phase of the SC and forms a drug's major route of penetration. Once the drug molecules pass the SC, they are able to pass the deeper epidermal tissues and the dermis and finally they reach the vascularised dermal layer. Then, they become available for absorption in the general circulation.

The solution for pain

A range of vehicles to meet your needs

In order to achieve optimal therapeutic results, Fagron has developed a range of compounding vehicles intended to cover the needs in pain management. The developed vehicles have excellent compatibility with a broad range of APIs, while improving patient comfort and compliance.

Pentravan®

Pentravan® is a ready to use cream base with a liposomal matrix that uses penetration enhancing ingredients that enable it to establish a greater rate and extent of absorption of the drug than other transdermal bases. Therefore, more of the drug will become available in a shorter time to establish the effect of the therapy. Besides that, Pentravan® is a true vanishing cream, leaving no sticky residue and providing a cosmetically elegant skin feel. Therefore, there is no need to cover the area of application in order to prevent transferring of the cream and to ensure effectiveness of therapy. It is preserved and fragrance-free.

Versatile™

Versatile™ is an elegant cream base with a unique formulation. The vehicle retains its consistency with a broad range and high concentration of APIs. Versatile™ has been designed according to the latest insights into topical vehicle safety and tolerance and it rapidly vanishes into the skin. In a clinical study using a variety of APIs compounded in Versatile™ base, significant pain reduction was shown in neuropathic patients.[28]

Suggested formulations for pain management

POSTHERPETIC NEURALGIA [2, 11, 20, 30]

Fagron Derma Pack GKALP

Gabapentin	10 g
Ketoprofen	5 g
Amitriptyline hydrochloride	2 g
Lidocaine hydrochloride	5 g
Pentravan®	qs 100 g

POSTHERPETIC NEURALGIA [10, 26, 31, 37]

Fagron Derma Pack KLP

Ketoprofen	10 g
Lidocaine hydrochloride	5 g
Pentravan®	qs 100 g

HEMORRHOIDS [14]

Fagron Derma Pack NLP

Nifedipine	300 mg
Lidocaine	1 g
Pentravan®	qs 100 g

PAIN [22, 35, 36, 39]

Calculated to make 100 g

Diclofenac Sodium	1.5%
Lidocaine	2.25%
Prilocaine	2.25%
Pentravan®	qs 100 g

NEUROPATHIC PAIN [6, 9, 15, 18, 19, 21]

Calculated to make 50 g

Ibuprofen	5 g
Gabapentin	3 g
Baclofen	1 g
Amitriptyline Hydrochloride	2 g
Lidocaine	2,5 g
Ethoxydiglycol	5 g
Propylene Glycol	2,5 g
Pentravan®	qs 50 g

NEUROPATHIC PAIN [8, 23]

Calculated to make 100 g

Diclofenac Sodium	5%
Gabapentin	6%
Topiramate	3%
Nifedipine	4%
Clonidine Hydrochloride	0.2%
Lidocaine	5%
Ethoxydiglycol	10%
Propylene Glycol	5%
Versatile™	qs 100 g

