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Transdermal Pharmacologic Treatment of Peripheral Pain: An Alternative to Systemic Treatment Using Opioids, High Dose NSAIDs and Psychoactive Drugs-A Health Policy Review

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Abstract

Background: The national crisis resulting from the wide-spread abuse of opioids and other psychoactive drugs and its relationship to the prescribing practices of physicians has led to governmental and public pressure for clinicians to consider alternative therapies to pain treatment. Unfortunately, while the need for alternatives is widely recognized, there is little consensus regarding the appropriate substitutes.

Objectives: The authors challenge the current pain treatment paradigm and its focus on the systemic treatment of pain, in particular peripheral pain, by the oral administration of opioids, high dose NSAIDS, anti-convulsants, and psychotropic drugs. The authors report that patients suffering from acute and chronic peripheral pain have benefitted in the physician's practice from the transdermal delivery of a combination of an anti-convulsant (gabapentin) and an anti-inflammatory (naproxen).

Study Design: A narrative review

Methods: Literature search was conducted.

Results: In this report the authors summarize how patients suffering from acute and chronic peripheral pain have benefitted in the physician's practice from the transdermal delivery of combination of an anti-convulsant (gabapentin) and an anti-inflammatory (naproxen) in a 10% to 5% ratio. This compounded transdermal combination drug therapy, in that ratio, is intended to target the pain at its source while avoiding the adverse systemic effects commonly associated with the oral administration of either drug.

Conclusion(s): The authors urge clinicians to consider local targeted transdermal pharmacologic treatment for a multitude of peripheral pain conditions, before implementing a systemic approach. Also, they raise concern that the insurance industry and their Pharmacy Benefit Managers (PBMs) are interfering with the ability of prescribers to provide their patients with less dangerous and less expensive alternatives to opioids and other systemic drugs by automatically denying reimbursement claims for transdermal medications and imposing pre-textual and burdensome demands for Prior Authorization (PA). These unnecessary barriers to care interfere with the doctor-patient relationship and the physician's solemn duty to "first do no harm." They prevent the patient from receiving pain treatment that has the best chance to restore well-being and function while minimizing or avoiding the deleterious effects to body and mind resulting from the systemic delivery of opioids, high dose NSAIDs, or powerful psychoactive drugs.

Keywords: Peripheral pain; Systemic treatment *vs* transdermal; Transdermal combination drug therapy; Gabapentin; NSAIDs; Insurance industry; Pharmacy benefit managers; Prior authorization

Urgent Need for Change

The need for effective pain treatment

The urgent need for effective pain treatment is well-appreciated by both the medical care profession and society in general. The 2019 comprehensive interagency review of pain and its treatment conducted by Health & Human Services (2019 HHS Pain Report) [1] recognized, the experience of pain is a national public health problem with profound physical, emotional, and societal costs [2]. How it is treated significantly impacts the American Health Care System [3]. Practitioners everyday must cope with the fact that millions of Americans are in pain, both chronic and acute, resulting

from disease, injury, and surgical intervention [4]. Although estimates regarding the size of the affected population vary depending on the methodology used to assess pain, federal authorities believe that pain, whether considered acute or chronic affects 50 million US adults, and 19.6 millions of those adults experience high-impact chronic pain that interferes with daily life or work activities [5]. The substantial human toll resulting from pain has a concomitant economic impact. The nation's annual cost of pain is estimated at between $560 billion and $635 billion annually [5].

Recognition the "systemic treatment of pain" paradigm needs to change

The human, social and economic impact of pain and the medical practitioner's mission [1,6] 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 [6-9]. Unfortunately, the dominant medical paradigm focuses on pain relief through the systemic delivery of powerful oral medications, in particular opioids, as the preferred or first line treatment modality regardless of the pain's origin. Under the "systemic treatment of pain" paradigm, oral administration of opioids, high dose NSAIDS, anti-convulsants, muscle relaxers and psychotropics are routinely prescribed to treat pain including localized peripheral pain [1,8-12]. Systemic treatment of pain with such powerful drugs can profoundly impact the patient's ability to function and the body's "inherent capacity for recovery" [8,9,13] and presents a significant risk of debilitating secondary adverse effects [5,9,12].

