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CASE REPORT

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Clinical Experience with Transdermal Combination Drug Therapy: Treatment of Various Pain Conditions with Transdermally Applied Combination of Gabapentin and Naproxen

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Abstract

Background: The authors challenged the current pain treatment paradigm and its focus on the systemic treatment of pain by the oral administration of opioids, high dose non-steroid anti-inflammatory drugs, anticonvulsants, and psychotropic drugs and studied and retrospectively analyzed the efficacy of a transdermal emulsion on various chronic pain conditions.

Case Reports: The clinician has an active chronic and acute pain practice and favors transdermal drug treatment for various pain conditions. The therapy consisted of a transdermal emulsion containing gabapentin and naproxen sodium in a 10% to 5% ratio. The treatment included 2-3/day application of emulsion to the target area. Substantial pain relief was obtained in the treatment of chronic and acute myofascial, musculoskeletal, and neuropathic pain.

Conclusion: The authors offer transdermal combination drug therapy as an appropriate peripheral pain treatment alternative to systemic drug therapy and avoid the human and societal costs of opioids, high dose NSAIDs and psychoactive drugs.

Keywords: Transdermal combination drug therapy; Gabapentin; Naproxen; Chronic pain conditions

Introduction

The staggering number of opioid-related morbidity and mortality in the United States and the origin of this epidemic in the prescribing practices of the medical profession including postoperative opioid use have led to the implementation of Multimodal Analgesia (MMA) to reduce opioid usage [1] and to accomplish a more effective pain management, through both central and peripheral anti-nociceptive mechanisms [2]. In the last two decades, evidence-based multimodal opiate-sparing analgesia has become increasingly widespread after non-cardiac surgery [2] and shown beneficial in other surgical practices as well [3-5]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have demonstrated opiate sparing effects in randomized trials after cardiac surgery, but cardiac surgeons and anesthesiologists have had safety concerns with NSAIDs regarding renal impairment, bleeding risk and increased risk for cardiovascular death [2,6]. The addition of GBP to a NSAID was intended to "provide synergistic analgesic and opiate sparing effects, and indeed this combination has demonstrated" such benefits in both cardiac [2] as well as "other surgical populations [3-5].

Combination drug therapies utilizing NSAIDs and gabapentinoid drugs are efficacious in management of various pain conditions [7,8], of particular importance stays in their ability to opioid sparing [8-12]. NSAIDs [13] and gabapentinoids [14-19] are also successfully used in transdermal delivery, and this latter delivery mode carries an additional benefit in reducing side effects of the pharmacologically active drug [20-24]. The above two drugs were also successfully delivered in combination therapies [25-29].

Reports in in vivo human and guinea pig models showed that transdermal drug therapy can be engineered to result in a reservoir of the drug in the deep tissues [30]. Application of transdermal NSAID to osteoarthritis knees resulted in modest uptake in the blood over 48hr period with peak levels at the 24hr mark in humans [30], while the bulk of the transdermal drug was found in the deep tissues in a guinea pig transdermal delivery model that was consistent with in vivo test results [30].

Despite the demonstrated benefits as an alternative to opioids, the use of orally administered MMA carries with it the substantial

adverse secondary effects of high dose NSAIDs and anticonvulsants [31,32]. To better receive the known analgesic benefits and avoid the serious adverse effects of NSAIDs, there is a growing consensus that many types of peripheral pain are better treated in the first instance with transdermal as opposed to systemic NSAIDs [31,33]. Similarly, there is a growing awareness among clinicians that transdermal GBP formulations can deliver high concentrations of the active at the site of administration [34].

The human, social and economic impact of pain and the medical practitioner's mission compel the profession to make use of treatment modalities for pain that best offer the patient targeted relief and the restoration of functionality with the least risk of harm or adverse secondary effects. The clinician of these studies has an active chronic and acute pain practice. Because of his concern regarding potential systemic and addictive effects of systemic drug treatment, the clinician has incorporated when feasible, alternate routes of drug administration to treat peripheral pain. A transdermal emulsion containing 100mg of gabapentin (GBP) and 50mg naproxen (NS) per gram has been favored.