References

1. Alexander K, Wynn T. Transdermal gel in the treatment of postoperative pain. International journal of pharmaceutical compounding. 2007; 11(3): p. 181-184.
2. Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. International Journal of Pharmaceutical Compounding: 15 (4). July/August 2011.
3. Argoff CE. Topical analgesics in the management of acute and chronic pain. Mayo Clin Proc. 2013;88(2):195-205.
4. Barkin R. Topical nonsteroidal anti-inflammatory drugs: the importance of drug, delivery, and therapeutic outcome. American journal of therapeutics. 2012. Epub ahead of print.
5. Bryant-Snure SJ, Muller G. Pain from degenerative disc disease. International journal of pharmaceutical compounding. 2010; 14(3): p. 187-190.
6. Boardman LA, Cooper AS, Blais LR, Raker CA. (2008). Topical gabapentin in the treatment of localized and generalized vulvodynia. Obstet Gynecol. 2008 Sep;112(3):579-85. doi: 10.1097/AOG.0b013e3181827c77.
7. Cabaleiro J. Assessing and treating neuropathic pain. Home healthcare nurse: the journal for the home care and hospice professional. 2002; 20(11): p. 718-723.
8. Chong, M. S., & Libretto, S. E. (2003). The rationale and use of topiramate for treating neuropathic pain. The Clinical journal of pain, 19(1), 59-68.
9. Cross PL et al (2005). TOIB Study. Are topical or oral ibuprofen equally effective for the treatment of chronic knee pain presenting in primary care: a randomised controlled trial with patient preference study. BMC Musculoskelet Disord. 2005 Nov 7;6:55.
10. Dubinsky, R. M., Kabbani, H., El-Chami, Z., Boutwell, C., & Ali, H. (2004). Practice parameter: treatment of postherpetic neuralgia. Neurology, 63(6): 959-65.
11. Dubinsky, R. M., Kabbani, H., El-Chami, Z., Boutwell, C., & Ali, H. (2004). Practice Parameter: Treatment of postherpetic neuralgia:[RETIRED]: An evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology, 63(6), 959-965.
12. Erickson B, Brown S. Pain from arthritis and postpolio syndrome. International journal of pharmaceutical compounding. 2010; 14(3): p. 183-186.
13. Franckum J, Ramsay D, Das NG et al. Pluronic lecithin organogel for local delivery of anti-inflammatory drugs. International journal of pharmaceutical compounding. 2004; 8(2): p.101-105.
14. Golfam F, Golfam P, Golfam B, Pahlevani P (2014). Comparison of topical nifedipine with oral nifedipine for treatment of anal fissure: a randomized controlled trial. Iran Red Crescent Med J. 2014 Aug;16(8):e13592. doi: 10.5812/ircmj.13592. Epub 2014 Aug 5.
15. Heustess A, Spigener S, Sweitzer S, Romero-Sandoval A, Asbill S (2015). Analgesic Efficacy and Transdermal Penetration of Topical Gabapentin Creams: Finding an Optimal Dose and Pretreatment Time. Int J Pharm Compd. 2015 Mar-Apr;19(2):167-73.
16. Jones M. Clinical nuggets and pearls: chronic neuropathic pain and opioid tolerance. International journal of pharmaceutical compounding. 2002; 6(1): p. 4-6.
17. Jorge LL, Feres CC, Teles VEP. Topical preparations for pain relief: efficacy and patient adherence. J Pain Res. 2011; 4:11-24.
18. Kenneth C. Hohmeier and Lyndsey M. Almon (2015). Topical and Intranasal Analgesic Therapy in a Woman with Refractory Postherpetic Neuralgia. Case Rep Med. 2015; 2015: 392874. Published online 2015 Apr 9. doi: 10.1155/2015/392874.
19. Keppel Hesselink JM, Kopsky DJ, Sajben N (2016). New topical treatment of vulvodynia based on the pathogenetic role of cross talk between nociceptors, immunocompetent cells, and epithelial cells. J Pain Res. 2016 Oct 3;9:757-762. Lynch ME et al. (2005).
20. Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. International Journal of Pharmaceutical Compounding; 16 (43). May/June 2012.
21. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ (2005). Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. J Pain. 2005 Oct;6(10):644-9.
22. Mark S. Nestor (2006). Safety of Occluded 4% Liposomal Lidocaine Cream. Journal of Drus in Dermatology. 5(7):618-621.
23. Meno, A., Arita, H., & Hanaoka, K. (2001). Preliminary report: the efficacy of clonidine hydrochloride ointment for postherpetic neuralgia. Masui. The Japanese journal of anesthesiology, 50(2), 160-163.
24. Mestayer III RF. Pain after spinal infusion. International journal of pharmaceutical compounding. 2010; 14(3): p. 191-192.
25. McNulty JP. Update on managing neuropathic pain. International journal of pharmaceutical compounding. 2009; 13(3): p. 182-190.
26. Oster, G., Harding, G., Dukes, E., Edelsberg, J., & Cleary, P. D. (2005). Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. The Journal of pain, 6(6): 356-363.
27. Peppin JF, Albrecht PJ, Argoff C, Gustorff B, Pappagallo M, Rice FL, Wallace MS. Skin Matters: A review of topical treatments for chronic pain: part 1. Pain Ther. 2015; 4:17-50.
28. Reyzelman AM, Vartivarian M, Bazarov I, Horne B. A Randomized, Double-blind, Placebo-controlled Study of a Topical Analgesic Cream for the Treatment of Neuropathic Pain. The Pain Practitioner. 2014 Fall;24 (3): 5-15.
29. Rogers M, Tang L, Madge DJ, Stevens EB. The role of sodium channels in neuropathic pain. Seminars in Cell & Developmental Biology. 2006; 17:571-581.
30. Rowbotham, M., Harden, N., Stacey, B., Bernstein, P., Magnus-Miller, L., & Gabapentin Postherpetic Neuralgia Study Group. (1998). Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. Jama, 280(21), 1837-1842.
31. Sampathkumar, P., Drage, L. A., & Martin, D. P. (2009, March). Herpes zoster (shingles) and postherpetic neuralgia. In Mayo Clinic Proceedings. 84 (3): 274-280.
32. Sawynok J. Topical analgesics for neuropathic pain: preclinical exploration, clinical validation, future development. Eur J Pain. 2014;18(4):465-81.
33. Sawynok J. Topical and peripherally acting analgesics. Pharmcol Rev. 2003;55(1):1-20.
34. Sharma N, Agarwal G, Rana AC et al. A review: transdermal drug delivery system: a tool for novel drug delivery system. International journal of drug development & research. 2011; 3(3): p. 70-84.
35. Sintov AC, Botner S. (2006). Transdermal drug delivery using microemulsion and aqueous systems: influence of skin storage conditions on the in vitro permeability of diclofenac from aqueous vehicle systems. Int J Pharm. 311(1-2):55-62.
36. Stanos SP, Galluzzi KE (2013). Topical therapies in the management of chronic pain. Postgrad Med. 125(4):25-33.
37. United States Pharmacopoeia, USP on compounding: A Guide for the Compounding Practitioner. United States Pharmacopeia Convention, Rockville MD USA; 2012.
38. Vadaurri V. Topical treatment of neuropathic pain. International journal of pharmaceutical compounding. 2008; 12(3): p. 182-190.
39. Van Kan, H. J. M., Egberts, A. C. G., Rijnvos, W. P. M., Ter Pelkwijk, N. J., & Lenderink, A. W. (1997). Tetracaine versus lidocaine-prilocaine for preventing venipuncture-induced pain in children. American journal of health-system pharmacy, 54(4), 388-392.
40. Various formulations for analgesic transdermal drug delivery systems. International journal of pharmaceutical compounding. 2010; 14(3): p. 185-194.

Fagron Hellas
12 km N.R. Trikala - Larisa
P.C. 42100, P.O. Box 32
Trikala, Greece

T +30 24310 83633-5
F +30 24310 83615
www.fagron.gr

Fagron personalizing medicine