Opioid use disorder and overdose death

Opioid treatment carries the substantial risks of misuse, opioid use disorder (addiction), overdoses, and death [14]. "The opioid epidemic," is considered to be "one of the worst public health disasters affecting the USA and Canada" [15]. This national calamity has been directly tied to the prescribing practices of the profession. "Millions of Americans [who] suffer from pain are often prescribed opioids to treat their conditions "despite" the dangers of prescription misuse, opioid use disorder, and overdose [which] has been a growing problem throughout the United States" [14]. Overdose deaths involving prescription opioids nearly increased by five times from 1999 to 2000 [14]. As distressing as the human toll exacted, these practices have not had an appreciable impact on the "amount of pain" that Americans report [14].

More disturbing is the fact that the dramatic increase in prescription related overdose deaths has been followed over time with a concomitant increase in overdose deaths due to street drugs like heroin, fentanyl, and other psychoactives [Figure 1]. Our nation's drug abuse crisis has led to a growing recognition by medical care professionals, policymakers, state and federal regulators, and the general public that there is an urgent need to develop effective alternatives to the treatment of acute and chronic pain [14,16-18]. Unfortunately, the search for alternative therapies too often is done through the prism of the dominant paradigm of systemic treatment. Reliance on the systemic treatment paradigm leads physicians to try and replace opioids with other systemically administered drugs - orally administered substitutes that carry their own substantial risk of serious impact on physical health and cognitive function.

High dose Nsaids, anti-convulsants and physchotropics and risk of substantial side-effects

Orally administered high dose NSAIDs can be associated with gastrointestinal bleeding, renal insufficiency, hypertension, and cardiac-related events [1,14,19,20]. Orally administered gabapentinoids can cause significant sedation, [1] somnolence, ataxia, and fatigue [21-23]. Gabapentin and its related forms have recently been associated with misuse and abuse with other drugs [21,22]. Orally administered psychotropic drugs carry the risk of dizziness, memory impairment, orthostatic hypotension, and cardiac conduction abnormalities [1].

Systemic paradigm marginalizes non-systemic transdermal treatment

The systemic treatment paradigm, however, remains dominant, stifles the consideration of non-systemic pharmacologic delivery, in particular, transdermal delivery. Transdermal delivery refers to the transmission of drug therapeutics "across" the skin barrier. The integumentary system is the largest organ in the body, also the largest underutilized system for delivery of medications to treat pain. Transdermally delivered pharmacologics are either topically applied through an ointment, gel, or cream, or contained in a patch that meters out the dose over time. It is commonplace that reference in the literature to topicals refers to medicines that are confined to the upper skin layers at the site of application [24,25]. In contrast, the term transdermal is often used to refer to delivery of a drug that on its own or with the aid of penetration enhancers diffuses deep into the tissues where the active is picked up by the circulatory system and delivered systemically [24,25]. Such traditional distinctions ignore the advancement in the science of transdermal technology that can be designed for slower acting uptake resulting in the bulk of the drug reservoiring in the deep tissues for local targeted treatment of the injured tissues [26].