Methods

Franz Cell Strat-M® diffusion tests show penetration with ratio's maintained

BioPhysics' Multi-phasic Transdermal Emulsion Technology employs multiple passive and active penetration modalities. The passive modalities are designed to passively move the pharmaceutical agents into skin by penetrating the stratum corneum and epidermal skin layers via emulsive phase change (lipophilic to hydrophilic) and mass action. The active penetration modalities, which are unique to the BioPhysics Multi-phasic Transdermal Emulsion Technology are designed to flush the pharmaceutical agents out of the skin and into either systemic circulation or deep localized tissue penetration via fluid dynamic enhancement with vasodilation and temporary dermal tissue structure modification through protein denaturing. The Transdermal Combination Drug Therapy (TD CDT) emulsion contains Penetration Agents (PA); Basement Membrane Disruptors (BMD); Vasodilators (V); and the Active Drugs (API).

The emulsion is sufficiently labile to overcome the hydrophilic and lipophilic structures in skin utilizing the penetration agents [Figure 1 frames 1 & 2] and basement membrane disruptors to open-up channels sufficient to transport the drug and vasodilator deep into the dermis [Figure 1 frames 3 & 4]. Once in the dermis, vasodilators dilate the capillary bed creating fluid dynamic flow (Figure 1 frames 5 & 6). The fluid dynamics can be engineered for either reservoiring the API in the local tissue or rapid systemic uptake. In either case, the vasodilation dynamic has the beneficial effect of increasing blood flow to the injured site which efficiently delivers the API, flushes away the mediators of inflammation and promotes healing.

Franz Cell testing using Strat-M® membrane [35] were conducted and compared the passive diffusion rates of three commercially

