THE RELEVANCE OF THE PERIPHERY IN PAIN MANAGEMENT AND THE VALUE OF COMPOUNDED NON-SYSTEMIC TRANSDERMAL (NST) PAIN CREAMS

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Current situation:
- Inadequate treatment for patients with chronic pain conditions
- Inability to address the complexity of the syndromes as multiple oral medications are poorly tolerated
- Inadequate understanding of the role and value of the topical treatment modality
- Increasing cost of treatment with decreasing results (patient improvement)
- The need for effective treatment options to mitigate the opiate conundrum

Relevance of the Periphery:
It should be appreciated that the nervous system and the epidermis are derived from the same tissue during fetal development (ectoderm) resulting in a massive sensory organ with considerable neural involvement and input to the CNS. This input contributes to the development, severity and chronicity of pain syndromes.

Definition of the problem:
Society’s current life style which consists of poor nutrition, sedentary living, stress, and exposure to toxins is resulting in an increasingly hyper-reactive nervous system and immune response. Insults that should be self-limiting are becoming a disease in themselves leading to chronic pain syndromes. This produces an ever increasing trend in debilitating conditions. There is also an increasing trend in prevalence and severity of debilitating syndromes without insult such as fibromyalgia and chronic fatigue syndrome.

There are over 100 million chronic pain patients in the United States with 44% being inadequately treated as currently available commercial medications and procedures cannot meet their needs. The total number of chronic pain patients outnumber those with cancer, heart disease, stroke, and diabetes; this composes the largest share in the health care burden.

Compounding specifically addresses biodiversity and the multiple causes leading to the inability to effectively manage these patients. It is the role of compounding to individualize and integrate therapeutic approaches to deliver improved patient outcomes which has contributed to the growth in compounding today.

Many of the factors leading to the chronicity of these syndromes is either unidentifiable or unknown by many physicians. New technology, science and applications are not being utilized as it relates to peripheral sensitization and neural input to the CNS.

These syndromes are complex and frequently the pathology and treatment options have been overly simplified leading to poor outcomes.

Additional limiting factors range from inadequate physician time to identify these factors to the removal or barriers to effective treatment options.

There is an enormous unmet need and suffering that is occurring as a result of focusing on the pharmacy costs without adequately considering that improved patient outcomes are the bottom line and reduce the total healthcare burden.
Many therapeutic options have been removed or barriers have been placed that are so onerous or unproductive they generate futility and discourage due diligence, especially in light of decreasing physician time availability per patient.

By addressing peripheral influences propagating and sustaining the chronic pain syndromes, patients are experiencing a reduction in pain enabling them to decrease the opiates inhibiting successful outcomes as well as medications compromising cognition or leading to Adverse Drug Reactions (ADR).

**The latest science on peripheral involvement and limitations to current treatment:**

It is now recognized that continual peripheral neural input (nociceptive and ectopic impulses) contributes to central inflammation and sensitization as well as direct pain (consider the Lidoderm patch).

Peripheral sensitization and modulation does occur, leading to the chronicity of these pain syndromes (keratinocyte inflammatory mediator production, TRP receptor sensitization, NMDA receptor sensitization, etc.).

It is recognized that topical approaches to pain management are low risk, well tolerated and safer than many solutions using oral and parenteral routes. What also needs recognition is that the latest outcome research of treating complex chronic pain syndromes topically is showing profound and robust improved patient outcomes (overall 71% of patients are seeing improvement with a 51% average reduction in pain for all patients). Typically these patients have not been successfully managed by all available therapies and procedures.

**Contributing compromising factors as a result of oversimplification or non-recognition:**

- Not addressing or recognizing inflammation’s role in neuropathic pain syndromes.
- Inflammation is complex and the lipoxygenase segment of the cascade produces mediators upregulating COX2 leading to a reduction in the effectiveness of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and other therapies.
- Polypharmacy is required many times to address the multiple cascading and compensatory events that are occurring.
- That traditional polypharmacy is poorly tolerated and does not address peripheral involvement which can lead to a reduction of oral and parenteral medications that are compromising pain management (i.e. opiate induced hyperalgesia) and cognition.
- There is a preoccupation with the final step in the pain process (perception) to the exclusion of the first three steps (transduction, transmission, modulation).
- That hormonal influences play a major role in pain syndromes (fibromyalgia, etc) and that certain treatments can impact recovery and treatment (opiates).

**The rationale behind the topical treatment modality and formulation design**

The basic science and principles behind the topical treatment modality:

- Recognition that many complex pain syndromes are inadequately treated using the current standard of care and identification of the contributory causes.
- Much higher tissue levels can be achieved than by the oral or parenteral route of administration; coupled with lower serum levels this allows for safer and better tolerated application of multiple medications to improve outcomes.
- This application addresses multiple peripheral mechanisms that are contributing to the perception and chronicity of pain.
• Multifaceted topical applications can influence the transduction, transmission, and modulation of pain impulses for better therapeutic responses (addressing peripheral inflammation, sensitization and "wind-up", spontaneous ectopic pain impulses, and nociceptive impulse contribution to central inflammation and sensitization).

The evidence of the safety and effectiveness of the topical treatment modality and relevant observations:

• Systemic formulations (oral and injectable) result in over half a million serious adverse events each year in the U.S.
• Adverse events from topical treatment applications are considered low risk relative to systemic formulations.
• Confusion in compounding medications exists due to high risk sterile-injectable compounded formulations vs. non-sterile topical compounded formulations.
• There is a growing body of evidence that the topical pain creams are delivering improved patient outcomes. Numerous studies have shown them to be of value.
• The clinical research organization Patient Outcomes Analytics utilizing an Institutional Review Board (IRB) approved design and protocol to survey and assess patient outcomes has determined that there is an average 51% reduction in pain with 71% of patients showing pain improvement at the 4 week point for all patients surveyed (n=3,587) with minimal adverse reactions (4.9% at 4 week point). There was a reduction in oral med use for 38% of the patients surveyed.