The 2022 CDC Guidelines do not exhibit an appreciation for the versatility and scope of transdermal delivery and the technology's capacity to deliver proven analgesics to the site of the injured or diseased tissue with minimal systemic uptake [14,25-32]. The Guidelines recognize the need for alternative therapies to pain management but emphasize replacing systemic opioids with other systemic drugs. Reference to use of non-systemic treatments to avoid the adverse effects of systemic delivery are mostly confined to local injection therapy and non-pharmacologic care such as physical and behavioral therapy, and western and eastern neuro-stimulation methods [14]. Very limited reference is given to non-systemic pharmacologic treatments. Such references are confined to use of topical NSAIDs is recommended in cases where "a single or a few joints near the surface of the skin (e.g., knee) are affected by osteoarthritis [14,33] or use of transdermal lidocaine for neuropathic pain, in particular Post-Herpetic Neuralgia (PHN) [14,28-31]. And transdermal fentanyl patch as an alternate method to systemically dose the patient's body with that powerful opiate [14,34].

Peripheral pain should first be treated at the periphery

The human and social cost of the systemic treatment paradigm has caused some [35] like the authors, to challenge the dominant medical care paradigm that pain, including peripheral pain, is best treated by the oral administration of powerful psychoactive drugs including opioids [34], anti-convulsants [36], and psychotropics, or high dose NSAIDs [33]. It is the position of the authors, that in order to best meet the need for effective treatment of pain while minimizing or avoiding the adverse effects of systemic drug administration, it is essential that the profession rigorously distinguish between peripheral pain [37] and pain originating or in deep organs. Most acute and chronic pain conditions confronting the practitioner originate at the periphery. Of the 17 health conditions afflicting the pain population considered in the 2019 HHS Pain Report [1], most involved peripheral pain i.e.,

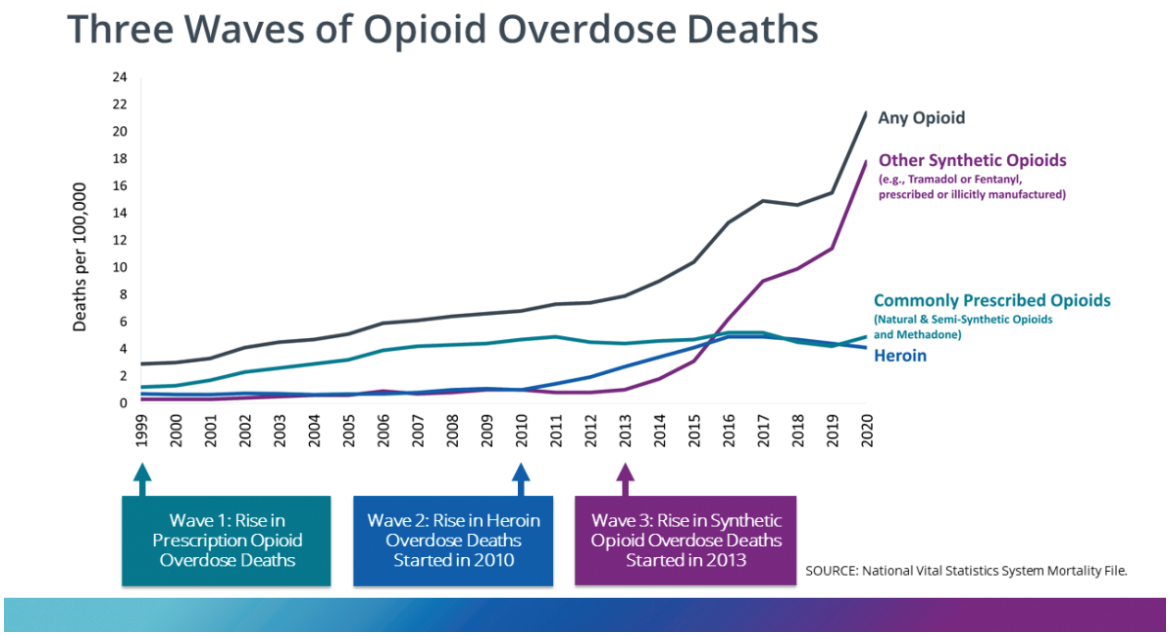

Figure 1: Three waves of opioid overdose deaths. This figure appears at: https://www.cdc.gov/opioids/basics/epidemic.html