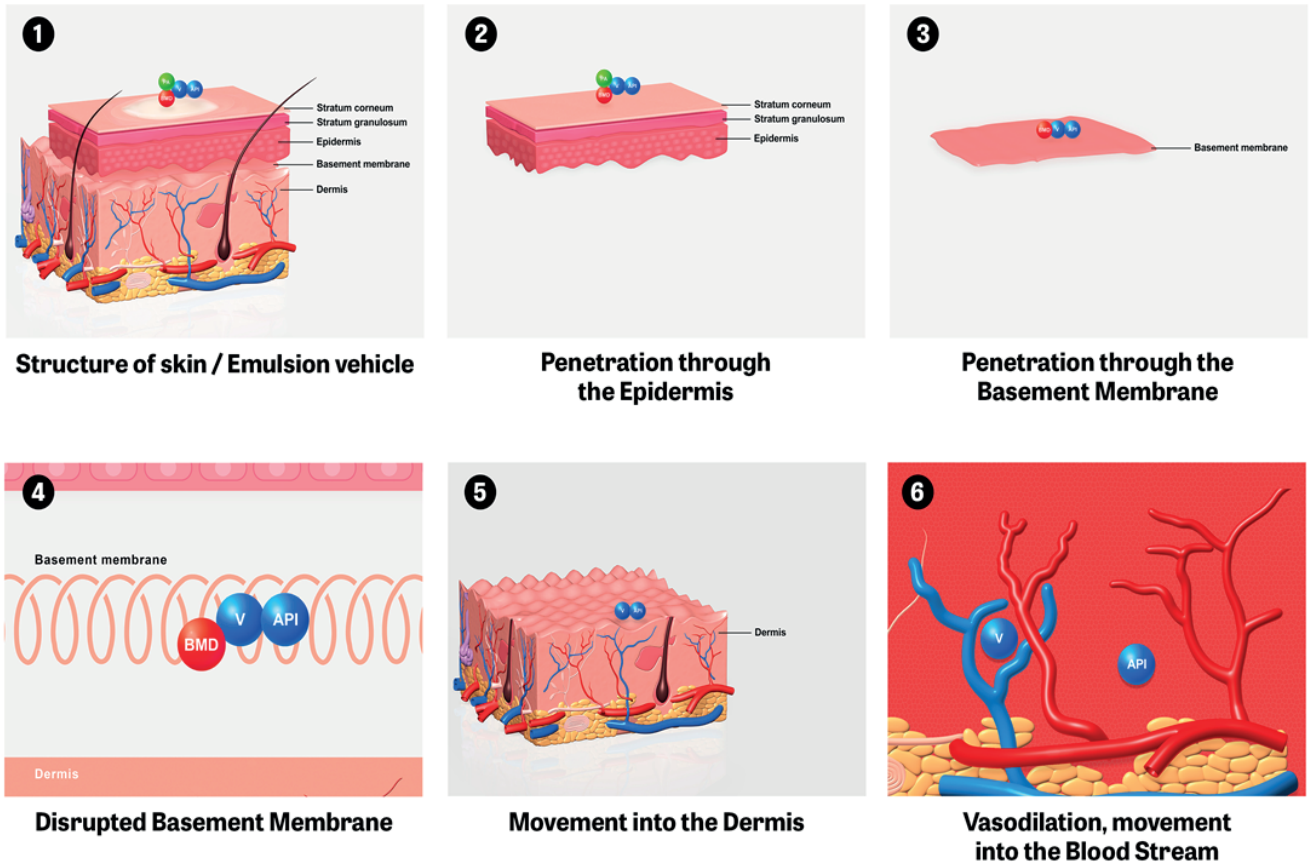

Figure 1: Transdermal delivery through the skin, courtesy of BioPhysics, Inc. The transdermal emulsion technology contains Penetration Agents (PA) Basement Membrane Disruptors (BMD), Vasodilators (V) and the Active Drugs (API).

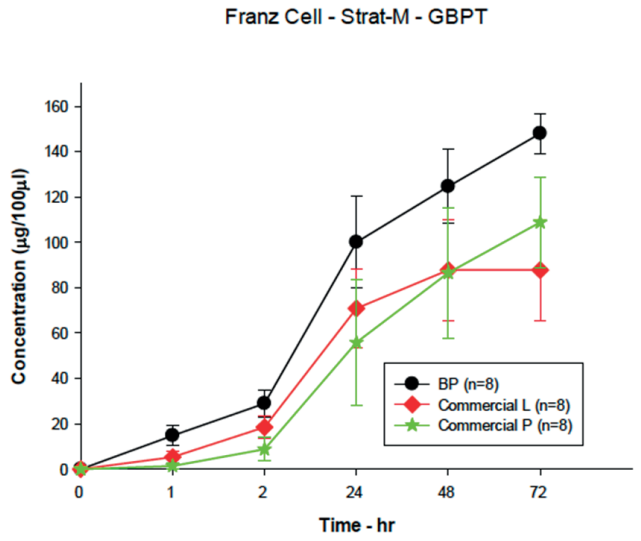

Figure 2: Penetration profile of Gabapentin through Strat-M membranes showing the effect of formulation loading on the permeation of Gabapentin. The data points are mean +/- SEM, n=8. The graph illustrates the penetration dynamics of the active pharmaceutical agent as they move through the Strat-M membrane over a 72-hour period. The results of comparative penetration studies using MTE and two commercially available cream formulations are depicted in Figures 2 and 3.

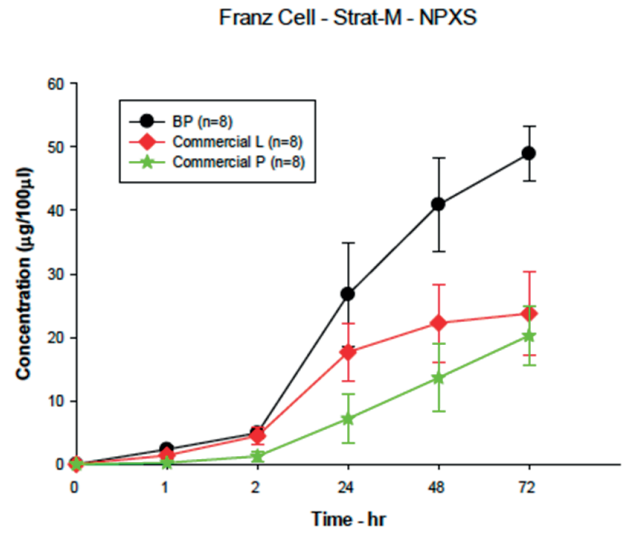

Figure 3: Penetration profile of Naproxen through Strat-M membranes showing the effect of formulation loading on the permeation of naproxen. The data points are mean +/- SEM, n=8.

available technologies has shown that transdermal technology can deliver a combination drug formulation of GBP and NS through an analog to human skin while maintaining the essential ratios of the two drugs to each other. The results demonstrated, based on successful passive diffusion through a synthetic analog to human skin that transdermal technology used in the clinician's practice ["BP" in Figure 2-3] is capable of transdermal delivery, in combination, of two qualitatively different drugs. We noted that the technology is designed to promote both passive diffusion through the upper layers of the skin and active uptake to promote either systemic or local delivery. We also concluded that the Franz Cell study demonstrated transdermal technology was "able to simultaneously accommodate two APIs with different partition coefficients, molecular structures, and drug classes [34].