pain associated with diseases or injuries originating in the musculo-skeletal and peripheral nervous and circulatory system, including neck, back, hips, limbs, feet, hands, joints, and skin as opposed to severe or recurrent headaches, migraines, or, disease or injury, to the internal viscera [3]. Peripheral pain offers unique opportunities to provide local targeted treatment with transdermal delivery of proven pharmacologics and a way to avoid adverse effects of systemic drug therapies. Further, given the history of side effects with systemic opioids including significant addiction issues as well as the well documented gastro intestinal bleeding, first pass liver effect and kidney issues associated with systemically administered NSAIDs, this paper and study is motivated by a timely and significant breakthrough in the safe and effective treatment of peripheral musculoskeletal pain with topically applied transdermal delivered medications.

Summary of Clinical Experience with Transdermal Combination Drug Therapy

The clinician 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. The emulsion uses penetration agents to overcome the lipophilic and hydrophilic structures of the epidermis and basement membrane disruptors to open up channels sufficient to transport the drug and vasodilator deep into the dermis. Once in the dermis, vasodilators dilate the capillary bed creating fluid dynamic blood flow engineered to encourage reservoiring of the Active Pharmaceutical Ingredients (API) in the deeper tissues, elimination of the mediators of inflammation and healing [38].

To date, the clinician has treated several hundred patients using transdermal combination drug therapy. The conditions treated have included myofascial, musculo-skeletal, and neuropathic pain - both chronic and acute. Most of the conditions were chronic which had responded poorly to systemic drug treatment as well as nerve blocks. The conditions included: plantar fasciitis; Reflex Sympathetic Dystrophy (RSD); Post Herpetic Neuralgia (PHN); tendonitis of various joints; osteoarthritis of multiple joints; sciatica; failed neck and back surgical syndromes; phantom pain of the lower extremities due to amputation or accident; and various neuromas resulting from accidents and surgery.

Summary of Supporting Science and Studies

The beneficial clinical experience regarding transdermal combination drug therapy is supported by the toxicology, pharmacokinetics, and *in vitro, in vivo* and peer reviewed studies, conducted by the authors and others [7,20,39-41]. Orally administered GBP is widely used for treatment of neuropathic pain, including postherpetic neuralgia [7,11,21,23,42,43] With oral GBP administration a relatively high percentage of patient population can expect to have some adverse events, some of those with debilitating impact, including dizziness, sedation, ataxia, slurred speech, nystagmus, rhinitis, bone density change, peripheral oedema, fatigue, somnolence, allergy and gait disturbance [23,44]. Oral NSAIDs have anti-inflammatory properties associated with safety risks including gastrointestinal side effects, renal insufficiency, hepatic toxicity, exacerbation of asthma, sodium retention, raised blood pressure, and resistance to anti-hypertensive drugs, as well as increased risk of thrombotic cardiovascular events for non-aspirin agents and increased risk of intracerebral hemorrhage and other bleeding with aspirin [19]. The delivery of the combination, *via* a transdermal emulsion, through the skin and into the peripheral tissue at the same time and in the concentrations needed to generate an augmented pain reducing effect has been shown in animal and Franz cell studies conducted by the authors. The dosage of drug contained in a transdermal emulsion (100mg GBP/g × 2g cream BID = 400mg/day)) is almost a third of that are customarily prescribed for oral administration (300mg GBP QID

= 1,200mg/day). Yet, transdermal delivery can result in substantially more drug delivered locally at the site of the painful condition (400mg impacting 3lbs of target tissue = 133.33mg/lb) than can be delivered locally through systemic drug treatment (1,200mg impacting 200lb patient = 18mg/3lbs of target tissue). *In vivo* human and guinea pig models reported by the researchers show transdermal can be engineered to result in a reservoir of the drug in the deep tissues [26]. The 2022 CDC Guidelines recognized the growing consensus that for certain types of peripheral pain the preferred choice should be transdermal NSAIDS rather than oral NSAIDs [7,14]. The Society of Pain and Neuroscience's Consensus Guidelines state "Topical NSAIDs are recommended before oral treatments because of their lower systemic exposure/toxicity [10,40,41,45,46]." A randomized clinical trial reported that application of 2gms of transdermal ibuprofen containing 200mg of the active to moderate to severe osteoarthritic knees, twice a day for fourteen days significantly reduced pain and increased function [26,33]. Transdermal GBP has shown efficacy in the treatment of peripheral neuropathic pain [30,36,47].

Transdermal Combination Drug Therapy Is Customized Cost-Effective Care

Prescription compounded pharmaceutical *vs* branded or generic drugs

Transdermal combination drug therapy is customized medicine. It requires a compounded drug preparation. Drug compounding is often regarded as the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient and includes the combining of two or more drugs [48]. A drug may be compounded for a patient who a physician has determined requires an alternative to treatment with an FDA-approved medication [48]. The alternatives include combination with another API or changing dosage and route of administration. In this way, providing compounded drugs to patients when an FDA-approved drug is not medically appropriate to treat them, can serve an important patient need [48].

Compounded drug therapy is as old as medicine. The mortar and pestle are tools of traditional pharmacy that has long been used as a pharmaceutical symbol in western medicine [49]. Regulation of medicine and physician's use of pharmacy prepared drugs has from the outset been a subject of state regulation. The jurisdiction of the FDA when it was formed to regulate the manufacture of food and drugs, was specifically restricted to branded drugs for general distribution that made specific health claims and exempted pharmacist prepared therapeutics made by a physician's patient specific request [50]. Concern for ensuring compounded drug safety in the wake of the 2012 incident involving the fungal contamination of a compounded sterile injection drug that caused many illnesses and deaths led to the passage of the 2013 Drug Quality and Security Act further expanding FDA jurisdiction over certain aspects of compounding practice [50]. Present day FDA regulations and guidelines include ensuring that the API's and ingredients used in compounding are safe and manufactured in accordance with FDA and USP standards for medicines and prepared in accordance with state law and FDA requirements regarding sanitary conditions [50].

Transdermal combination drug therapy is physician directed therapy that uses a combination of two FDA approved APIs, gabapentin and naproxen, in a specific ratio (10%-5%), that is compounded by a state licensed pharmacist pursuant to a patient specific prescription into a transdermal emulsion for topical application. It does not make use of an over the counter, conventionally manufactured FDA approved branded drug product. Compounded drugs are not branded drugs that have gone through the FDA drug approval process to determine their safety and efficacy, appropriate directions and warnings, and indications for treatment of particular conditions [50]. At the direction of a physician, they are drug products containing FDA approved ingredients that have been specially prepared by a state licensed pharmacist in order to provide treatment that is not otherwise available. Regarding this therapy, the FDA has approved drug products containing either gabapentin or naproxen for systemic administration in either a pill or liquid form to treat various forms of peripheral pain. However, there is no FDA approved drug product containing the two drugs in combination as a pill or liquid, and no FDA approved transdermal emulsion drug product containing these two drugs in combination for topical application in any ratio. Therefore, in order for a patient to receive the locally delivered therapy to the site of the patient's peripheral pain in the ratios deemed effective and avoid the serious adverse effects of systemic opioids and other powerful systemic drugs described above, it is essential that the transdermal drug combination be specially prepared by a state licensed pharmacist. Transdermal combination drug therapy has been assigned by the manufacturer with the appropriate National Drug Code (NDC) designations and the NDC information has been provided to the relevant industry registries [51].

In addition to the substantial benefits to patient health, restoration of function and well-being of non-systemic alternatives, the econometrics also support transdermal combination drug therapy. Non-systemic drug therapy by its nature provides cost savings in avoided costs. These avoided costs include substantial costs associated with systemic pharmacologics; invasive interventional therapy; and the secondary care for adverse effects. These avoided additive costs should be considered when comparing the cost of a compounded alternative to a systemic drug either brand name or cheaper generic.