Clinician's transdermal combination drug therapy pain practice

The clinician has an active chronic and acute pain practice. Over the course of a year, the clinician personally treated and managed more than 1,000 patients for a variety of acute and chronic pain conditions. Also, like many of his colleagues, he is concerned regarding the potential systemic and addictive effects of systemic drug therapy [33]. For that reason, for the past five years, the clinician has attempted to incorporate, when feasible, alternative routes of drug administration to treat peripheral pain, including: injection therapy and Transdermal Drug Therapy (TDT). The clinician favors Transdermal Combination Drug Therapy (TD CDT) that targets the injured tissue through local delivery using a multi-phasic emulsion that combines GBP (10%) and NS (5%). The emulsion contains 100mg GBP and 50mg NS per gram.

TD CDT involving GBP and NS was chosen because the APIs have long been approved by the FDA as systemic pain medications with a well-known efficacy and toxicity profile, individually and in combination [9,20,23,25,28,32,36-42]. This was the preferred vehicle to realize the drugs' demonstrated ability to relieve peripheral pain while avoiding GBP's impact on cognitive function and the CNS; and high dose NSAIDs on the gastro-intestinal, renal, hepatic and cardiovascular systems [11,12,24,28,38,42-46].

Therapy application

Depending on the location and condition, treatment has consisted of 2-3x/day application of approximately 1-6 grams of emulsion to the target area. The emulsion is allowed to be absorbed over 15 minutes before washing or exposure to clothing. Depending on the need and to allow for a greater amount of emulsion to be absorbed, a temporary occlusive barrier has sometimes been applied such as Tegaderm™. Sustained substantial pain relief has been reported by approximately 70% of the treatment population. Patients usually experience substantial relief of pain within minutes of application and a noticeable increase of range of motion. In many cases, use of the treatment progresses from 2-3x/day to an "as needed basis," with many patients reporting that pain relief has allowed them to suspend treatment for an extended period.

Routine drug urine tests of treated patients on long term therapy for chronic pain conditions have been negative for TD GBP at the detection levels for such tests. The absence of both cognitive deficits and detectable levels of GBP in urine have removed patient concern that TD CDT could interfere with performance at work or cause the patient to fail employer required drug screening. Because of these benefits, and the fact that treatment consists of targeted use of orders of magnitude less drug and the practical avoidance of systemic risks normally associated with SDT, the clinician considers TD CDT to be a frontline first use treatment.

Summary of conditions treated

To date, the clinician has treated several hundred patients using TD CDT. The conditions treated have included myofascial, musculoskeletal, and neuropathic pain - both chronic and acute. Most of the conditions were chronic which had responded poorly to SDT as well as nerve blocks. The conditions included: Post Herpetic

Neuralgia (PHN); Osteoarthritis (OA) of multiple joints; Plantar Fasciitis; Mechanical pain; post-surgical neuroma; Sciatica; failed neck and back surgical syndromes; Reflex Sympathetic Dystrophy (RSD); Tendonitis of various joints; phantom pain of the lower extremities due to amputation or accident; and various neuromas resulting from accidents and surgery.

Results

Case reports

The authors present particular case reports as indicative of the type of success obtained with transdermal combination drug therapy as a frontline treatment and initial alternative to systemic drug therapy.

Post Herpetic Neuralgia: The authors followed the progress of 3 patients suffering from PHN including some who were recently diagnosed and others who had been dealing with the symptoms for many years with minimal or no relief from standard therapy. In all three instances, the patients substantially benefitted from TD CDT in contrast to the failed use of opiates, gabapentin, pregabalin, lidocaine, and anti-depressants. Examples follows:

93-year-old female with a 12-year history of unresolved constant PHN pain involving the left L1-5 dermatomes. Minimally responsive to Vicodin® and Percocet®. Patient experienced serious CNS side effects which she wished to avoid. Also tried Lidoderm™ patch with little effect. Additionally, patient received occasional nerve blocks including Epidural Steroid Injection (ESI) and intercostal nerve blocks. Pain reported as a constant 10 out of 10. Within 10 minutes of application covered by Tegaderm™ barrier patient reported substantial reduction in pain leaving her with minimal discomfort. Follow up phone call at 48 hours, patient reported she was pain free using 1 application and a Tegaderm™ cover which gave relief for 24 hours. At 6 days Patient reported applying emulsion 1x a day with Tegaderm cover continuing to give complete relief. At five months Patient reported "minimal discomfort," "nothing else has done better," and she was "very pleased" with the treatment. Patient now uses 1-2x/wk and has eliminated oral meds for pain.