The substantial costs associated with prescribed systemic drug therapy opioids and NSAIDs are well-documented. Numerous studies have shown that opioids are associated with the occurrence of opioid-related symptoms, the development of opioid use disorder, and overdose [52]. The 2022 CDC Guidelines recognized "observational studies [have] found that opioid use for acute low back pain or postoperative pain was associated with increased likelihood of long-term opioid use," and clinical evidence reviews [that] found observational evidence that opioid use for acute pain is associated with long-term opioid use and that a greater amount of early opioid exposure is associated with greater likelihood of long-term use", noting recent evidence for a dose- and duration-dependent effects [14]. Exposure to opioids can lead to an increase in healthcare resource utilization such as prolonged hospital length of stay, elevated readmission rates, and increased overall healthcare costs [14]. High dose systemic NSAID therapy is also associated with substantial risk of prolonged stays, secondary care, and increased healthcare costs associated with the secondary effects on the gastro-intestinal, renal, and cardiovascular systems [53]. Individuals with chronic musculoskeletal pain conditions may be particularly susceptible to high-cost utilization [54]. High variability in care and a poor understanding of which pain treatments are most effective often lead to unnecessary care escalation, poor clinical outcomes, persistent health care needs, and avoidable opioid use [54]. The result is substantial cost associated with treatment of musculoskeletal pain (54) up to $650 billion annually [55].

Denial of Reimbursement for Alternate Care

Reimbursement resistance by the insurance industry and their pharmacy benefit managers

Despite state and federal policies and public pressure, the insurance

reimbursement industry through the Pharmacy Benefit Managers (PBMs) they use to make reimbursement decisions actively discourage patients receiving non-systemic alternate care. The profession's myopic focus on the systemic administration of pharmacologics has allowed the medical reimbursement industry to routinely deny coverage for alternate treatments outside the dominant paradigm pressuring the physician and patient to resort to systemic therapy, in particular opioids [1]. Federal regulators recognize that "requiring patients and health care professionals to navigate burdensome and variable coverage policies may contribute to slow development, adoption, and implementation of timely and effective pain treatments and may force providers to treat patients in a less-than-optimal fashion" and "consistently forcing providers to try a series of non-first-line treatments prior to authorizing treatment plans can be problematic, hindering appropriate patient care, creating tremendous inefficiency, and resulting in a loss of time and resources" [1].

A PA requires providers to qualify for payment by obtaining approval before performing a service [56]. This purported "health plan cost-control process" is recognized by leading governmental and professional authorities, including the American Medical Association (AMA), to be overused, costly, inefficient, opaque and responsible for patient care delays [57]. AMA surveys of the profession have shown that: 88% describe the burden associated with PA as high or extremely high; 93% report "delays access to necessary care; 82% leads to patients abandoning their recommended course of treatment; of the 91% who treat patients 18-65 "currently in the workforce, 51% "report that PA has interfered with a patient's ability to perform his or her job responsibilities; and 34% report that PA has led to a serious adverse event for a patient in their care [57].

The Office of Inspector General of HHS (OIG) in its investigation of denials of care payments by Medicare Advantage Organizations (MAO) found "widespread and persistent problems related to denials of care and payment" citing "56 percent of audited contracts made inappropriate denials" and "45 percent of contracts [sent] denial letters with incomplete or incorrect information which may inhibit beneficiaries' and providers' ability to file a successful appeal [58]. The OIG found there may have been an incentive to deny preauthorization of services for [Medicare] beneficiaries and payments to providers, in order to increase profits [58].

The industry and their PBMs' unfair practices that directly impact patient access to quality health care has prompted both bi-partisan sponsored federal legislation [59] and an investigation by the Federal Trade Commission (FTC) [60]. The FTC has determined that PBMs are "powerful middlemen [who] have enormous influence over the U.S. prescription drug system" and "which drugs are prescribed to patients" [60]. The FTC investigation "will shine a light on these companies' practices and their impact on pharmacies, payers, doctors, and patients" through various practices including "complicated and opaque methods to determine pharmacy reimbursement" and the "prevalence of prior authorizations and other administrative restrictions [60].

The barriers to appropriate, timely and cost-effective care presented by the abuse of the PA process that afflicts medical practice across the board are magnified by an order of magnitude regarding denial of treatments involving compounded topical medications.

The clinician and pharmacist report that over the five-year period the clinician has issued hundreds of prescriptions for transdermal combination drug therapy. Despite the proven benefits, substantial scientific support, substantial savings in human and economic cost, and existence of NDC codes [51] assigned to the therapy, reimbursement requests have been peremptorily denied by the major insurers. Only a small percentage of the total requests submitted were granted reimbursement. Those few cases involved self-insured employers or specialty plans. The denials by the majors routinely have been followed by pre-textual and burdensome requirements for the clinician to fill out detailed "Prior Authorization" requests. Sometimes the clinician has been given an opportunity to present the justification for treatment to a PBM selected medical consultant. In each instance the PBM consultant listened without meaningful comment or discussion. Every PA submitted, no matter the condition treated, the history presented, or the medical need identified, whether preceded or followed by a telephone call with a PBM selected consultant, has been rejected, except one. In that one instance, the PBM, after extended communication involving the clinician, the patient, the PBM representatives and the PBM selected consultant, and the citation to extensive medical support, the PBM reversed its decision and authorized payment for transdermal combination drug therapy for chronic cervicalgia. However, a follow-up request for the same treatment, for the same patient with the same condition, was perfunctorily denied. The reason for the denial reported by the PBM was that the PBM had "changed" consultant services. The history of the clinician's PBM experience regarding denial of reimbursement for transdermal combination drug therapy lays bare the hollow claims of the industry that PBM decision making is "evidence based" or performs a "cost saving" function. Each denial passes the cost of the treatment onto patients who often have limited resources. In those instances, treatment has been maintained through the manufacturer waiving their charges and the pharmacist accepting substantially reduced dispensing fees. Such a situation is not economically sustainable or commensurate with the investment in research and innovation, and costs of manufacture or professional services. Unless and until the PBM roadblock is removed, every practitioner will be stymied, as the clinician has been, in their attempt to find safer and less costly alternatives than the ones currently given undue preference by the reimbursement industry under the systemic paradigm.

The Systemic Paradigm Underserves Many Patients Populations

Underserved patient populations would benefit from local targeted treatment

The reported success with the treatment of a wide variety of peripheral pain conditions and the concomitant reduction of, transition away from, or complete avoidance of opiates and other powerful systemic drugs, underscores the importance of a change in focus regarding patient care. A rigorous understanding of the origination of the patient's pain and the appreciation of the availability of non-systemic pharmacologic alternatives, provides the patient with an opportunity, too often denied, for a fuller restoration of function, preservation of well-being, and return to daily activities - participation in daily life without the debilitating risk of drug induced sequelae.

This choice, that the informed practitioner can offer their patients, has profound meaning for the vast majority of the pain population. Pain reduction to a manageable level allows "the body's inherent capacity for recovery" to complete the healing process [13]. A healing patient soon becomes a full and productive participant in life's activities. The ability of physicians to accord millions of their suffering patients a path out of the darkness of pain with substantially less risk of iatrogenic injury benefits every patient who wishes to promote recovery and healing while maintaining their sentient faculties. The approach detailed in

this report should be considered in the first instance for every sufferer of acute or chronic peripheral pain regardless of age, occupation, or stage of life.