This patient was seen and evaluated as a recommendation from prior doctor. The patient had been diagnosed with Zoster and postherpetic neuralgia in 2007. On this visit the patient reported chronic pain (pain level was 10/10). Prior failed treatment history included Lidoderm, oral Gabapentin, Opioids, Lyrica®, ICNBs, ESI all failed. Prescribed treatment with TD CDT 10%/5% Gabapentin/Naproxen which resulted near complete relief from pain within 15 minutes. At a one day follow up, the patient reported 100% relief where the pain level went down to 0/10 upon TD CDT treatment. Patient reported sleeping well. Two day follow up, the pain is still at 0/10. One week follow up, the patient reported no pain with the use of TD CDT 1-2 times a day. At two months follow up visit, patient states using TD CDT every other day with near total relief. Patient calls the treatment life changing.

55-year-old female patient was diagnosed with PHN and chronic pain in the left arm and hand. Patient reported pain score 7/10 and complained that the pain wakes her up from sleep. The patient took several prescription drugs, including Hydrochlorothiazide (HCTZ), Albuterol; Ventolin, Tramadol, Qvar® (Beclometazone dipropionate) and Montelukast, most of them primarily were not applicable for treatment of PHN. For over a period of one month she used the TD CDT formulation that contained 10% gabapentin and 5% naproxen. Prior transdermal treatment(s) of gabapentin with a compounded transdermal product using a different technology from a different company had failed. Note: the patient could not use of tricyclic pain medications due to side effects. She reported 30% pain reduction upon application of TD CDT and she feels that the use of arms was 100% better.

78-year-old female patient was diagnosed with Zoster, postherpetic neuralgia. The condition lasted approximately 8 months, involved location T4-T8 LT approximately and manifested in burning allodynic pain. Previously, she used oral gabapentin, Tramadol 50 mg and Percocet, and all these pharmacological regimens failed to control her pain. She reported pain level of 8-9/10. Using the TD CDT technology with 10% Gabapentin and 5% naproxen 3 times a day appeared effective, and it brought down the pain score to 5/10. While the patient continued use of opioids, she was able to decrease the dose.

Osteoarthritis: 86-year-old male. The patient suffers from osteoarthritis for 10 years; in fingers, RLBP and muscle spasm. When episodes occurred, he suffered pain level 10/10. He took prescriptions such as oral gabapentin and opioids prior to TD CDT G10-/N5 and their effectiveness appeared moderate. We advised two times a day application of TD CDT-G10-/N5. Since application of TDE pain decreased greatly, he was able to sleep.

55-year-old male. Patient complained about pain level 5/10 in the knee for about 1 week. The diagnosis established severe osteoarthritis in the left knee. No prior treatment and no prescription medication was used. We suggested application of TD CDT-G10-/N5 at the site of pain. At reevaluation patient claimed 0-1/10 pain level.

58-years-old male. Patient complained about pain of 5/10 at the elbow and in the upper arm. The diagnosis is Tennis elbow, left, left upper arm muscle pain. No prior prescription drug was used. We suggested use of TD CDT-G10-/N5 3x/day. At reevaluation patient reported pain level 2/10. Pain on tennis elbow decreased, but on upper arm muscle appeared ineffective. Patient advised to use the product 3x a day for max efficiency.

77-year-old female with right knee OA. Status post NSAIDs and steroid injections. 6-7 out of 10 on pain scale. Reached limit of injections and cannot tolerate NSAIDs. Application with Tegaderm cover. Patient reported 3x/day use and minimal discomfort with significant improvement in range of motion. Patient reported that she was able to maintain function without use of oral meds. At 1 month interval she reported she was using emulsion PRN.

48-year-old female with history of total left knee replacement on initial opioid therapy by surgeon. At 10-day post-operative called reporting moderate-severe pain and requesting additional opioids. Prescribed the emulsion as an alternative which patient applied 3x/day with substantial relief and avoidance of opioids during 2-month post-operative period.

Plantar fasciitis: 56-year-old female with long history of plantar fasciitis and bunion on right foot treated by injections, NSAIDs and physical therapy with poor response. Patient reported severe pain, 7 out of 10 on pain scale. Application with Tegaderm™ cover. Patient reported, at 30 minutes, substantial reduction (50%) and following day reported further significant reduction. Patient now applying 3x/day. Patient avoided further injections and oral medications.

Post-surgical neuroma: 48-year-old male, carpenter, with history of colectomy/temporary colostomy that developed severe ostomy site pain/neuroma. Pain described as 8 out of 10 on pain scale. Injection therapy with anesthetic and steroid only provided short term relief. Failed to respond to anticonvulsants. Patient avoided opioids because he uses heavy machinery. Applied emulsion and covered with

Tegaderm. Pain score within 15 minutes went from 8 to 0 out of 10 and provided 24 hours of relief. Patient continued to apply 1x/day covered by Tegaderm™ which he would leave on for the duration of the day. Emulsion therapy has allowed Patient to work full time with no appreciable pain and have uninterrupted sleep without being awoken by neuropathic pain. Patient has avoided all need for nerve blocks or neuroma insulating surgery. After 1 month Patient reported that he received sufficient pain relief with 2-3x/wk application with a Tegaderm™ cover.

Phantom pain associated with paraplegia: 48-year-old male paraplegic from navel down caused by traffic accident with a four-year history of shooting burning pain of his lower extremities poorly responsive to high dose oral meds of gabapentin, Oxycontin™ - 10 out of 10 on the pain scale reduced 7 out of 10 by oral meds with serious CNS effects substantially impairing mental and physical function. Within 1 week of BID application, pain went from 7 out of 10 to 0-1 out of 10, reported uninterrupted sleep and ability to fully function and had curtailed opioid use and substantially reduced oral gabapentin.

Failed cervical surgery syndrome: 38-year-old female, nurse, working mother with young children with history of multiple cervical surgery for neuropathic disc disease. History of oxycodone, hydrocodone, anticonvulsants, and NSAIDs. Oral meds provided minimal relief with serious CNS side effects interfering with work and daily routine. 8 out of 10 pain score with minimal range of motion. Applied to neck with Tegaderm™ cover. Patient reported significant relief within 30 minutes to 2 out of 10 pain score with significant range of motion. Patient continued 1x/day application usually at night allowing uninterrupted sleep and ability to perform daily routine with minimal discomfort and significantly improved range of motion. At 2-month interval Patient reports applying at night and PRN during day and completely curtailed oral meds.

Failed back syndrome: 53-year-old male contractor with a 20-year history of radicular low back pain disc disease. Back surgery six months previous. Had been on high dose opioid therapy (over 600mg/day) but had weaned off as of the visit. Patient reported moderate to severe 5-6 out of 10 pain scale. After several days of application 3x/day Patient reported that the pain level had reduced by 50%. At 1 month interval, patient reported that he was applying emulsion at night and as needed during the day. Therapy has reduced pain level to minimal and has allowed Patient to sleep through the night and function as a contractor without need for any oral medications including opioids.

Discussion

Benefits of therapy

The clinician has experienced a very high rate of success in freeing the patient from the debilitating impact of pain on their daily routine as well as avoiding the need for more invasive or riskier treatment modalities. This has relevance for many patient populations who are particularly vulnerable to the adverse impact of systemic drug therapy on function and cognition. These populations include: the elderly; bariatric surgical population; young athletes; high performing individuals; and patients subject to employer mandated drug screening.

Unlike opioid medication which impacts the sensory effect on the central nervous system [47], the clinician reports many instances, involving tendonitis or other related myofascial inflammatory/nerve spasm-based syndromes responding with a therapeutic effect. These include patients suffering post herpetic neuralgia. It appears to have broken the cycle of pain, reduced inflammation, calmed peripheral nerve spasm, and induced increased blood flow to the target area, allowing the underlying condition to heal while at the same time increasing the patient's functionality and productivity. The treatment has allowed patients to avoid the risks associated with oral medications or nerve blocks. TD CDT has provided both substantial pain relief and restoration of function to many patients suffering moderate and severe acute and chronic peripheral pain without any evident adverse clinical effects on cognitive function or physical, or mental, well-being, commonly associated with SDT. The rapidity of effect also has allowed the clinician, within days, to make appropriate adjustments or changes to the pain management plan as opposed to the weeks and months normally required to titrate systemic medications.