A particularly vulnerable population that can benefit from non-systemic pharmacologic treatment is the elderly. The natural aging process changes the "pharmacokinetic and pharmacodynamic" ability of the body to process medication including: gastric motility, renal clearance, and hepatic metabolism, and age related decline in mobility and balance, and central nervous system deficits, make the elderly particularly vulnerable to the negative effects of systemic drugs [24]. "It is well known that NSAIDs are not safe for chronic use in the elderly" because of the risk of gastrointestinal bleeding, peptic ulceration, nephrotoxicity and cardiovascular events [24]. In addition, "prescribers and older adult patients continue to have an aversion to the use of opioid analgesics" which is "attributed to a general fear of opioids, addiction, or risk of opioid-induced side effects" [24] including "falls, fractures, and delirium" [61].

Non-systemic pharmacology also has significance to any patient whose livelihood and self-respect depends on maintaining clear focus and self-control such as:

- Health care workers
- Law enforcement and fire personnel
- Athletes
- Business/Science/Research/legal professionals
- Armed Forces personnel
- Administrative personnel
- Factory workers
- Workers skilled in the trades
- Any person whose daily activities others are dependent on

Non-systemic drug therapy for pain has equal significance for patients whose compromised physiology or prior history of substance abuse removes consideration of systemic analgesics. These populations include:

- Bariatric patients
- Organ transplant patients
- Incarcerated population
- Patients undergoing drug abuse rehabilitation.

In addition, the medical care approach discussed, with its promise of targeted cost-effective care, should be of significance to any association, organization, employer, or federal, state, or local authority that is tasked with the responsibility of providing self-insured or governmental benefits. Such groups include workers compensation, union health insurance, self-insured employers, Centers for Medicare, and Medicaid services, etc.

Conclusion

The opioid crisis has forced the profession and society to engage in an introspective examination of the practices and behaviors that contributed to our national emergency regarding drug misuse and abuse. Such introspection should involve a frank assessment of the limitations and perils of our continued reliance on the dominant medical care paradigm that sees systemic drug therapy as the mainstay of medical practice. The clinical practice reported herein demonstrates that there are safer and more effective pharmacologic therapies for treating peripheral pain that do not include the administration of powerful systemic drugs. Transdermal CDT allows for targeted low dose non-systemic treatment of a wide variety of peripheral pain conditions. The gabapentin and naproxen 10%-5% emulsion allows the clinician to make safer use of the drugs and their very well understood efficacy and toxicity profiles. The targeted low dose non-addictive therapy offered by this transdermally delivered combination means that the practitioner can maximize the known benefits of these drugs to relieve moderate to severe peripheral pain while substantially avoiding any significant risk of the drugs systemic side effects. First use consideration of this approach for peripheral pain treatment allows medical care professions to treat a multitude of underserved pain patient populations with an opportunity to reduce pain to a manageable level so that they can more rapidly assume fuller participation in the activities of daily life without the risk of drug induced sequelae while the body completes the healing process. Such an approach deserves the attention and active support of medical care professionals, governmental authorities, and the insurance reimbursement industry. In that way, the medical profession will better fulfill its noble mission to heal by first doing no harm.

Abbreviations

Active drug, Active Pharmaceutical Ingredient: API
Basement Membrane Disruptors: BMD
Central Nervous System: CNS
Epidural Steroid Injection: ESI
Federal Trade Commission: FTC
Gabapentin: GBP
Intercostal Nerve Block: ICNB
Multimodal Analgesia: MMA
Naproxen: NS
National Drug Code: NDC
Non-Steroid Anti-Inflammatory Drug: NSAID
Osteoarthritis of multiple joints: OA
Penetration Agents: PA
Post Herpetic Neuralgia: PHN
Pregabalin: PGB
Prior Authorization: PA
Primary Benefit Managers: PBM
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

Authorship: HDC contributed to conception and design, ZZ made data acquisition and literature search, WB drafted the article, GV critically revised and wrote the article.

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