Changed opioid prescribing practice

TD CDT has markedly changed the clinician's prescribing practice and has had a substantial and positive impact on patient use and demand for opioids. It has been a reason that patients have avoided opioids at the outset and all the risks of associated side effects: addiction and serious gastro-intestinal and central nervous system disorders. Because of this therapy, patients with a history of opioid use have been able to substantially reduce or completely curtail use.

TDT NSAID studies

The American Society of Pain and Neuroscience found that regarding the treatment of patients with chronic back pain or, hip, or knee osteoarthritis pain with NSAIDs or opiates there "was significant improvement in pain intensity in the non-opioid group when compared to opioids" and that "the opioid group had greater medication-related side effects and adverse events" [48,49]. The 2022 CDC Guidelines recognized the growing consensus that for certain types of peripheral pain the preferred choice should be TDT NSAIDs rather than SDT NSAIDs. The 2022 Guidelines grudgingly acknowledge, "if a single or a few joints near the surface of the skin (e.g. knee) are affected by osteoarthritis, use of topical NSAIDs is recommended [50]. The Society of Pain and Neuroscience's Consensus Guidelines state "NSAIDs are an effective treatment for mild to moderate pain secondary to osteoarthritis knee pain" and "Topical NSAIDs are recommended before oral treatments because of their lower systemic exposure/toxicity" [49].

TDT GBP Studies

GBP is currently licensed for the treatment of partial epileptic seizures and peripheral Neuropathic Pain (NP) conditions, such as vulvodynia, post-herpetic neuralgia and painful diabetic peripheral neuropathy [34]. In recent years GBP has been used as part of multimodal regimens after non-cardiac surgery [2].

It is "considered to be better tolerated with fewer side effects than other anti-epileptics drugs" but "treatment of NP with oral GBP is still often limited by adverse effects, such as dizziness, somnolence, ataxia .and fatigue [34]. TD "drug delivery has been shown to limit the adverse effects of systemically delivered medications for NP whilst providing high concentrations of active at the site of administration [34,51]. TD GBP has shown efficacy in the treatment of peripheral neuropathic pain [52-54].

GBP-NSAID combination therapy

Animal research using rats demonstrated that the oral combination of GBP and an NSAID found "together these agents interact in an additive fashion if delivered concurrently" and this "combination may prove useful in managing post injury pain states in humans [41]." A subsequent study demonstrated the combination of GBP and NSAIDs is effective for postoperative pain and enhances functional recovery

after surgery and intrathecal administration of GBP or NSAIDs inhibits hyperalgesia in a rat postoperative pain model [40]. Further animal studies demonstrated that a transdermal emulsion combing GBP and NSAID at various ratios demonstrated substantial ratio-dependent severe pain relief in Sprague-Dawley rats [29]. The need to have both drugs in the combination to amalgamate in the same tissue at the same time is an essential feature of the therapy. This is critically important with peripheral pain, especially when targeting the peripheral nerve tissue, including the first synapse.

Conclusion

TD CDT has transformed the clinician's pain practice. Prescribing, as a first line treatment, GBP and NS in a transdermal emulsion, has provided targeted substantial relief of acute and chronic peripheral pain without the negative systemic effects of oral administration of these drugs, and substantially reduced or avoided use of opioids or other psychoactives. The positive clinical experience is well-supported by the authors' original work as well as by the reported work of others. The need for a change in the dominant SDT paradigm so that the medical profession can best make use of this therapy and avoid unnecessary secondary harm is more fully discussed in a related report [55].

Abbreviations

Active drug, Active Pharmaceutical Ingredient: API

Basement Membrane Disruptors: BMD

Central Nervous System: CNS

Epidural Steroid Injection: ESI

Gabapentin: GBP

Intercostal Nerve Block: ICNB

Multimodal Analgesia: MMA

Naproxen: NS

Non-Steroid Anti-Inflammatory Drug: NSAID

Osteoarthritis of multiple joints: OA

Penetration Agents: PA

Post Herpetic Neuralgia: PHN

Pregabalin: PGB

Reflex Sympathetic Dystrophy: RSD

Systemic Drug Therapy: SDT

Three times a day (ter in die): t.i.d.

Transdermal combination drug therapy: TD CDT

Twice a day (bis in die): b.i.d.

Vasodilators: V

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